Cardiovascular Reactivity during Stress Induction Differentiates ADHD Subtypes

William T. Utendale

A Thesis
in
The Department
of
Psychology

Presented in Partial Fulfillment of the Requirements
for the Degree of Master of Arts at
Concordia University
Montréal, Québec, Canada

September 15th, 2005

© William T. Utendale

Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 0-494-10189-X
Our file Notre référence
ISBN: 0-494-10189-X

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

ABSTRACT

Cardiovascular Reactivity during Stress Induction Differentiates ADHD Subtypes

William T. Utendale

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most pervasive childhood mental health problems in Canada. Research examining how autonomic physiological systems are associated with ADHD has been inconclusive, often yielding contradictory results. One confounding issue may be the very high prevalence of comorbid problems in children with ADHD. Another issue may be the heterogeneity of symptom sets exhibited by children with ADHD. Children's ability to self-regulate their physiological arousal under conditions of challenge or stress is likely to be influenced by comorbid problems and ADHD subtype. In this investigation, 142 elementary school-aged children with ADHD wore cardiac monitors while undergoing a stress-inducing event: having their blood drawn in a hospital clinic. Continuously recorded cardiac inter-beat intervals were used to assess heart rate (arousal), vagal tone (parasympathetic regulation), and SNS Index (sympathetic regulation). Parental reports of comorbid problems were assessed using the CPRS-R and the DISC-IV. Comorbid disruptive behavior disorders and anxiety disorders did not strongly predict cardiac reactivity. Significant variability in cardiovascular reactivity distinguished between ADHD subtypes; in particular, children with hyperactive-impulsive problems showed strongly atypical vagal and SNS reactivity. These results have implications for the diagnosis and treatment of ADHD.

Acknowledgements

I wish to thank my supervisor, Dr. Paul Hastings, for his unswerving guidance and support. His insight and dedication are inspiring, and are so very much appreciated. Dr. Lisa Serbin and Dr. Jennifer McGrath, as members of my examining committee, I thank you both for your comments and suggestions on improving this work, and for your kind words of encouragement. I also wish to thank Dr. Isabel Fortier, Dr. Philip Robaey, and François L'Heureux for their contribution to data collection. To the ABCD Lab members, thank you for your suggestions and comments, and thank you to Sara Levine for her help in processing the raw inter-beat interval files.

Table of Contents

page

List of Tables

List of Figures

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a major Canadian public health issue, and accounts for up to 50% of referrals of children to mental health clinics (Waschbusch et al., 2002). Increasing understanding of this disorder in order to inform policy decisions aimed at reducing the negative impact of ADHD on children, families, and schools, is a necessary aspiration of the mental health community (Frick, 1998; Hinshaw, 1994). Estimates of the prevalence of ADHD vary, but a commonly accepted figure is that ADHD occurs in approximately 10% of school-age children (Voeller, 2004). ADHD and its associated behaviour problems result in numerous difficulties in social functioning (Santosh & Mijovic, 2004; Wheeler & Carlson, 1994). Children exhibiting ADHD are at a disadvantage in terms of academic performance (Barkley, Anastopoulos, Guevremont, & Fletcher, 1991). Peer rejection is common (Waschbusch et al., 2002) and children with ADHD often exhibit poor social competence (Greene et al., 1996). Family disruption occurs often for these children (Barkley, Anastopoulos, Guevremont, & Fletcher, 1992). Children with ADHD are also likely to earn less as adults than their non-ADHD counterparts (Waschbusch et al., 2002). Thus, the seriousness and potential impact of this disorder should not be underestimated.

Examining the underlying physiological processes of ADHD could produce insight that would lead toward more effective treatment protocols. Understanding the physiological correlates of ADHD symptomatology could lead to treatment strategies less reliant on pharmacotherapy and more reliant on behavioural interventions targeting physiological regulatory systems. By examining cardiovascular reactivity in relation to ADHD symptom constellations, specific physiological correlates of ADHD subtypes and comorbid problems may lead to better screening procedures, better targeting of treatment modalities, and more positive prognoses.

Attention-Deficit Hyperactivity Disorder

Children with ADHD demonstrate two major categories of dysfunction (American Psychiatric Association, 2000), inattentiveness and hyperactivity-impulsivity, which may occur separately or together. Children with predominantly inattentive symptoms have been characterized as "dreamy" and tend toward a low capacity for attending to stimuli (Voeller, 2004). This characteristic has been termed "sluggish cognitive tempo" (Hartman, Willcut, Rhee, & Pennington, 2004; Lahey, Schaughency, Hynd, Carlson, & Nieves, 1987). A preponderance of inattentive symptoms appears highly related to a general trend of poor academic performance (Gadow et al., 2004). Children demonstrating predominantly hyperactive-impulsive symptoms are over-active and hard to manage (Gadow et al., 2004). Combining elements of both hyperactivity-impulsivity and inattentiveness, the group demonstrating mixed symptomatology is arguably the most impaired when academic, cognitive, and social performance factors are assessed via parent and teacher ratings of psychiatric symptoms; this group also tends to demonstrate the most severe hyperactive and inattentive symptoms (Gadow et al., 2004).

Children with ADHD provide a frequent source of frustration for parents and teachers, and are themselves challenged in many aspects of their lives. Paying attention during school instruction or at home with family is difficult. Children with inattentive symptoms are forgetful and lose items constantly. They daydream, do not remain on-task, and generally have very little in the way of attention span. Those with hyperactive symptoms tend to be reactive, impulsive, fidgety, loud, talkative and rambunctious. They are constantly active and may be quite oppositional. The parent with a child who has

ADHD may dread any outing with the child, as a tantrum is likely to occur at some point throughout the day. Siblings as well may have difficulty in dealing with their brother or sister with ADHD. ADHD symptoms affect almost every aspect of the child's social interactions, and result in such major disruptions that the child's ability to reach his or her potential may be severely limited.

The age of onset for ADHD is variable depending on the types of symptoms present. Data presented from the DSM-IV field trials indicate ADHD symptoms typically occur before age 7 (Applegate et al., 1997). However, age of onset differed across inattentive, hyperactive-impulsive, and combined groups of children. The hyperactive-impulsive group demonstrated symptoms slightly earlier than the combined group, and much earlier than the inattentive group. The hyperactive-impulsive group had first symptom onset at 4.21 years and the comparable figure for the combined group was 4.88 years. These children were considered markedly impaired before the age of 7 (98% and 82% respectively) in comparison to the inattentive group, who presented with marked symptomatology at 6.13 years. Of these inattentive children, 57% were symptomatic before the age of 7. The work of Willoughby, Curran, Costello, and Angold (2000) parallels these findings.

Boys and girls differentially exhibit ADHD symptoms in terms of both frequency of diagnosis and propensity toward each of the three subcategories. Boys are diagnosed with ADHD at a rate of 6 to 12 times that for girls as assessed from clinic-referred samples (Voeller, 2004). Lower estimates have been derived using epidemiological samples, with boys receiving diagnoses at about 3 times that for girls. The sex difference is smaller for inattention-only cases; boys have a much higher rate of hyperactive problems, usually reported as being many times that for girls depending on the setting (community or clinic) (American Psychiatric Association, 1994).

Subtypes of ADHD

Examining ADHD as a global construct rather than looking at the elements of the individual subtypes makes this group highly heterogeneous. Individuals vary considerably in exhibited behaviours, and this heterogeneity may introduce confounds into ADHD investigation. Evidence for the validity of three subtypes of ADHD has been presented in the literature, and these consist of the inattentive, hyperactive-impulsive, and combined subtypes (American Psychiatric Association, 2000). However, ADHD may indeed represent at least two distinct disorders, one consisting of attentional deficits, and one consisting of hyperactivity-impulsivity (Hartman et al., 2004). These two disorders may or may not co-occur. Understanding more about the biological bases of the distinct ADHD subtypes could provide support for this idea. Differences among individuals with respect to physiological correlates of ADHD should therefore be examined in the more homogenous groups represented by the three subtypes.

Neuropsychological Profiles

Fundamental differences in neurophysiological functioning appear to be inherent elements of ADHD as a global construct, distinct from children without ADHD. However, across the subtypes, various domains of dysfunction and associated symptom constellations are present. Children exhibiting the combined subtype of ADHD may be incapable of appropriately regulating inhibition (Barkley, 1998). Beyond the general dysfunction in neurophysiology, other physiological indices may be related to these specific dysfunctional elements. With regard to children exhibiting the other subtypes, those children demonstrating the inattentive subtype have been postulated to have an inability to focus attention on external cues (Barkley, 1998), and this may derive from somewhat different pathological physiology than that for the other groups.

Barkley (1998) has suggested that the neurological deficits present in children exhibiting ADHD are indicative of an inherent neurophysiological dysfunction of inhibitory control. Chhabildas, Pennington, and Willcut (2001) examined children of combined, inattentive, and hyperactive-impulsive subtypes, and children without ADHD. Measures of processing speed, vigilance, and inhibition demonstrated that behaviours associated with the inattentive subtype were characteristic of the most neuropsychological impairment. They also found that both the inattentive and combined subtypes had similar patterns of impairment on the measures, and that the hyperactive-impulsive children demonstrated no significant impairment on these measures when symptoms of inattentiveness were taken into account.

This research demonstrated that the hyperactive symptom set may represent a different pattern of pathology than that exhibited by children of the combined and inattentive subtypes, consistent with an argument for inherently different patterns of physiological dysfunction among these three groups. If this is the case, subtype and symptom differences may be reflected in assessments of physiological functioning; cardiovascular indices of stress reactivity may show variation across children with the different subtypes of ADHD.

Stress and Cardiac Physiology

The normal stress response was first conceptualized by Hans Selye in 1936. Selye exposed rats to various stressful events, such as infections and noxious chemicals, and found that life-threatening events consistently triggered enlargement of adrenal glands, disruptions in the immune response, gastric ulcers, and increases in corticosterone secretion (Lovallo & Thomas, 2000). These physiological changes occur through chronic activation of the hypothalamic-pituitary-adrenocortical axis (HPA), and high levels of adrenocorticotropin (ACTH) and glucocorticoid secretion. The sympathetic-adrenomedullary (SAM) system is also activated during stress induction, and serves to increase release of catecholamines. Activation of this system produces increases in blood pressure, cardiac output, and respiration rate (Brownley, Hurwitz, & Schneiderman, 2000). Both hormonal regulatory systems and the central nervous system (CNS) interact to regulate metabolic activity and reallocation of resources to maintain homeostasis during periods of stress, whether such stress is environmental or psychological (Lovallo & Thomas, 2000). The interplay between hormonal mediators and neurological processes is quite complex, and for the purposes of this study only cardiovascular reactions to stress will be discussed.

Individual differences in neural regulation of the autonomic nervous system (ANS) contribute to two key behavioural characteristics: reactivity and self-regulation (Rothbart, 1989). Reactivity refers to motoric, attentional, and emotional responses that are elicited by external stimuli. Self-regulation reflects an individual's ability to appropriately and adaptively modulate these responses according to both social and environmental contextual demands. Autonomic regulation contributes to behavioural control and visceral tone whereby the person may systematically focus attentional processes in order to engage or disengage with stimuli. Children exhibiting ADHD may demonstrate significant and debilitating dysfunction in both their reactivity, and self-regulation. It would seem plausible to propose that children with ADHD may have difficulties in terms of the physiological mechanisms involved in attentional selectivity, and self-regulation in social interactions. These may appear as manifestations of behavioural self-regulation (Eisenberg, 1996).

In general, initial exposure to a stressor results in increased sympathetic nervous system (SNS) activity, while parasympathetic nervous system activity (PNS) activation is withdrawn. Given this scenario, heart rate would be expected to increase, while vagal tone would be expected to decrease. This reciprocal nature of the ANS branches is a widely accepted conceptualization of physiological control, but it does not leave room for alternative and more finely tuned physiological responses. The efferent activity to the vasculature, especially the cardiac muscle itself, may not be so clear-cut. There is not perfect coupling between the two autonomic branches (Öhman, Hamm, & Hugdahl, 2000). Most notably, heart rate (HR) and cardiac contractility may be most affected by high levels of both SNS and PNS activity, the two branches serving to coactivate each other. The simple paradigm of independence among the two branches only occurs during the special case of one branch being activated while the other is not. When the influence of one branch is withdrawn, and the other remains at baseline, the latter provides relatively greater influence on physiological systems. During withdrawal of one branch, and activation of the other, reciprocal activation is observed. For the final scenario, that of a concomitant decrease in efference of both branches, coinhibition is observed.

Grossman and Svebak (1987) examined cardiovascular reactivity to an aversive event. They measured cardiovascular activity in undergraduate students with and without threat of electric shock for inferior performance during a videogame task. PNS activity was lower during the task than during baseline, and threat of shock was associated with increased HR and reduced PNS. They also found that SNS influence on HR exceeded the reciprocal PNS effect during the aversive condition for those exposed to the threat condition. This study indicates the necessity of accounting for both PNS and SNS effects during the stress response.

It is important to understand how the two branches of the autonomic nervous system interact to regulate physiological systems. Indeed, not accounting for both parasympathetic and sympathetic influences on reactivity may provide an incomplete picture of how individuals' behaviours and characteristics are related to differing ANS regulation. The PNS regulates cardiac activity through the influence of the tenth cranial nerve, or vagus nerve, which originates in the ventrolateral medulla (Hastings & Utendale, in press). Efferent influence on the heart through the SNS originates via thoracic spinal ganglia (Hastings & Utendale, in press). Vagal influence on cardiac function appears to be greater than that of the SNS; heart rate variability and average heart rate are more affected by PNS regulation (Brownley, Hurwitz, Shneiderman, 2000; Katona, McLean, Dighton, & Guz, 1982; Weinberg & Pfeifer, 1984).

The ANS stress response has been described as occurring in two different patterns (Brownley et al., 2000), behavioural strategies associated with activation (or defense) and inhibition (or vigilance). These can be alternatively dominant over the course of a stressful event. The activational system represents physiological systems that increase vasodilation in skeletal muscle, cardiac output, and systolic blood pressure. The inhibitional system acts to increase skeletal muscle vasoconstriction, and diastolic blood pressure. For a procedure such as having one's blood drawn, a relatively aversive event, the first part of the stress response may be conceptualized as a period of anticipatory anxiety. The expectation of pain and injury involves increased SNS arousal and a decrease in PNS efference, with a corresponding increase in heart rate and decrease in vagal tone. This is followed by the period of the actual blood draw, which can potentially produce fear-related bradycardia: an increase in vagal tone, and a decrease in systolic blood pressure. In some cases, presyncope state can be severe enough to result in a fainting spell, although such extreme responses are uncommon. During recovery from the procedure, after the blood draw is completed, a return toward baseline would be expected for all indices.

Understanding and predicting the elements of cardiac changes during stress is complicated by the fact that perspective is important. Either heart rate acceleration or deceleration may occur during various stages of a stressful event, and the moderating element that seems to determine which occurs is the perceived or phenomenological nature of the stressor (Brownley, Hurwitz, & Schneiderman, 2000; Öhman, Hamm, & Hugdahl, 2000). Heart rate deceleration is characteristic of anticipatory attentional processes, but heart rate acceleration tends to occur during acute periods of focused attention on anticipated stimuli (Porges & Smith, 1980). This attentional component relating cardiovascular reactivity and parasympathetic arousal is a key concept in Porges' polyvagal theory, and energy allocation during homeostatic regulation. In response to a purely aversive event, HR acceleration is likely to occur during presentation of the stimulus. For instance, when those suffering from phobias are presented with the object of their fear, clear and consistent patterns of HR acceleration are observed (Fredrikson, 1981). However, when an aversive event may involve a period of attention before application of the stimulus, HR deceleration may be associated with this attentional phase.

The Vagal System and Behavioural Correlates

Porges (1995) suggested that quantification of respiratory sinus arrhythmia (RSA) amplitude (vagal tone) can serve as an index of one's ability to cope with homeostatic disruption, and that this will be related to behaviours associated with reactivity, expressiveness, and self-regulation. In Porges' (1995) polyvagal model, the vagal regulatory system serves to hierarchically coordinate physiologic responses necessary for organization and support in feeding behaviours, social interactions, and soothing. Higher cardiac vagal tone has been associated with healthier newborns (Porges, 1992), greater behavioural reactivity in infants (Porges, Doussard-Roosevelt, Portales, & Suess, 1994), and greater social competence in young children (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997; Eisenberg et al., 1995).

Huffman and colleagues (1998) have demonstrated that infants with higher baseline vagal tone, as indexed through RSA, were rated as having fewer negative behaviours than infants with lower baseline vagal tone and were less disrupted by the experimental procedure, which involved the child being moved during a calm state to an infant seat. Those infants who had greater decreases in vagal tone during the laboratory assessment were rated as having longer attention spans by maternal report and were more easily soothed. Porges, Doussard-Roosevelt, Portales, and Greenspan (1996) demonstrated quite elegantly that temperamentally difficult infants were less likely to have decreased cardiac vagal tone during social and attentional tasks at 9 months. Infants with weaker vagal suppression exhibited significantly more behavioural problems at 3 years of age than did other infants who showed stronger decrease in their vagal tone during the assessment.

A decrease in vagal tone during attentional demands is referred to as the vagal brake (Huffman et al., 1998), and represents the withdrawal of vagal influence on cardiovascular activity. The vagal brake stems operationally from Porges' polyvagal theory (Porges, 1997). This theory provides a neuroanatomical and neurophysiological justification for examining cardiac vagal tone as a correlate of behavioural indices, based on an evolutionary perspective. The polyvagal system is composed of the "primitive," unmyelinated dorsal motor nucleus of the vagus and the more evolutionarily recent myelinated nucleus ambiguus. Heart rate regulation through efferent fibers of the dorsal motor nucleus of the vagus to the nucleus ambiguus is related to environmental selection for behavioural strategies related to emotional expression, communication, and movement. Porges' theory provides an explanation for how the three elements of the ANS (the nucleus ambiguus vagal system, sympathetic nervous system, and dorsal motor vagal system) relate to emotional expression, social engagement, and visceral regulation.

Vagal tone is indexed as the influence of the nucleus ambiguus on the cardiac muscle. The efferent fibers of the nucleus ambiguus terminate in the sino-atrial node of the heart and produce a heart rate pattern that has a characteristic rhythm based on the respiratory cycle, called respiratory sinus arrhythmia (RSA; Richter & Spyer, 1990). Measuring both the basal (baseline) level of vagal tone and the ability to withdraw and re-engage the vagal influence (the vagal brake) can provide an index of reactivity and regulation, and differences among individuals based on behavioural characteristics may be compared (Huffman et al., 1998). Differences do exist in how baseline vagal measures and vagal brake measures relate to various behavioural manifestations. Baseline levels of vagal tone have been associated with behavioural reactivity, whereas the vagal brake has been associated with social and attentional behaviours that require an individual be aware of environmental stimuli, and act to engage or disengage from stimuli (Porges et al., 1996).

Cardiophysiology in Children with ADHD

Control of the cardiovascular system is a complicated process. Cardiovascular reactivity involves multiple systems, and elucidating the relationship among these systems is important in examining physiological correlates of behaviour. In examining ADHD and the behavioural correlates of cardiovascular physiology, accounting for change through incorporating measurement of all systems involved in cardiovascular stress reactivity is necessary in obtaining consistent, informative data.

Since the vagal regulatory system is closely tied to attentional processing (Porges, 1995, 1997), and in essence mediates the distribution of energy resources depending on these attentional processes, attentional dysfunction may be tied to the vagal regulatory system. Differences in the symptomatology of ADHD subtypes may be mirrored in differences with respect to cardiovascular arousal. Children with ADHD demonstrate decrements in performance efficiency that increase as task complexity increases, compared to non-ADHD children (Van der Meere, Shalev, Börger, & Gross-Tsur, 1995). It would follow that children with ADHD may be exhibiting dysfunctional energy reallocation during periods of focused attention, and this may be observed as differences in the relative influence of PNS and SNS over-arousal, compared to children without ADHD, during tasks that require complex cognitive performance. The presence or absence of attentional deficits is a key distinguishing factor between the ADHD subtypes, which may suggest that differences in the degree of vagal dysregulation may distinguish between them.

There is relatively little research examining cardiovascular reactivity in children with ADHD (Shibagaki & Furuya, 1997). One early study provided initial strong support for this line of research. Children exhibiting inattentive symptoms appeared to demonstrate a significantly lower degree of heart rate deceleration during the anticipatory phase of a reaction time task than children without these symptoms (Sroufe, Sonies, West, & Wright, 1973). Interestingly, when children were given Ritalin their pattern of heart rate acceleration became more similar to that of control children, and a significant association between cardiac deceleration and reaction time emerged. This could be seen as a pharmacological test of the role of ANS regulation over attentional processes.

Some studies have found significant physiological differences between children with ADHD and those without ADHD. Jennings, van der Molen, Pelham, Brock, & Hoza (1997) measured inhibitory control cued with a stop signal and observed success, latency and effect on HR. Children with ADHD decreased their average HR from baseline during the task, whereas control children increased their average HR. Children with ADHD also showed trends toward greater cardiac deceleration during the anticipatory phase and while inhibiting the stop signal than the controls.

Lower levels of SNS activity, as indexed by skin conductance (SC), have been observed in ADHD children during extinction after removal of a reward during a contingency protocol compared to controls (Iaboni, Douglas, & Ditto, 1997). This effect occurred independent of whether children with ADHD presented with comorbid Disruptive Behaviour Disorders (DBD), indicating the atypical autonomic response was related specifically to ADHD.

Children with ADHD demonstrate disruptions in sensory processing and present with a decreased ability to adapt to changing demands and circumstances. Schaaf, Miller, Seawell, and O'Keefe (2003) compared children with sensory processing deficits to control children on a sensory challenge task. Children with sensory processing disturbances demonstrated lower vagal tone than children without such deficits. Dykman and colleagues (1992) examined whether heart rate acceleration and deceleration during tasks assessing reaction time were different for children with various ADHD problems. They examined children on two trials of a key-pressing task, one trial where reward was contingent on reaction time and one where it was not. Anticipatory stimuli consisted of a visual warning signal that occurred 5 seconds before a tone indicated the start time. Normal controls were compared to attention-only (ADD-only), ADD with hyperactivity (ADDH), and ADD with aggression (ADDHA) children. Results indicated that ADD-only and control boys had similar HR levels and reactivity patterns. ADD-only boys had greater HR deceleration to the warning signal and acceleration to the tones than the other two ADD groups. This indicates that cardiovascular indices may differentiate disruptive and non-disruptive ADHD subtypes.

Comorbidity of ADHD

It is typical for children with ADHD to present with a host of other problems (Vaessen & Van der Meere, 1990), and comorbidity may be considered an inherent element of this disorder. More research has been done in examining the ANS correlates of problems comorbid with ADHD. Disruptive Behaviour Disorders occur at a high rate (Beauchaine & Gartner, 2003), and in 50% of ADHD cases Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) is apparent (Szatmari, Boyle, & Offord, 1989; Waschbusch et al., 2002). Girls with ADHD demonstrate lower rates of comorbid DBD, showing CD and ODD at about half the rate of boys with ADHD (Greene et al., 2001). However, they demonstrate higher rates of DBD than girls without ADHD (Faraone et al., 2000), and girls with ADHD are more likely than boys to have social problems (Greene et al., 2001).

Affective disorders also manifest at a high rate in these children; Bipolar Disorder occurs at a rate of 22% (Biederman et al., 1996), and depression at a rate of about 12% (Power, Costigan, Eiraldi, & Leff, 2004) as children enter adolescence. High levels of anxiety can be expected to occur in about 25% of children with ADHD (Biederman, Newcorn, & Sprich, 1991; Strauss, Lease, Last, & Francis, 1988). Comorbidity is likely a major confound in ADHD research, if not accounted for.

Accounting for comorbidity is a necessary step in studying the physiological correlates of ADHD. Physiological measures of autonomic reactivity may be related to these comorbid problems. Aspects of physiological activity could be misattributed to one disorder if a comorbid condition was undetected, and physiological indices associated with one disorder may be moderated by the presence or absence of another (Beauchaine et al, 2000). It would be prudent then to undertake an examination of PNS and SNS regulation of cardiovascular function in ADHD children in terms of comorbidity.

Lower vagal tone has been observed in children exhibiting more externalizing problems (Calkins & Dedmon, 2000; Pine et al., 1998), suggesting PNS dysregulation might be characteristic of children with ADHD and comorbid DBD. Greater heart rate acceleration has been observed in children with ADHD and comorbid DBD in response to low levels of aggression-inducing provocation than for children with ADHD only, or DBD only (Waschbusch et al., 2002).

In the Jennings et al. (1997) study described earlier, differences were found in physiological reactivity among ADHD children with and without comorbid ODD. Inhibition latencies were longer for boys with ADHD compared to controls, and this was particularly evident for boys with ADHD and comorbid ODD.

Snoek, Van Goozen, Matthys, Buitelaar, & Van Engeland (2004) examined stress responsivity in children with externalizing behaviour disorders. They included ODD, ADHD, combined ODD-ADHD, and control groups. They found that when children were presented with tasks designed to induce frustration and aggression, there was a significant difference among the control, combined, and ADHD groups versus the ODD group with HR being lower for the latter over both baseline and reactive phases. This was, however, determined to be due to methylphenidate (Ritalin) treatment in the combined and ADHD groups.

Anxiety has been examined in the literature as a comorbid problem in children with ADHD. Non-anxious and anxious ADHD children demonstrate similar baseline levels of cardiovascular activity (Urman, Ickowicz, Fulford, & Tannock, 1995). However, cardiovascular response to methylphenidate administration in these children produces a much more exaggerated increase in diastolic blood pressure for the anxious ADHD subgroup (Urman et al., 1995). This exaggerated cardiovascular response to methylphenidate administration has been hypothesized to indicate overactive noradrenergic function in children with anxiety and ADHD compared to non-anxious children with ADHD. Paralleling these findings, Halperin and colleagues (1994) observed that aggressive boys with ADHD were more reactive to methylphenidate administration than non-aggressive ADHD boys, possibly indicating serotonergic sensitivity in this group. These differences among physiological responses linked to comorbid problems in children with ADHD point to the complexity of identifying the key physiological processes specifically linked to ADHD, and the importance of distinguishing between children with and without a variety of comorbid conditions.

Investigating PNS and SNS influences on cardiovascular reactivity in a sample of ADHD children would be relatively novel in terms of the current state of the literature.

Implications

Understanding the complexity of the relations between ADHD and cardiovascular physiology could have the potential for improving existing nosological systems for diagnosing this disorder. Increased specificity in diagnosing groups with distinct symptom clusters would be facilitated by knowing how they are distinguished by characteristic profiles of physiological dysfunction. As well, physiological differences might indicate distinct etiological factors for the ADHD subtypes, such that this research would also assist with the development of more specific and more effective treatment protocols. A redefinition of ADHD in terms of the behavioural diversity with which it appears may be on the horizon as more physiological data is gathered.

Current Study

Given the current literature on autonomic reactivity in children with ADHD, and associations of autonomic reactivity with diagnoses comorbid with ADHD, an examination of cardiovascular reactivity to an aversive event in a large sample of children with ADHD was carried out. Different ADHD subtypes may present different patterns of cardiovascular reactivity in terms of vagal regulation during periods of stress. Problems that frequently occur with ADHD, such as DBD and anxiety, have also been associated with cardiovascular indices. Children with ADHD who exhibit different comorbid problems may be distinguished from each other based on differences in PNS and SNS arousal.

The present study was designed to investigate differences between children with ADHD, in cardiovascular reactivity and with varying comorbid conditions. Children had their cardiovascular activity recorded during a blood draw in a hospital clinic, as well as during a baseline period. Anticipatory cardiac activity, cardiac activity during the blood draw, and recovery cardiac activity were then compared across individuals. The contribution of both ANS branches to cardiac reactivity was examined.

Hypotheses

Given that cardiovascular reactivity research on children with ADHD is relatively limited, this study is in part exploratory in nature. Hypotheses are general to reflect this.

1) It was hypothesized that physiological reactivity would differ across ADHD subtypes.
    a) Children in the hyperactive-impulsive group were expected to demonstrate greater reactivity over the stress-induction procedure compared to the inattentive group and the combined group. Children with the combined subtype were expected to demonstrate greater reactivity over the stress-induction procedure compared to the inattentive group.
2) It was hypothesized that physiological reactivity would differ for children with varying problems comorbid with ADHD.
    a) It was hypothesized that children with comorbid anxiety disorders would demonstrate greater reactivity in response to the stress-induction procedure.
    b) It was hypothesized that children with comorbid DBD would demonstrate lower reactivity in response to the stress-induction procedure.

Method

Participants

Participants were recruited through referral to St. Justine's Hospital by community family physicians and psychiatrists. Families with a child suspected of having ADHD were invited to contact the ADHD program at St. Justine's. Families attending the ADHD clinic received information about the study, and were asked if they would participate. Families wanting to participate were provided with more information, informed consent packets, and were asked to sign consent forms for both themselves and their children.

The sample consisted of 114 boys and 28 girls with confirmed diagnoses of ADHD. Mean age for this sample was 8.32 years (*SD* = 1.60) with a range from 5 to 11. All participants were Francophone. Parents were administered the NIMH Diagnostic Interview Schedule for Children, Version IV (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to confirm ADHD diagnosis according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994). The sample consisted of 37% inattention only subtype, 14% hyperactive-impulsive subtype, and 49% combined subtype. Within each subtype, 37 boys and 15 girls were of the inattentive subtype, 18 boys and 2 girls were of the hyperactive-impulsive subtype, and 59 boys and 11 girls were of the combined subtype. There was also substantial comorbidity with other diagnoses.

Specifically, ODD occurred at a rate of 49%, CD at a rate of 24%, and presence of either DBD at a rate of 56%. Presence of any anxiety disorder occurred at a rate of 39%; Social Phobia was present in 9% of the sample, Separation Anxiety Disorder occurred at 11%, Specific Phobia at 27%, Agoraphobia at 2%, and Generalized Anxiety Disorder at 2%.

Measures

NIMH Diagnostic Interview Schedule for Children Version IV (DISC-IV).

The DISC-IV (Shaffer et al., 2000) is a structured, clinical interview used with parents to assess the presence of DSM-IV diagnoses in children and adolescents (ages 6 to 17). It evaluates the presence of over 30 diagnoses across three time frames, past 4 weeks, past year, and whole life. It is a respondent-based instrument designed to be given by lay interviewers to obtain epidemiological data. Screening questions and decision trees are used to facilitate the interview process. Initial broad questions are asked about the presence of core diagnostic symptoms, and endorsement is followed by a series of items that rate symptom severity. Computer algorithms provide diagnoses. A French version of the DISC-IV was generated by translation and back-translation for the purposes of this study.

Conners' Parent Rating Scales – Revised (CPRS-R).

The CPRS-R (*Conners, 1997*) is a norm-based behaviour rating scale used for assessment in children aged 3-17 in the areas of attention, conduct, cognition, family, social problems, academics, perfectionism, emotion, anger control, and anxiety (Conners, 2000). Parents answer questions on a Likert-type rating scale (0 = not true, 3 = very much true). Raw scores are converted to *T*-scores ($M = 50$, $SD = 10$). Male and female norms were standardized using a total sample of 2482 children, including separate samples from the U.S. and Canada. Subscale internal consistency ranges from .67 to .95, and internal reliability coefficients range from .73 to .94 (Conners, 2000). Subscales on the CPRS-R include Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious/Shy, Perfectionism, Social Problems, Psychosomatic, Conners' Global Index, DSM-IV Symptom Subscales, and the ADHD Index. The Oppositional and Anxious/Shy subscale were used in this study. The Conners' Oppositional subscale consists of 10 items regarding rule-breaking, problems with authority, irritability and anger. The Anxious/Shy subscale questions parents regarding children's worries, fears, sensitivity to criticism, anxiousness in unfamiliar situations, shyness, withdrawn behaviour, and degree of emotional behaviour their child demonstrates compared to children of a similar age.

Procedure

Families attended a three-hour testing session at St. Justine's hospital. Upon arrival, children were given some time to get used to their surroundings and spent an hour participating in various testing procedures as part of the larger study. After an hour, children were given a break from testing procedures. At this time, a cardiac monitor was attached to record inter-beat intervals (IBI). IBI was measured using the MiniLogger Series 2000 (Mini-Mitter Company, Inc., 1999) a non-invasive, ambulatory cardiac monitor suitable for use with children. The MiniLogger Series 2000 was worn by children for two hours during the visit. After the monitor was attached, the child was asked to sit quietly during a break from procedures. A 5-minute baseline period of cardiac activity was recorded during this break. Testing procedures resumed after the break. An hour after the baseline cardiovascular activity was recorded, the child was taken to a nurse's office to have blood drawn. The blood draw was done to provide samples for ongoing genetic research; however, for the purposes of this study, the blood draw provided an opportunity to record cardiovascular activity during stress-induction. Children received an anesthetic gel on the skin over the area from which the blood was to be drawn, effectively eliminating most of the pain associated with the procedure.

The period from one minute prior to the venipuncture up to the needle insertion was identified as the "anticipatory" period. The minute following the venipuncture was identified as the "blood draw" period, or the period during which blood was being taken. The minute from the end of the blood draw up to two minutes after the blood draw was identified as the "recovery" period.

While children were being assessed on cognitive and behavioural measures, their parent was interviewed in a separate room. Parents completed the CPRS-R. Parents were also interviewed using the DISC-IV to confirm ADHD diagnosis and to determine the presence of comorbid diagnoses.

After the session was completed and the family departed, the cardiac data was uploaded from the MiniLogger Series 2000 onto a computer for editing and analysis. Cardiovascular activity was examined via three methods: HR, PNS activity as indexed by Vagal tone (V), and SNS activity as indexed by HR residuals. Prior to computing values, the raw IBI values were inspected to correct recording errors.

The author and an undergraduate student were trained to edit the IBI data to preserve variance according to Byrne's (1993) Mxedit training manual. Training files were used to compare degree of agreement between the students and a supervisor certified in editing IBI intervals. Completion of the students' training was considered achieved when supervisor-student inter-rater reliability exceeded .95.

V was computed from IBI using Porges' (1985) algorithm in the Mxedit software package (Porges, 1988). Vagal tone, in $\ln(\mathrm{msec})^2$, is a quantification of RSA, "the degree of ebbing and flowing of heart rate during the respiratory cycle" (Beauchaine, 2001, p. 185), which reflects variability in cardiac function that is specifically attributable to the influence of the parasympathetic nervous system via the 10th cranial nerve (vagus nerve).

For the sympathetic component, a gross estimate of SNS activity was assessed by statistically removing the HR variability attributable to vagal tone. Sympathetic activity was indexed by regressing standardized V scores onto standardized HR (Beauchaine et al., 2000). This represents statistical removal of the PNS-based component of HR variability; residual scores calculated in this way represent SNS (and non-neural) influences on HR (Grossman & Svebak, 1987).

Results

Descriptive Statistics

Descriptive statistics for cardiovascular indices are provided in Table 1. Visual inspection of the data shows that, as expected, children's average mean heart rate was lower during baseline than during the three stages of the stress-induction (anticipatory, blood draw, and recovery). V was lower during the anticipatory and recovery periods than during baseline or the blood draw. Because the SNS Index was standardized, it was not possible to infer patterns of differences across the four measures.

Preliminary Analyses

The inter-relations of sex, age, ADHD subtype and comorbid diagnoses were examined in a series of chi-square analyses, *t*-tests, and analyses of variance (ANOVA). Whether boys and girls with ADHD differed in their likelihood of having a comorbid anxiety disorder or DBD was examined in two 2 X 2 (Sex by Comorbid Diagnosis) chi-square analyses. No differences existed among boys and girls in terms of the probability of having either an anxiety disorder $\chi^2(1, N = 142) = .13$, or DBD $\chi^2(1, N = 142) = .57$, as assessed by parent report on the DISC. A 2 X 3 χ^2 was used to examine if boys and girls differed with respect to ADHD subtype. Girls were over-represented in the inattentive subtype, adjusted residual = 2.1, and this analysis approached significance χ^2 (2, $N =$ 142), $p < .10$.

Whether children with varying ADHD subtypes differed in comorbid disorders was then examined in two 3 X 2 χ^2 analyses. A trend was observed toward fewer than expected children of the hyperactive-impulsive subtype having an anxiety disorder, adjusted residual = -1.9, but more children of the combined subtype having one, adjusted

Table 1

Means and Standard Deviations for Cardiovascular Indices

	N	Minimum	Maximum	*M*	*SD*
BHR	135	61.27	120.49	87.72	10.28
AHR	139	64.16	137.10	94.11	14.42
BDHR	142	61.45	141.66	90.07	14.65
RHR	141	63.81	130.24	91.76	13.25
BV	134	3.56	8.11	6.26	0.87
AV	139	1.55	8.68	6.14	1.12
BDV	141	2.77	8.85	6.22	1.14
RV	141	1.86	8.73	6.00	1.14
BSNS	134	-3.07	2.65	-0.05	1.00
ASNS	139	-1.89	4.06	-0.01	1.02
BDSNS	141	-2.03	4.38	-0.01	1.01
RSNS	141	-2.10	3.02	-0.04	0.96

Note. BHR = Baseline Heart Rate, AHR = Anticipatory Heart Rate, BDHR = Blood Draw Heart Rate, RHR = Recovery Heart Rate, BV = Baseline Vagal Tone, AV = Anticipatory Vagal Tone, BDV = Blood Draw Vagal Tone, RV = Recovery Vagal Tone, BSNS = Baseline SNS Standardized Residual, ASNS = Anticipatory SNS Standardized Residual, BDSNS = Blood Draw SNS Standardized Residual, RSNS = Recovery SNS Standardized Residual.

residual = 2.0, $\chi^2(2, N = 142) = 5.42, p < .10$. DBD tended to occur more frequently in these two groups, and were very uncommon in children of the inattentive subtype, adjusted residual = -2.9, $\chi^2(2, N = 142) = 9.42, p < .01$.

A one-way ANOVA was conducted to assess whether different ADHD subtypes differed in age. A trend was observed, $F(2, 139) = 2.38, p < .10$, with children of the hyperactive-impulsive subtype being younger ($M = 7.85, SD = 1.5$) than the inattentive ($M = 8.67, SD = 1.6$) and combined ($M = 8.32, SD = 1.6$) subtypes. Two *t*-tests were used to see if children with and without anxiety disorders and DBD differed in age. Neither test was significant, $t < .52$ for both.

Age and sex were examined in relation to the 12 cardiovascular measures, to determine if these demographic characteristics needed to be controlled in subsequent analyses. Age was significantly correlated with almost all cardiovascular measures, absolute mean $r = .29$, 10 out of 12 were significant. Sex, however, did not appear to be related with cardiovascular indices, all $t < 1.75$. Therefore, only age was controlled in subsequent analyses.

Cardiovascular Reactivity across ADHD Subtypes

Separate analyses were used to examine the three indices of cardiovascular reactivity, HR, V and SNS-index, across the ADHD subtypes. Three two-way 3 X 4 (ADHD subtype by Measurement across stress-induction) mixed-design ANCOVAs, controlling for age, were computed.

Heart rate. In the analysis of HR reactivity, the effect for Measurement approached significance, $F(3, 384) = 2.57, p = .06$. The effects for ADHD Subtypes and Subtype by Measurement were not significant, indicating that the children with different ADHD symptom profiles showed similar HR reactions to the blood draw procedure.

Paired *t*-tests with alpha set at .01 were used to compare HR across the four measurements (see Table 2). HR was higher during the anticipatory and recovery phases than during baseline, and anticipatory HR was also higher than HR during the blood draw.

Vagal tone. In the analysis of V reactivity, there was a significant effect for Measurement, $F(3, 378) = 3.02, p < .05$. Paired *t*-tests with alpha set at .01 were used to compare V across the four measurements (see Table 3). V was significantly lower during the recovery period than during baseline and during the blood draw. However, this was moderated by a significant interaction between Measurement and ADHD subtype $F(6, 378) = 2.21, p < .05$ (see Figure 1).

To examine how children of different ADHD subtypes showed PNS reactivity to the procedure, separate one-way repeated measures ANCOVAs, controlling for age, were computed for each subtype. The effect of Measurement was not significant for hyperactive-impulsive, $F(3, 45) = 1.61$, but approached significance for inattentive, $F(3, 138) = 2.47, p < .10$, and combined, $F(3, 189) = 2.36, p < .10$. Although the overall *F*-value was not significant for the hyperactive-impulsive subtype, subsequent paired *t*-tests revealed that they had lower V during the anticipatory period than during the blood draw, $t(19) = -3.46, p < .01$. The inattentive subtype group tended to have higher V during the blood draw, compared to the recovery period. The combined subtype group had lower V during the recovery period than during the preceding three periods. As well, to examine whether the three ADHD subtype groups differed significantly in V at any of the four measurement periods, four one-way ANCOVAs were computed. Only one approached

Table 2

Paired t-tests for Heart Rate

		Mean Difference	*t*	*df*	Significance (2-tailed)
Pair 1	Baseline - Anticipatory	-6.35	-5.75	132.00	0.00
Pair 2	Baseline – Blood Draw	-2.26	-2.34	134.00	0.02
Pair 3	Baseline - Recovery	-4.11	-4.91	133.00	0.00
Pair 4	Anticipatory – Blood Draw	3.90	4.60	138.00	0.00
Pair 5	Anticipatory - Recovery	2.36	2.41	137.00	0.02
Pair 6	Blood Draw - Recovery	-1.66	-2.28	140.00	0.02

Table 3

Paired t-tests for Vagal Tone

		Mean Difference	*t*	*df*	Significance (2-tailed)
Pair 1	Baseline - Anticipatory	0.13	1.36	131.00	0.18
Pair 2	Baseline – Blood Draw	0.04	0.54	132.00	0.59
Pair 3	Baseline - Recovery	0.26	3.31	132.00	0.00
Pair 4	Anticipatory – Blood Draw	-0.08	-1.03	137.00	0.30
Pair 5	Anticipatory - Recovery	0.13	1.49	137.00	0.14
Pair 6	Blood Draw - Recovery	0.22	3.28	139.00	0.00

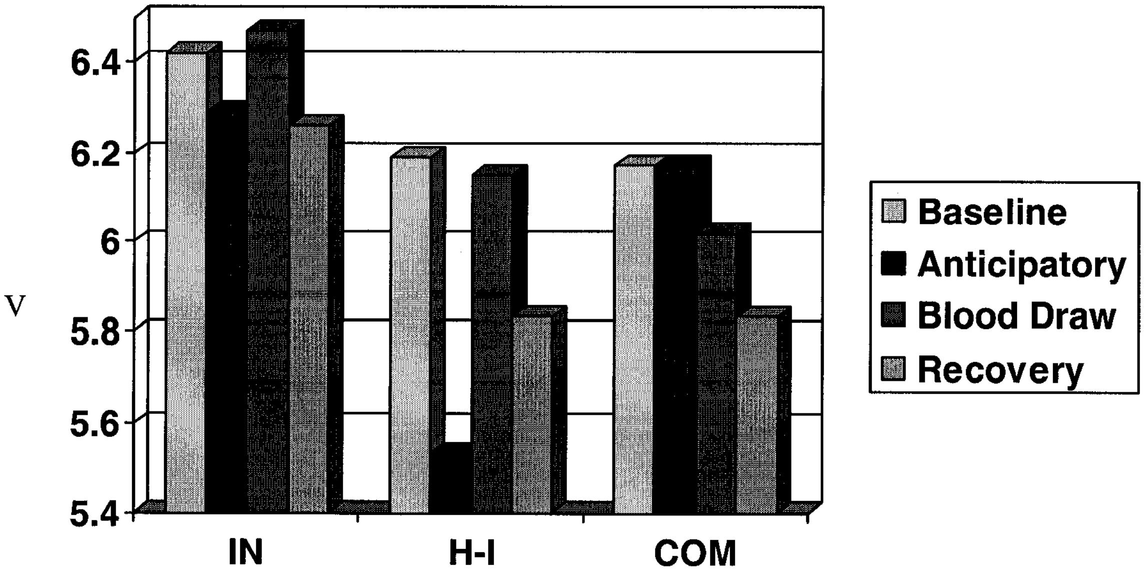

Figure 1. Interaction between Measurement and ADHD Subtype for V.

Note. V = Vagal Tone, IN = Inattentive Subtype, H-I = Hyperactive-Impulsive Subtype, COM = Combined Subtype.

significance, for anticipatory V, $F(2, 136) = 2.46$, $p < .10$. The hyperactive-impulsive subtype tended to have lower V than the other two subtypes during the anticipatory period.

SNS Index. In the analysis of SNS reactivity, there was a significant effect for Measurement, $F(3, 378) = 3.21$, $p < .05$. Paired *t*-tests with alpha set at .01 were used to compare SNS activity across the four measurements (see Table 4). None of these were significant. However, a significant interaction between SNS activity and ADHD subtype $F(6, 378) = 2.59$, $p < .05$ was present (see Figure 2). To examine how children of different ADHD subtypes showed SNS reactivity to the procedure, separate one-way ANCOVAs, controlling for age, were computed for each subtype. The effect of Measurement was not significant for inattentive, $F(3, 138) = .39$, or hyperactive-impulsive subtypes, $F(3, 45) = .78$, but was significant for combined, $F(3, 189) = 3.10$, $p < .05$. The combined subtype demonstrated a linear decrease in the SNS Index across the procedure. They had lower SNS arousal during the anticipatory period compared to baseline, and during the blood draw the SNS Index moved even lower. During the recovery period, the SNS Index decreased further still. To examine whether the three ADHD subtype groups differed significantly in SNS activity at any of the four measurement periods, four one-way ANCOVAs were computed. The hyperactive-impulsive subtype tended to have a higher SNS Index, $F(2, 138) = 2.83$, $p < .10$, than the other two subtypes during the blood draw period, and had a significantly higher SNS Index, $F(2, 138) = 4.52$, $p < .05$, during the recovery period.

Table 4

Paired t-tests for SNS Index

		Mean Difference	*t*	*df*	Significance (2-tailed)
Pair 1	Baseline - Anticipatory	-0.03	-0.25	131	0.80
Pair 2	Baseline – Blood Draw	-0.05	-0.42	132	0.68
Pair 3	Baseline - Recovery	-0.05	-0.43	132	0.67
Pair 4	Anticipatory – Blood Draw	0.00	0.02	130	0.99
Pair 5	Anticipatory - Recovery	0.00	0.00	130	1.00
Pair 6	Blood Draw - Recovery	-0.01	-0.12	131	0.91

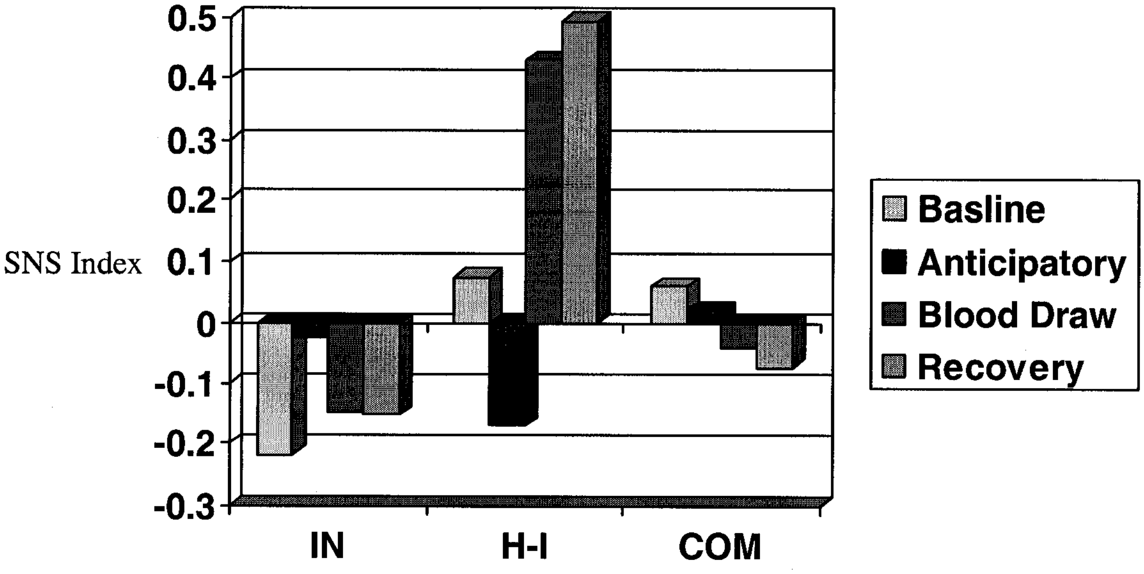

Figure 2. Interaction between Measurement and ADHD Subtype for SNS Index

Note. IN = Inattentive Subtype, H-I = Hyperactive-Impulsive Subtype, COM = Combined Subtype.

Hierarchical Regression Analyses

Overview.

In order to explore the relations between disorders comorbid with ADHD and cardiovascular reactivity, a series of hierarchical regression analyses were performed. The goal of these analyses was to assess the extent to which comorbid DBD and anxiety problems predicted cardiovascular reactivity indices. Separate regressions were used to predict reactivity from continuous problem scores of the CPRS-R, and from the discrete diagnoses of the DISC-IV. Separate regressions were also run for predicting HR, V, and SNS reactivity in each of the three components of the blood draw. Therefore, 18 regression analyses were computed. Sex and age were controlled as covariates by entering them into step one of each model. Baseline cardiovascular activity was controlled by entering it into step two of each model. Residualized change scores for cardiac indices were used as the dependent variables.

Change scores. Floor effects, ceiling effects, regression towards the mean, and intra-individual variability can confound interpretations of apparent physiological responses. Two commonly used techniques for minimizing these statistical issues are computing arithmetic change scores: subtracting the baseline measure from the measure(s) of reaction, and residualized change scores: regressing the measure(s) of reaction onto baseline measure. In both techniques, the baseline measure is controlled in the analysis of predictors of physiological change. Residualized change scores and arithmetic change scores while controlling for baseline produce the same results (Kamarck, personal communication, 2005). There were no substantive differences in findings produced by analyses using residualized change scores, arithmetic change scores, or raw scores. Therefore, regression analyses using residualized change scores are presented.

Oppositional and Anxious-Shy Symptoms Predicting Cardiovascular Reactivity

Regression analyses for parental ratings of oppositional and anxiety symptom severity on the CPRS-R predicting cardiovascular reactivity are presented in Tables 5, 6, and 7. Three regressions are presented for each cardiovascular index, HR, V, and SNS Index, for prediction of residualized change scores in the anticipatory period, the blood draw period, and the recovery period.

Heart rate. The standardized beta for Age was negative for the prediction of blood draw change, such that older children had less HR change (smaller increases or even decreases) from baseline to the blood draw, $t = -2.14$, $p < .05$. However, no trends or significant results were obtained in predicting HR change scores from parental reports of oppositional and anxious-shy symptom severity on the CPRS-R.

Vagal tone. No trends or significant results were obtained in predicting V change scores from parental reports of oppositional and anxious-shy symptom severity on the CPRS-R.

SNS Index. No trends or significant results were obtained in predicting SNS Index change scores from parental reports of Oppositional or Anxious-Shy symptom severity on the CPRS-R.

Diagnosis of DBD and Anxiety Disorders Predicting Cardiovascular Indices

Regression analyses predicting cardiovascular indices from DISC-IV diagnosis of DBD and anxiety disorders are presented in Tables 8, 9, and 10. Three regressions are presented for each cardiovascular index, HR, V, and SNS, as was done previously. Older children had less HR change (smaller increases or even decreases) from baseline to the blood draw, $t = -2.14$, $p < .05$. Step one was significant for the change in SNS Index from baseline to the blood draw, $\Delta R^2 = .07$, $p < .01$, accounting for 7% of the variability in SNS Index change. For the recovery phase, the standardized beta for DBD was positive and approached significance, $t = 1.72$, $p < .10$, indicating that children with DBD had more SNS Index change (greater increases) from baseline. No significant effects were found in predicting any cardiovascular index from DISC-IV diagnosis of DBD or anxiety disorders.

Table 5

Summary of Hierarchical Regression Analysis for CPRS-R Oppositional Symptoms and Anxious-Shy Symptoms as Predictors of Children's Heart Rate Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	*df*	ΔF	Predictor	β	*t*
ACS	1	.02	2, 127	1.59	Age	.01	.07
					Sex	.16	1.76†
	2	.00	1, 126	.10	BMHR	.03	.32
	3	.01	2, 124	.38	CPO	0.03	0.36
					CPAS	-0.08	-0.86
BCS	1	.03	2, 129	2.30	Age	-0.18	-2.14*
					Sex	0.02	.24
	2	.01	1, 128	1.12	BMHR	-0.10	-1.10
	3	.01	2, 126	0.72	CPO	0.09	0.98
					CPAS	0.04	0.46
RCS	1	.02	2, 128	1.05	Age	-.13	-1.43
					Sex	.04	0.43
	2	.00	1, 127	.24	BMHR	-.05	-.49
	3	.01	2, 125	0.81	CPO	.12	1.26
					CPAS	-.04	-0.42

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BMHR = Baseline Mean Heart Rate, CPO = CPRS-R Parent: Oppositional Symptom Severity, CPAS = CPRS-R Parent: Anxious-Shy Symptom Severity. $^{\dagger}p < .10$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table 6

Summary of Hierarchical Regression Analysis for CPRS-R Severity of Oppositional Symptoms and Anxious-Shy Symptoms as Predictors of Children's Vagal Tone Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	*df*	ΔF	Predictor	β	*t*
ACS	1	.03	2, 126	1.68	Age	-.06	-.71
					Sex	-.14	-1.60
	2	.00	1, 125	.08	BMV	.03	.28
	3	.01	2, 123	.39	CPO	-.02	-.21
					CPAS	.08	.89
BCS	1	.00	2, 127	.16	Age	.03	.23
					Sex	-.05	-.52
	2	.00	1, 126	.00	BMV	.00	.03
	3	.02	2, 124	1.15	CPO	-.14	-1.49
					CPAS	.06	.61
RCS	1	.04	2, 127	$2.45^{\dagger}$	Age	.16	$1.79^{\dagger}$
					Sex	-.13	-1.50
	2	.00	1, 126	.04	BMV	-.02	-.19
	3	.02	2, 124	1.17	CPO	-.09	-1.04
					CPAS	.12	1.33

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BMV = Baseline Mean Vagal Tone (20 second epochs), CPO = CPRS-R Parent: Oppositional Symptom Severity, CPAS = CPRS-R Parent: Anxious-Shy Symptom Severity. $^{\dagger}p < .10$, * $p< .05$, ** $p < .01$, *** $p < .001$.

Table 7

Summary of Hierarchical Regression Analysis for CPRS-R Severity of Oppositional Symptoms and Anxious-Shy Symptoms as Predictors of Children's SNS Index Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	*df*	ΔF	Predictor	β	*t*
ACS	1	.01	2, 126	.44	Age	-.06	-.71
					Sex	.06	.69
	2	.00	1, 125	.00	BMSNS	-.01	-.05
	3	.00	2, 123	.05	CPO	.03	.32
					CPAS	-.02	-.16
BCS	1	.08	2, 127	5.30	Age	-.27	-3.19
					Sex	-.02	-.23
	2	.01	1, 126	1.71	BMSNS	-.12	-1.31
	3	.01	2, 124	.83	CPO	-.02	-.22
					CPAS	.11	1.28
RCS	1	.03	2, 127	1.80	Age	-.06	-.70
					Sex	-.15	-1.68†
	2	.00	1, 126	.00	BMSNS	-.00	-.01
	3	.02	2, 124	1.24	CPO	.08	.92
					CPAS	.10	1.05

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BMSNS = Baseline Mean SNS Index, CPO = CPRS-R Parent: Oppositional Symptom Severity, CPAS = CPRS-R Parent: Anxious-Shy Symptom Severity. $^{\dagger}p < .10$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table 8

Summary of Hierarchical Regression Analysis for DISC-IV Diagnosis of Disruptive Behaviour Disorders and Anxiety Disorders as Predictors of Children's Heart Rate Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	*df*	ΔF	Predictor	β	*t*
ACS	1	.02	2, 130	1.53	Age	.02	.17
					Sex	.15	1.71†
	2	.00	1, 129	.07	BMHR	.03	.26
	3	.01	2, 127	.60	DA	-.08	-.90
					DDBD	.05	.56
BCS	1	.03	2, 132	2.28	Age	-.18	-2.14*
					Sex	.02	.19
	2	.01	1, 131	1.00	BMHR	-.10	-1.00
	3	.01	2, 129	.53	DA	.00	-.05
					DDBD	.09	1.03
RCS	1	.01	2, 131	.76	Age	-.11	-1.21
					Sex	.03	.37
	2	.00	1, 130	.29	BMHR	-.05	-.54
	3	.02	2, 128	1.58	DA	-.09	-.99
					DDBD	.13	1.49

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BMHR = Baseline Mean Heart Rate, DDBD = DISC-IV Diagnosis of Disruptive Behaviour Disorders, DA = DISC-IV Diagnosis of Anxiety Disorders. $^{\dagger}p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 9

Summary of Hierarchical Regression Analysis for DISC-IV Diagnosis of Disruptive Behaviour Disorders and Anxiety Disorders as Predictors of Children's Vagal Tone Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	df	ΔF	Predictor	β	t
ACS	1	.03	2, 129	1.69	Age	-.06	-.63
					Sex	-.14	.-1.64
	2	.00	1, 128	.05	BMV	-.02	.23
	3	.01	2, 126	.51	DA	.09	.-1.01
					DDBD	.00	-.00
BCS	1	.00	2, 130	.20	Age	.03	.31
					Sex	-.05	-.56
	2	.00	1, 129	.00	BMV	.00	-.04
	3	.01	3, 126	.34	DA	.04	.42
					DDBD	-.06	-.71
RCS	1	.04	2, 127	$2.70^{\dagger}$	Age	.16	$1.90^{\dagger}$
					Sex	-.14	-1.60
	2	.00	1, 129	.10	BMV	-.03	-.31
	3	.01	2, 126	.58	DA	.08	.92
					DDBD	-.05	-.58

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BMV = Baseline Mean Vagal Tone (20 second epochs), DDBD = DISC-IV Diagnosis of Disruptive Behaviour Disorders, DA = DISC-IV Diagnosis of Anxiety Disorders. $^{\dagger}p < .10$, * $p < .05$, **$p < .01$, ***$p < .001$.

Table 10

Summary of Hierarchical Regression Analysis for DISC-IV Diagnosis of Disruptive Behaviour Disorders and Anxiety Disorders as Predictors of Children's SNS Index Change Scores during the Stress-Induction

Change Period	Step	ΔR^2	*df*	ΔF	Predictor	β	*t*
ACS	1	.00	2, 129	.24	Age	-.04	-.48
					Sex	.05	.55
	2	.00	1, 128	.03	BMV	-.02	-.16
	3	.01	2, 126	.30	DA	.00	-.03
					DDBD	.07	.78
BCS	1	.07	2, 130	5.10*	Age	-.23	-3.12**
					Sex	-.03	-.36
	2	.01	1, 129	1.95	BMV	-.13	-1.40
	3	.01	2, 127	.34	DA	.02	.27
					DDBD	.07	.77
RCS	1	.03	2, 130	1.86	Age	-.03	-.30
					Sex	-.16	-1.86†
	2	.00	1, 129	.08	BMV	-.03	-.28
	3	.02	2, 127	1.57	DA	-.04	-.45
					DDBD	.15	1.72†

Note. ACS = Anticipatory Change Score, BCS = Blood Draw Change Score, RCS = Recovery Change Score, BSNS = Baseline Mean SNS Index, DDBD = DISC-IV Diagnosis of Disruptive Behaviour Disorders, DA = DISC-IV Diagnosis of Anxiety Disorders. $^{\dagger}p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

Discussion

The goal of this study was to examine cardiovascular reactivity in children with ADHD. Two general issues were examined, whether cardiovascular activity was different across ADHD subtypes during a stress induction task, and whether the presence of comorbid DBD and anxiety disorders predicted cardiovascular reactivity. A blood draw procedure was used to induce stress in the children. As expected, HR demonstrated a normal pattern of stress reactivity; HR was significantly higher during the anticipatory phase compared to baseline measures. Recovery HR was higher than HR during the blood draw and lower than during the anticipatory phase. Evidence for ADHD subtype differences in reactivity was found, although comorbid problems did not predict reactivity. The most striking finding was that those children classified as being of the hyperactive-impulsive subtype demonstrated a large increase in SNS arousal during the blood draw and in the following recovery period, whereas the inattentive subtype and combined ADHD subtype had relatively low SNS arousal during these periods. Children of the hyperactive-impulsive subtype also had lower PNS influence during the anticipatory period preceding the blood draw, compared to children with the other ADHD subtypes. However, children demonstrated essentially the same pattern of HR change across the stress-induction, independent of subtype. Thus, it was important to examine the *pattern* of contributions made by both PNS and SNS activity to HR. These findings suggest that distinguishing the subtypes according to their patterns of cardiovascular reactivity may be feasible, which has implications for both diagnosis and treatment.

Cardiovascular Reactivity across ADHD Subtypes

The pattern of HR reactivity was similar for all subtypes, but for both V and SNS Index, distinct and characteristic patterns of reactivity for each subtype were evident.

This suggests that regulatory neural processes underlying the stress response in these subtypes was not identical. Children of the inattentive subtype had the most prototypical autonomic response. They demonstrated coupling between the PNS and SNS, which conformed to the usually expected pattern of reciprocating dominance. During the anticipatory phase these children demonstrated vagal suppression and sympathetic activation. Over the blood draw phase they demonstrated vagal activation and sympathetic suppression. During the recovery phase this group experienced vagal suppression, with continued low SNS activity. Given this fairly normative pattern of ANS co-regulation, the inattentive subgroup might be expected to cope more effectively with stress, that is, more similarly to children without ADHD, compared to the other two subtypes.

It was somewhat surprising that children of the inattentive subtype consistently had the highest vagal tone across the phases of the procedure. According to Porges' polyvagal theory (1995, 1997) attention problems could be expected to accompany lower V and less effective vagal regulation. However, past studies have utilized cognitive stressors rather than physical stressors. The blood draw procedure may not have activated these children's dysregulated attentional processes.

The hyperactive-impulsive group had a large decrease in vagal efference during the anticipatory phase. This difference represented a significant change from baseline within the group. Surprisingly, they also manifested lower levels of SNS activity at this point. During the blood draw vagal tone returned to baseline levels, while SNS activity went up substantially more. During the recovery period V again decreased slightly, while SNS activity increased even more. The hyperactive-impulsive children appeared to be demonstrating a very reactive profile, with exaggerated vagal withdrawal during anticipation of the venipuncture, and an exaggerated, counterintuitive SNS profile, with an unexpected increase in SNS activity during the recovery phase. With coinhibition during the anticipatory phase, coactivation during the blood draw, and reciprocal SNS activation during the recovery phase (Öhman et al., 2000), these children may have been demonstrating a general dysfunction in PNS/SNS coupling. Thus, one might expect their stress reactivity to be less adaptive or predictable than the other two subtypes. Hyperactive-impulsive children tend to be temperamentally difficult, and low V in difficult infants has been shown to predict poor behavioural outcome (Porges et al., 1994).

The combined subtype also demonstrated a somewhat unexpected response. They demonstrated a linear decrease in both PNS and SNS enervation during the stress-induction procedure. Very little V withdrawal occurred from baseline to the anticipatory phase, with a moderate decrease during the blood draw, and a further decrease during the recovery phase. Relatively small decreases occurred in SNS activity consistently across the procedure. This unexpected profile of continuing coinhibition was very atypical of most models of stress reactivity.

Combining the PNS and SNS Index may provide a clinical tool to identify group membership and inform treatment decisions. Ideally, increased awareness of subtype differences in cardiovascular reactivity could provide diagnostic information and selection of appropriate treatments. The groups did not differ in HR, and they did not differ at baseline on any of the cardiovascular indices. This implies that it is through the dynamic regulatory functions of the two branches of the ANS during stress that one is able to detect meaningful distinctions between subtypes. Their phenotypic similarity (same HR profile) belies their underlying neural distinctions. This may have implications for categorizing ADHD as one disorder with three faces, versus two disorders, that are often comorbid. Neuropsychological evidence for the presence of two separate, comorbid conditions within ADHD has been described by Chhabildas and colleagues (2001). They found that inattentive symptoms best predicted measures of cognitive performance when comparing combined, inattentive, and hyperactive-impulsive subtypes. Inattentive and combined subtypes had similar patterns of impairment on tasks measuring speed, vigilance and inhibition, and the hyperactive-impulsive children had no significant impairment when the effects of inattentiveness were accounted for. It would appear that inattention is the primary mediator in cognitive impairment for ADHD children rather than hyperactivity-impulsivity. Conversely, the current data suggest hyperactivity-impulsivity is the more central element of dysregulated reactions to physical challenges in children with ADHD. The combined subtype may actually be two comorbid disorders, one characteristic of inattention and one characteristic of hyperactivity-impulsivity, with a symptom profile and reactivity tendencies that blend these disorders.

The observed differences in V and SNS arousal may be explained by examining the trend in comorbidity for the hyperactive-impulsive and inattentive subtypes. Those children who fell within the inattentive group were significantly less likely to have a diagnosis of DBD, compared to children diagnosed as having the hyperactive-impulsive subtype who were more likely to have DBD. This may have influenced how hyperactive-impulsive children perceived the implications of being subjected to the blood draw. Cardiovascular reactivity can vary depending on how stressful stimuli are viewed (Brownley et al., 2000; Öhman et al., 2000). In this case, if hyperactive-impulsive children viewed the blood draw as a forced event, and given that they were particularly oppositional, they may have been more likely to respond with anger and hostility. This may imply that increased SNS activity during the blood draw and recovery periods was associated with the extreme oppositional behaviours in the hyperactive group.

In response to stressful demands, children with persisting high SNS arousal probably would be harder to calm, and may remain more reactive for a longer period. An association of increased SNS activity during the recovery period with more extreme disruptive and emotional behaviours would make children very hard to manage. If they were to manifest this pattern of reactivity at home or school, hyperactive-impulsive children could elicit strongly negative responses from parents or teachers. Conversely, the reaction profiles of the inattentive subtype were more "typical" and akin to expected normative ANS arousal. Indeed, children of the inattentive subtype are more manageable and less disruptive, and usually elicit fewer negative responses from others (Waschbusch et al., 2002). Thus, ADHD subtype differences in physiological patterns of stress reactivity may contribute to their social behaviour. These results highlight the importance of understanding how physiology and ADHD are associated, especially in terms of the complexity of ADHD symptom presentation and comorbidity.

The Role of Comorbidity in Cardiovascular Reactivity

This study found no strong associations between diagnostic status or symptom severity and cardiovascular indices. Given that cardiovascular reactivity has been shown in the literature to be associated with problems comorbid with ADHD (Beauchaine & Gartner, 2003; Biederman et al., 1996; Biederman et al., 1991; Strauss, Lease, Last, & Francis, 1988; Vaessen & Van der Meere, 1990), this is a surprising finding. One issue that may shed light on this is the degree of "stress" inducted in the stress-induction procedure. Most research examining ANS reactivity has been done by examining attentional or social processes, using cognitive challenges (Börger et al., 1999), reaction time tasks (Dykman et al, 1992), or interpersonal interactions (Snoek et al., 2004). The arousal generated by such tasks may not be comparable to the degree of arousal produced by a blood draw, especially in a sample of 5 to 11 year-old children. The event in this study may have been so strongly aversive as to produce universal arousal that overrode any subtle differences in cardiovascular reactivity typically seen when children with differing comorbid problems encounter mild stressors. Whether they had DBD, anxiety disorder, or no comorbid conditions, all children may have been frightened by the impending, imminent threat of a needle.

There was one weak association between DBD and SNS activity for the recovery phase: children with comorbid DBD had greater SNS arousal. Interestingly, children of the hyperactive-impulsive subtype had greater SNS reactivity during recovery than the other groups, and they also tended to be over-represented in the DBD group. Similarly, Waschbusch and colleagues (2002) found that boys with ADHD and comorbid DBD were more reactive (had higher HR acceleration) to low levels of provocation and responded to such provocation with more aggression than ADHD-only or DBD-only boys. It is very plausible that oppositional and hyperactive-impulsive children viewed the blood draw as confrontational, and this may have provoked an aggressive response in terms of physiological reactivity rather than only apprehension. However, given the number of regressions that were run, and the fact that this finding was a trend, it is also possible that this result occurred entirely by chance.

Research Limitations and Future Directions

Some limitations of the study should be noted. A major confound may have been differences in perception of the blood draw. Children may have differed, according to subtype, on how aversive the event was. An objective measure of how the blood draw was perceived by the children could have proved useful. Perhaps a Likert-type rating scale administered to assess degree of aversion to the procedure may have been given, and then the measure used to control for subjectivity during analyses. Even a qualitative report of children's behaviour during the procedure may have been coded and used as a control. The small sample size of the hyperactive-impulsive group also served to dramatically reduce power to detect subtype differences. Stratified recruitment to control for the relatively low occurrence of this group among children with ADHD could prove useful in future investigations. Also, as mentioned previously, the blood draw may have been too aversive a procedure, and subsequent investigation should use a less invasive/stressful inductor. Alternatively, including both a frightening physical procedure and cognitive or social procedures could reveal whether ADHD subtypes are differentially reactive to different kinds of stressors.

Summary

This study demonstrated that cardiovascular reactivity differences exist among children of different ADHD subtypes. The exact nature of the differences was only partially fleshed out, but in sum, it appears that hyperactive-impulsive children are more reactive in terms of ANS activity, especially with respect to the contribution of the SNS. This group appears to remain reactive after an aversive event, and this may be related to their manifestations of oppositional behaviour. These children may be interpreting relatively benign demands as confrontational, and reacting with a more intense physiological response (in preparation for fight/flight) than the children of the other two subtypes. It is quite conceivable that this would manifest in the child's environment as oppositional, defiant, and reactive behaviour.

Given this knowledge, standard treatment protocols may be modified to incorporate differences in physiological reactivity among the subtypes. Targeting medication to particular aspects of physiological dysfunction in ADHD would be a major step in increasing efficacy. Also, implications for cognitive-behavioural interventions are evident if these children differ in their biological reactivity to stressful events, where stressful events may be deemed, in part, parental/teacher demands. Ultimately, further research in this area may fully delineate the physiological processes underlying stress response differences in children with ADHD, and further the effectiveness of treating this very problematic disorder.

References

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text revision). Washington, DC: Author.

Applegate, B., Lahey, B. B., Hart, E. L., Biederman, J., Hynd, G. W., Barkley, R. A., Ollendick, T., Frick, P. J., Greenhill, L., McBurnett, K., Newcorn, J.H., Kerdyk, L., Garfinkel, B., Waldman, I., Shaffer, D. (1997). Validity of the age-of-onset criterion for ADHD: A report from the DSM-IV field trials. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 1211-1221.

Barkley, R. A., Anastopoulos, A. D., Guevremont, D. C., & Fletcher, K. E. (1991). Adolescents with ADHD: Patterns of behavioral adjustment, academic functioning, and treatment utilization. *Journal of the American Academy of Child and Adolescent Psychiatry, 30,* 752-761.

Barkley, R. A., Anastopoulos, A. D., Guevremont, D. C., & Fletcher, K. E. (1992). Adolescents with Attention Deficit Hyperactivity Disorder: Mother-child interactions, family beliefs, and conflicts, and maternal psychopathology. *Journal of Abnormal Psychology, 20,* 263-288.

Barkley, R. A. (1998). *Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment* (2nd ed.). New York: The Guilford Press.

Beauchaine, T. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology, 13,* 183-214.

Beauchaine, T. P., & Gartner, J. (2003). A linear growth curve analysis of inpatient treatment response by conduct-disordered, ADHD, and comorbid preadolescents. *Aggressive Behavior, 29,* 440-456.

Beauchaine, T. P., Gartner, J., & Hagen, B. (2000). Comorbid depression and heart rate variability as predictors of aggressive and hyperactive symptom responsiveness during inpatient treatment of conduct-disordered, ADHD boys. *Aggressive Behavior, 26,* 425-441.

Biederman, J., Faraone, S. V., Milberger, S., Jetton, J. G., Chen, L., Mick, E., Greene, R. W., & Russell, R. L. (1996). Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? Findings from a four-year follow-up study of children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 1193-1204.

Biederman, J., Newcorn, J., & Sprich, S. (1991). Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety and other disorders. *American Journal of Psychiatry, 148,* 564-577.

Brownley, K. A., Hurwitz, B. E., & Schneiderman, N. (2000). Cardiovascular psychophysiology. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd ed., pp. 224-264). Cambridge, UK: Cambridge University Press.

Byrne, E. A. (1993). *Inter-beat-interval editing for heart period variability analysis: An integrated training program with standards for student reliability assessment.* College Park: MD. University of Maryland.

Calkins, S. D., & Dedmon, S. E. (2000). Physiological and behavioral regulation in two-year-old children with aggressive/destructive behavior problems. *Journal of Abnormal Child Psychology, 28*, 103-118.

Chhabildas, N., Pennington, B. F., & Willcut, E. G. (2001). A comparison of the neuropsychological profiles of the DSM-IV subtypes of ADHD. *Journal of Abnormal Child Psychology, 29,* 529-540.

Conners, C. K. (1997). *Conner's Rating Scales – Revised.* North Tonawanda, NY. Multihealth Systems, Inc.

Conners, C. K. (2000). *Conners' Rating Scales: Revised technical manual, instruments for use with children and adolescents.* North Tonawanda, NY. Multi-Health Systems, Inc.

Doussard-Roosevelt, J. A., Porges, S. W., Scanlon, J. W., Alemi, B., & Scanlon, K. (1997). Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. *Child Development, 68*, 173-186.

Dykman, R. A., Ackerman, P. T., & Oglesby, D. M. (1992). Heart rate reactivity in attention deficit disorder subgroups. *Integrative Physiological and Behavioral Science, 27,* 228-245.

Eisenberg, N. (1996). Meta-emotion and socialization of emotion in the family – A topic whose time has come: Comment on Gottman et al. (1996). *Journal of Family Psychology, 10,* 269-276.

Eisenberg, N., Fabes, R. A., Murphy, B., Maszk, P., Smith, M., & Karbon, M. (1995). The role of emotionality and regulation in children's social functioning: A longitudinal study. *Child Development, 66*, 1360-1384.

Faraone, S. V., Biederman, J., Mick, E., Williamson, S., Wilens, T., Spencer, T., Weber, W., Jetton, J., Kraus, I., Pert, J., & Zallen, B. (2000). Family studies of girls with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 157,* 1077-1083.

Fredrikson, M. (1981). Orienting and defensive reactions to phobic and conditioned fear stimuli in phobics and normals. *Psychophysiology, 18,* 456-465.

Frick, P. J. (1998). *Conduct disorders and serious antisocial behavior.* New York: Plenum Press.

Gadow, K. D., Drabick , D. A. G., Loney, J., Sprafkin, J., Salisbury, H., Azizian, A., & Schwartz, J. (2004). Comparison of ADHD subtypes as source-specific syndromes. *Journal of Child Psychology and Psychiatry, 45,* 1135-1149.

Greene, R. W., Biederman, J., Faraone, S. V., Oullette, C. A., Penn, C., & Griffin, S. M. (1996). Toward a new psychometric definition of social disability in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 571-578.

Greene, R. W., Biederman, J., Faraone, S. V., Monuteaux, M. C., Mick, E., DuPre, E. P., Fine, C. S., & Goring, J. G. (2001). Social impairment in girls with ADHD: Patterns, gender comparisons, and correlates. *Journal of the American Academy of Child and Adolescent Psychiatry, 40,* 704-710.

Grossman, P., & Svebak, S. (1987). Respiratory sinus arrhythmia as an index of parasympathetic cardiac control during active coping. *Psychophysiology, 24,* 228-235.

Halperin, J. M., Vanshdeep, S., Siever, L. J., Schwartz, S. T., Matier, K., Wornell, G., & Newcorn, J. H. (1994). Serotonergic function in aggressive and nonaggressive boys with attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 151,* 243-248.

Hartman, C. A., Willcut, E. G., Rhee, S. H., & Pennington, B. F. (2004). The relation between sluggish cognitive tempo and DSM-IV ADHD. *Journal of Abnormal Child Psychology, 32,* 491-503.

Hastings, P.D., & Utendale, W. T. (In press). Biological and physiological origins of social withdrawal. In A. LoCoco, K. Rubin, & C. Zappulla (Eds.), *Social Withdrawal in Childhood.* Unicopli: Palermo, Italy.

Hinshaw, S. P. (1994). *Attention deficits and hyperactivity in children* (Vol. 29). Thousand Oaks, CA: Sage Publications.

Huffman, L. C., Bryan, Y. E., del Carmen, R., Pedersen, F. A., Doussard-Roosevelt, J. A., & Porges, S. (1998). Infant temperament and cardiac vagal tone: Assessments at twelve weeks of age. *Child Development, 69*, 624-635.

Iaboni, F., Douglas, V. I., & Ditto, B. (1997). Psychophysiological response of ADHD children to reward and extinction. *Psychophysiology, 34,* 116-123.

Jennings, J. R., van der Molen, M. W., Pelham, W., Debsi, K. B., & Hoza, B. (1997). Inhibition in boys with Attention-Deficit Hyperactivity Disorder as indexed by heart rate change. *Developmental Psychology, 33,* 308-318.

Katona, P. G., McLean, M., Dighton, D. H., & Guz, A. (1982). Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *Journal of Applied Physiology, 52,* 1652-1657.

Lahey, B. B., Schaughency, E. A., Hynd, G. W., Carlson, C. L., & Nieves, N. (1987). Attention deficit disorder with and without hyperactivity: Comparison of behavioral characteristics of clinic-referred children. *Journal of the American Academy of Child Psychiatry, 26,* 718-723.

Lovallo, W. R., & Thomas, T. L. (2000). Stress hormones in psychophysiological research: Emotional, behavioral, and cognitive implications. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd ed., pp. 224-264). Cambridge, UK: Cambridge University Press.

Mini-Mitter Company, Inc. (1999). *Mini-logger series 2000.* Sunriver, OR: Author.

Öhman, A., Hamm, A., & Hugdahl, K. (2000). Cognition and the autonomic nervous system: Orienting, anticipating, and conditioning. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd ed., pp. 224-264). Cambridge, UK: Cambridge University Press.

Pine, D. S., Wasserman, G. A., Coplan, J. D., Miller, L., Bagiella, E., Kovelenku, P., Myers, M. M., & Sloan, R. P. (1998). Heart period variability and psychopathology in urban boys at risk for delinquency. *Psychophysiology, 35,* 521-529.

Porges, S. W. (1985). *Method and apparatus for evaluating rhythmic oscillations in periodic physiological response system.* (Patent number: 4,510,944). Washington, DC: US Patent Office.

Porges, S. W. (1988). *Mxedit v2.01. Inc.* Bethesda, MD: Delta-Biometrics.

Porges, S. W. (1992). Vagal tone: A physiological market of stress vulnerability. *Pediatrics, 90,* 498-504.

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications to our evolutionary heritage. A Polyvagal Theory. *Psychophysiology, 32,* 301-318.

Porges, S. W. (1997). Emotion: An evolutionary by-product of the neural regulation of the autonomic nervous system. In C. S. Carter, B. Kirkpatrick, & I. I. Lederhendler (Eds.), The integrative neurobiology of affiliation. *Annals of the New York Academy of Sciences, 807,* 62-77.

Porges, S. W., Doussard-Roosevelt, J. A., Portales, A. L., & Greenspan, S. I. (1996). Infant regulation of the "vagal brake" predicts child behavior problems: A psychobiological model of social behavior. *Developmental Psychobiology, 29,* 697-712.

Porges, S. W., Doussard-Roosevelt, J. A., Portales, A. L., & Suess, P. E. (1994). Cardiac vagal tone: Stability and relation to difficulties in infants and three-year-olds. *Developmental Psychobiology, 27,* 289-300.

Porges, S. W., & Smith, K. M. (1980). Defining hyperactivity: Psychophysiological and behavioral strategies. In C. K. Whalen & B. Henker (Eds.), *Hyperactive children: The social ecology of identification and treatment* (pp. 75-104). New York: Academic Press.

Power, T. J., Costigan, T. E., Eiraldi, & Leff, S. S. (2004). Variations in anxiety and depression as a function of ADHD subtypes defined by DSM-IV: Do subtype differences exist or not? *Journal of Abnormal Child Psychology, 32,* 27-37.

Richter, D. W., & Spyer, K. M. (1990). Cardiorespiratory control. In A. D. Loewy & K. M. Spyer (Eds.), *Central regulation of autonomic functions* (pp. 189-207). New York: Oxford University Press.

Rothbart, M. K. (1989). Biological processes of temperament. In G. A. Kohnstamm, J. E. Bates, & M. K. Rothbart (Eds.), *Temperament in childhood* (pp. 77-110). New York: Wiley.

Santosh, P. J., & Mijovich, A. (2004). Social impairment in hyperkinetic disorder: Relationship to psychopathology and environmental stressors. *European Child and Adolescent Psychiatry, 13,* 141-150.

Schaaf, R. C., Miller, L. J., Seawell, D., & O'Keefe, S. (2003). Children with disturbances in sensory processing: A pilot study examining the role of the parasympathetic nervous system. *American Journal of Occupational Therapy, 57,* 442-449.

Selye, H. (1936). Thymus and adrenals in the response of the organism to injuries and intoxications. *British Journal of Experimental Pathology, 17,* 234-248.

Shaffer, D, Fisher, P., Lucas, C., P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). MINH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 28-38.

Shibagaki, M. & Furuya, T. (1997). Baseline respiratory sinus arrhythmia and heart-rate responses during auditory stimulation of children with attention-deficit hyperactivity disorder. *Perceptual and Motor Skills, 84,* 967-975.

Snoek, H., Van Goozen, S. H. M., Matthys, W., Buitelaar, J. K., & Van Engeland, H. (2004). Stress responsivity in children with externalizing behavior disorders. *Development and Psychopathology, 16,* 389-406.

Sroufe, L. A., Sonies, B. C., West, W. D., & Wright, F. S. (1973). Anticipatory heart rate deceleration and reaction time in children with and without referral for learning disability. *Child Development, 44,* 267-273.

Strauss, C. C., Lease, C. A., Last, C. G., & Francis, G. (1988). Overanxious disorder: An examination of developmental differences. *Journal of Abnormal Child Psychology, 16,* 433-443.

Szatmari, P., Boyle, M., & Offord, D. R. (1989). ADDH and conduct disorder: Degree of diagnostic overlap and differences among correlates. Journal of the American Academy of Child and Adolescent Psychiatry, 28, 865-872.

Urman, R., Ickowicz, A., Fulford, P., & Tannock, R. (1995). An exaggerated cardiovascular response methylphenidate in ADHD children with anxiety. *Journal of Child and Adolescent Psychopharmacology, 5,* 29-37.

Van der Meere, J. J., Shalev, R., Börger, N. A., & Gross-Tsur, V. (1995). Sustained attention, activation, and MPH in ADHD: A research note. *Journal of Child Psychology and Psychiatry, 36*, 697-703.

Vaessen, W. & Van der Meere, J. J. (1990). Issues in the selection of hyperactive/ADDH children for experimental clinical studies. In A. F. Kalverboer (Ed.), *Developmental biopsychology: Experimental and observational studies in groups at risk.* Ann Arbor, MI: The University of Michigan Press.

Voeller, K. K. S. (2004). Attention-Deficit Hyperactivity Disorder (ADHD). *Journal of Child Neurology, 19,* 798-814.

Waschbush, D. A., Pelham, W. E., Jennings, J. R., Greiner, A. R., Tarter, R. A., & Moss, H. B. (2002). Reactive aggression in boys with disruptive behavior disorders: Behavior, physiology, and affect. *Journal of Abnormal Child Psychology, 30,* 641-656.

Weinberg, C. R., & Pfeifer, M. A. (1984). An improved method for measuring heart-rate variability: Assessment of cardiac autonomic function. *Biometrics, 40,* 855-861.

Wheeler, J., & Carlson, C. L. (1994). The social functioning of children with ADD with hyperactivity and ADD without hyperactivity: A comparison of their peer relations and social deficits. *Journal of Emotional and Behavioural Disorders, 2,* 2-12.

Willoughby, M. T., Curran, P. J., Costello, E. J., & Angold, A. (2000). Implications of early versus late onset of attention-deficit/hyperactivity disorder symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 1512-1519.