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Specificity of Reward Sensitivity and Parasympathetic-Based Regulation Among Children with Attention-Deficit/Hyperactivity and Disruptive Behavior Disorders

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder affecting approximately 11% of children, aged 4–17 years, in the United States (Visser et al., 2014). ADHD is characterized by inattention, hyperactivity, and/or impulsivity, as well as associated impairment across multiple contexts (American Psychiatric Association, 2013). There is also substantial heterogeneity in symptom presentation among children with the disorder as exhibited by the DSM 5 presentations of inattentive, hyperactive/impulsive, and combined type (American Psychiatric Association, 2013; Steinberg & Drabick, 2015). Further, there is documented heterogeneity within the disorder that goes beyond the currently recognized nosology (Costa Dias et al., 2015; Fair et al., 2013; Karalunas et al., 2014), as well as substantial heterogeneity with respect to comorbidities associated with the disorder (Anastopoulos et al., 2011).

Approximately two-thirds of youth with ADHD also meet diagnostic criteria for another disorder (Jensen et al., 2001). Disruptive behavior disorders (i.e., conduct [CD] and oppositional defiant disorders [ODD]) are characterized by conduct problems, defiance, irritability, and/or oppositional behavior (Frick & Nigg, 2012) and are among the most frequently co-diagnosed with ADHD. These disorders (i.e., ADHD and CD and/or ODD) have comorbidity rates of 30–50% in epidemiological studies and 54–67% in clinical samples, and shared risk factors among the disorders likely contribute to their co-occurrence (Nigg & Barkley, 2014; Steinberg & Drabick, 2015). Improved understanding of shared and distinct mechanisms underlying ADHD and disruptive behavior disorders may aid in the understanding of the etiology of these disorders, as well as improve treatment matching and prediction of treatment response (Frick & Nigg, 2012; Jensen, Martin, & Cantwell, 1997; Karalunas et al., 2014; Nigg, Goldsmith, & Sachek, 2004; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005).

One theoretical model which has been proposed to explain both behavioral and etiological heterogeneity in ADHD is the dual pathway model (Sonuga-Barke, 2002, 2003). This model proposes separate pathways in the development of ADHD, involving disruptions in reward processing (e.g., delay aversion; reward sensitivity) and/or executive dysfunction (e.g.,

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behavioral disinhibition, deficient self-regulation; Nigg et al., 2004; Sonuga-Barke, 2002, 2003). Specifically, the dual pathway model proposes that disruptions in reward processing and executive dysfunction may lead independently or interactively to the development of ADHD and these distinct pathways may account for the heterogeneity observed in ADHD presentations and comorbid disorders (Sonuga-Barke, 2002, 2003).

In complement to the dual pathway model, current National Institute of Mental Health priorities (e.g., Research Domain Criteria [RDoC]) are focused on elucidating etiology and developing improved treatments by targeting specific transdiagnostic domains (e.g., positive valence systems, cognitive systems, and arousal/modulatory systems) across multiple levels of analysis (behavior, physiology, neural circuitry; Cuthbert & Insel, 2013; Insel et al., 2010; Nelson et al., 2013). According to both the dual pathway model and RDoC, one domain of particular interest in ADHD is positive valence systems (Costa Dias et al., 2015; Nigg & Casey, 2005), of which reward processing is one component (Cuthbert & Insel, 2010; Nelson et al., 2013). A second domain of interest in ADHD is that of cognitive systems (i.e., executive function systems; Barkley, 1997; Martel, Nikolas, & Nigg, 2007; Wilcutt, Doyle, Nigg, Faraone, & Pennington, 2005), of which self-regulation is one component (Barkley, 2001; Nigg & Casey, 2005). This study sought to examine reward processing and self-regulation at multiple levels of analysis (i.e., behaviorally and via psychophysiological indexes of autonomic nervous system functioning) in youth with ADHD and typically developing youth, as well as to determine whether reward processing and self-regulation help to explain comorbidity observed in youth with ADHD.

ADHD and Reward Sensitivity

Reward sensitivity can be defined as the processing and responding to pleasurable and/or reinforcing stimuli (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Reward sensitivity has been associated with increased approach behavior and impulsive responding in children with ADHD (Luman, Tripp, & Scheres, 2010; Nigg, 2016; Shaw et al., 2014). Reward sensitivity can be further parsed into external reward sensitivity defined as behaviorally based approach motivation in response to reward (i.e., reward-seeking behavior; Luman et al., 2010) and internal reward sensitivity defined as the nervous system's threshold for responding to reward (e.g., indexed via activity of the sympathetic nervous system and/or nucleus accumbens and/or dopamine rich fronto-striatal circuits; Beauchaine, 2012; Brenner, Beauchaine, & Sylvers, 2005; Gatzke-Kopp & Beauchaine, 2007; Gatzke-Kopp et al., 2009). Importantly, prior literature has suggested that excessive external reward sensitivity (i.e., reward seeking behavior) may be related to reduced internal reward sensitivity (i.e., underactive autonomic and/or central nervous system functioning in response to reward; Beauchaine et al., 2013; Gatzke-Kopp & Beauchaine, 2007; Gatzke-Kopp, Raine, Loeber, & Stouthamer-Loeber; Sagvolden, Johansen, Aase, & Russell, 2005). Further, it has been hypothesized that increased external reward sensitivity (i.e., reward seeking behavior) occurs, in part, to upregulate a persistently underactive mesolimbic dopamine system (i.e., low internal reward sensitivity; Beauchaine, 2012; Beauchaine et al., 2013).

With respect to external reward sensitivity among children with ADHD, results have been mixed (Luman, Oosterlaan, & Sergeant, 2005). Some studies have found that children with

ADHD display increased external reward sensitivity, indexed by a preference for small immediate compared to larger delayed rewards, across tasks including: signal detection (Tripp & Alsop, 2001), delay discounting (Bitsakou, Thompson, & Sonuga-Barke, 2009; Marco et al., 2009; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2010), and risk taking tasks (Humphreys & Lee, 2011). Other studies have found no differences in external reward sensitivity on such tasks when compared to typically developing youth (Scheres et al., 2006).

In line with the theory that ADHD and disruptive behavior disorders have overlapping etiologies, both CD and ODD have also been linked to disruptions in external reward sensitivity (for a review see Luman et al., 2005). Specifically, youth with both CD and ODD have demonstrated increased external reward sensitivity (Beauchaine, 2012; Byrd, Loeber, & Pardini, 2014; Gatzke-Kopp et al., 2009; Luman et al., 2009; Marini & Stickle, 2010; Van Goozen et al., 2004).

Importantly, prior studies examining external reward sensitivity in youth with ADHD have often either 1) failed to account for comorbid CD and/or ODD (Humphreys & Lee, 2011; Marco et al., 2009; Scheres et al., 2006; Sonuga-Barke et al., 1992), or 2) combined disruptive behavior disorders into a single diagnosis failing to examine the unique contributions of these diagnoses (i.e., treating ADHD, CD, and ODD as one group; Bitsakou et al., 2009; Tripp & Alsop, 2001). The inclusion or exclusion of youth with CD and/or ODD may account, in part, for the inconsistent associations between ADHD and external reward sensitivity, and as such, additional research is needed to examine the specificity of disruptions in external reward sensitivity within or across these disorders.

Autonomic indices may help clarify the nature of the association between ADHD and reward sensitivity by reflecting internal reward sensitivity (i.e., sympathetic-based responding to rewarding stimuli; Brenner et al., 2005). One autonomic index of internal reward sensitivity is cardiac pre-ejection period (PEP). PEP is the systolic time interval extending from left ventricular polarization to the onset of ejection of blood into the aorta (Brenner & Beauchaine, 2011). PEP is influenced by reward-related striatal dopamine responding as evidenced by links from the sinoatrial node of the heart to dopamine projections of the beta-adrenal system (Beauchaine, 2012; Cacioppo et al., 1994). Approach behaviors require energy mobilization and increased cardiac output controlled by sympathetic-mediated changes in the contractile force of the left ventricle (Sherwood, Allen, Orbist, & Langer, 1986), as such PEP shortening is thought to be associated with greater internal reward sensitivity (Beauchaine et al., 2013; Brenner et al., 2005; Richter & Gendolla, 2009).

With respect to sympathetic-based internal reward sensitivity in youth with ADHD, preschoolers with ADHD and comorbid disruptive behavior problems have demonstrated reduced PEP reactivity (i.e., low SNS-based internal reward sensitivity) to incentives relative to children with ADHD without comorbid disruptive behavior problems (Beauchaine et al., 2013). Additionally, pure disruptive behavior problems in youth without an ADHD diagnosis have been associated with reduced PEP reactivity to a monetary incentive task (i.e., low SNS-based internal reward sensitivity; Beauchaine, Gatzke-Kopp, & Mead, 2007).

However, it remains unclear whether reward sensitivity disruptions are unique to ADHD, unique to disruptive behavior disorders more broadly, or help to explain when and why the conditions co-occur. This study sought to examine behaviorally-based external reward sensitivity and SNS-based internal reward sensitivity (via PEP) in youth with ADHD only, ADHD and co-occurring disruptive behavior disorders, and typically developing youth to clarify this relationship.

ADHD and Parasympathetic-Based Regulation

In line with the dual pathway model, deficits in self-regulation have also been implicated in youth with ADHD (Musser et al., 2011; Shaw et al., 2014). These deficits in self-regulation are thought to emanate from disruptions in prefrontal cortical regions (Petrovic & Castellanos, 2016; Phillips, Ladouceur, & Drevets, 2008). Importantly, self-regulation has also been linked to parasympathetic-based control of the heart by the vagus nerve, which has been indexed noninvasively via respiratory sinus arrhythmia (RSA). RSA is the waxing and waning of heart rate during respiration and a unique index of parasympathetic-based regulation as demonstrated by pharmacological blockade (Porges, 2003, 2007).

With respect to ADHD, a recent meta-analysis linked ADHD to deficient parasympathetic-based regulation, as indexed via both tonic RSA and reactivity of RSA to challenge (Rash & Aguirre-Camacho, 2012). Specifically, ADHD has been associated with reduced RSA at rest and excessive RSA reactivity baseline during social and emotional challenges (Graziano & Derefinko, 2013; Musser et al., 2011). Additionally, different patterns of RSA reactivity have been linked to behavioral- and temperament-based heterogeneity within ADHD (Bunford et al., 2016a; Karalunas et al., 2014).

With respect to disruptive behavior disorders and parasympathetic-based dysregulation, some studies have reported reduced RSA withdrawal when examining youth with high levels of disruptive behavior compared to youth with low levels of disruptive behavior (Calkins & Dedmon, 2000; Calkins, Graziano & Keane, 2007; El-Sheikh, 2001), while others report no such differences in RSA withdrawal when comparing healthy youth to those with conduct disorder (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Beauchaine et al., 2007). This study sought to examine PNS-based self-regulation in youth with ADHD, ADHD and comorbid disruptive behavior disorders, and typically developing youth.

The Present Study

In summary, prior work has demonstrated that sensitivity to reward and parasympathetic-based regulation appear to play an important role in ADHD, as well as related disruptive behavior disorders (Beauchaine, 2012; Beauchaine et al., 2001, 2013; Musser et al., 2011). This study sought to examine behaviorally based external reward sensitivity, as well as sympathetic-based internal reward sensitivity and parasympathetic-based regulation, within the context of ADHD and comorbid disruptive behavior disorders. To do so, a behavioral risk taking paradigm (i.e., BART) was used to index external reward sensitivity, while electrocardiogram and impedance cardiography were obtained, to derive indices of

sympathetic-based internal reward sensitivity (i.e., PEP) and parasympathetic-based regulation (i.e., RSA).

In line with prior research and the dual pathway model, it was hypothesized that when comparing children with ADHD to typically developing youth: 1) ADHD will be associated with increased behaviorally-based external reward sensitivity (indexed by task performance on the BART) and reduced sympathetic-based internal reward reactivity (indexed by PEP lengthening from a resting baseline to the BART) and 2) ADHD will be associated with parasympathetic-based dysregulation (indexed by reduced RSA reactivity from resting baseline to the BART). Additionally, it was hypothesized that the presence of comorbid ODD and/or CD would help to account for these patterns of reward sensitivity and self-regulation among youth with ADHD. That is, it is expected that disruptions in reward sensitivity (i.e., increased external reward sensitivity, reduced SNS-based internal reward sensitivity) in ADHD will be explained, in part, by comorbid ODD and/or CD diagnoses, and parasympathetic-based regulatory deficits will be most prominent among youth with ADHD and comorbid ODD and/or CD. To further examine the specificity of effects, continuous symptom domains of inattention, hyperactivity/impulsivity, CD, and ODD will be examined in follow-up analyses.

Method

Participants and Diagnostic Procedures

Participants—Participants were 117 children (72.6% male; 87.2% Hispanic) aged 6 to 12 years (mean age=8.24, $SD=1.84$ years). Sixty-nine met *DSM-IV* and *DSM 5* (American Psychiatric Association, 2000, 2013) criteria for ADHD (15 inattentive, 9 hyperactive/impulsive, and 45 combined presentation) and 48 were typically developing comparison youth. The local institutional review board approved the study and all procedures were in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Parents provided written consent, and children provided written assent.

Recruitment and identification—Children with ADHD were recruited from a Summer Treatment Program (STP) and reflect a subset of participants enrolled in a double-blind, cross-over study examining tolerance to stimulant medication. Participants in the STP were recruited from several sources, including a university treatment center, referrals from school personnel and physicians, and advertisements (billboards, radio, newspaper, direct mail). All STP participants were required to meet *DSM-IV*¹ diagnostic criteria for ADHD, to have an estimated Full, Verbal, or Perceptual Reasoning IQ score >80, and to have no documented contraindication for use of methylphenidate or documented intolerance to methylphenidate or a failed trial of osmotic-release oral system (OROS) methylphenidate at full therapeutic dose. Children were excluded if they received psychotropic medication for conditions other than ADHD in the past six months or if they had active medical or psychiatric conditions that could be worsened by stimulant medication (seizures, pregnancy, arrhythmias,

¹Participants also met criteria based on DSM-5

hypertension, Tourette's Disorder, psychoses and mania). Youth who met full DSM-IV criteria for Autism or Asperger's Disorder were also excluded.

Typically developing youth were recruited from the community through advertisements and were pre-screened for the following exclusion criteria: use of psychoactive medication, pervasive developmental or neurological disorder, estimated IQ<80, and the presence of four or more ADHD symptoms.

All children (both ADHD and typically developing) were identified for the study via a multi-gate, best-estimate confirmation procedure. Parents of all children completed a questionnaire to obtain basic demographic information (e.g., age, ethnicity, race, sex, etc.). A parent/guardian completed the Diagnostic Interview Schedule- Child Version (DISC-IV; Shaffer et al., 2000) with a trained master's-level clinician. Further, parent-report and teacher-report on the Disruptive Behavior Disorders Rating Scale (Pelham, Gnagy, Greenslade, & Milich, 1992) and the Pittsburgh Modified Conner's Rating Scale (Pelham et al., 2005) were obtained for all children with ADHD. Only parent-report (i.e., no teacher-report) was obtained on the Disruptive Behavior Disorders Parent Rating Scale and the Pittsburgh Modified Conner's Parent Rating Scale for typically developing children. All children completed the Wechsler Abbreviated Scale of Intelligence 2nd edition (WASI-II; Wechsler, 2011) and the word reading, spelling, and numerical operations sub-tests of the Wechsler Individual Achievement Test, 3rd edition (WIAT-III; Wechsler, 2009). Children with ADHD were washed out of stimulant medications (equivalent to 7 half-lives of their current preparation) prior to participation in all procedures.

Diagnoses of ADHD were made according to best-practice recommendations (Pelham, Fabiano, & Massetti, 2005) and included parent and teacher ratings of *DSM-IV* symptoms (i.e., the Disruptive Behavior Disorders Rating Scale; Pelham et al., 1992), a structured parent interview (DISC-IV; Shaffer et al., 2000), and parent and teacher ratings of impairment (Impairment Rating Scale; Fabiano et al., 2006). Two Ph.D. level clinicians reviewed all available data from the initial assessment to confer diagnoses of ADHD and disruptive behavior disorders (i.e., CD and/or ODD) and ensure children met inclusion criteria. If disagreements occurred (less than 1% of cases), a third clinician reviewed the file and majority decision was used.

For the purposes of this study, all other comorbid diagnoses (excluding ODD and CD) were determined based on endorsements of parent report on the Diagnostic Interview Schedule for Children IV (DISC-IV; Shaffer et al., 2000). For all analyses, comorbid diagnoses were collapsed into the following categories: 1) "anxiety disorder" (including generalized anxiety, separation anxiety, and/or social anxiety disorders); 2) ODD; and 3) ODD+CD (of note, all 7 children in the sample who met criteria for CD also met criteria for ODD).

Clinical Measures

Diagnostic Interview Schedule- Child Version (DISC-IV; Shaffer et al., 2000)—

The DISC-IV is a highly structured diagnostic interview designed to assess psychiatric disorders occurring in children and adolescents (Shaffer et al., 2000). The psychometric properties of the DISC-IV ADHD module are favorable, including adequate test-retest

reliability (0.79), and internal consistency (0.60) (Shaffer et al., 2000). With respect to the anxiety disorder modules, adequate test-retest reliability (all $>.54$) and diagnostic reliability (.56) have been established (Shaffer et al., 2000). Items endorsed by parents on the separation anxiety, social anxiety and general anxiety disorder modules were included in the total anxiety symptoms employed in the secondary analyses of the current study (coefficient $\alpha=.74$).

Impairment Rating Scale (IRS; Fabiano et al., 2006)—The IRS is a parent and teacher report measure that assesses the child's severity of a problem across domains and the need for treatment and special services on a 0 (no problem/definitely does not need treatment) to 6 (extreme problem/definitely needs treatment) scale. The IRS has demonstrated acceptable to excellent stability over time, convergent, concurrent and discriminate validity and was highly effective for discriminating between children with and without ADHD (Fabiano et al., 2006; Pelham, Fabiano, & Massetti, 2005).

Disruptive Behavior Disorders Rating Scale (DBD; Pelham et al., 1992)—The DBD has a parent and teacher version that each consists of 45 items. Symptoms of ADHD, ODD and CD are endorsed on a scale from not at all to very much. Symptoms that were endorsed as pretty much or very much on the parent-rating scale were counted as total symptoms and examined as total ADHD (coefficient $\alpha=.97$), total ODD (coefficient $\alpha=.93$) and total CD (coefficient $\alpha=.71$) symptoms respectively. The three factors have demonstrated good internal consistency (Pelham, Fabiano, & Massetti, 2005).

Primary Study Procedures

Balloon analogue risk task (BART)—The BART was developed to assess risk-taking behavior in a laboratory setting by balancing the potential for reward versus loss with the goal to receive as many points as possible. Task procedures are identical to those described in Lejuez et al., 2007. Children with ADHD completed the task individually, during the STP, in a quiet, private classroom set up specifically for this study. Typically developing youth completed the task in a laboratory setting on the FIU campus with a configuration identical to that of the STP classroom. Participants completed 30 trials. External reward sensitivity was indexed by total pops across the 30 trials, such that more pops were indicative of greater reward sensitivity. Each trial balloon had a predetermined pop-threshold (ranging from 4 to 125 pumps with a mean of 64.5 pumps), which when reached, resulted in the loss of all points in the Current Points Earned bank and the beginning of the next trial. Each pump inflated the balloon (about 0.125 in. [0.3 cm] in all directions) and 10 points were accrued per pump. During the trial, the participant was able to choose to stop pumping and transfer the points to the permanent Total Points Earned bank, followed by a slot-machine tone and the beginning of the next trial.

Reliability and validity for the task has been established across a range of samples and testing conditions (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005; Crowley et al., 2006; Lejuez et al., 2002; MacPherson et al., 2010; White, Lejuez, & de Wit, 2008). Performance on the task has been operationally defined as total pumps across all trials, as well as total pops across all trials, both of which have been correlated with self-reports of risk-taking

behaviors, such as stealing, unprotected sex, smoking, and substance abuse in both child and adult samples (Lejuez et al., 2003; Lejuez et al., 2004; Lejuez et al., 2007; Schonberg et al., 2012).

Physiological Recording

Overview—Procedures were identical to those described in Musser et al., 2011. In brief, disposable silver/silver-chloride electrodes were placed in an electrocardiogram (ECG) and impedance cardiography (ICG) configuration. ECG and ICG were recorded continuously throughout a 2-minute resting baseline period and the BART.

Cardiac pre-ejection period (PEP; SNS-based external reward sensitivity)—

PEP was derived in 60-second epochs using ECG and ICG. Specifically, PEP was indexed as the interval in milliseconds from the onset of the Q-wave to the B-point of the dZ/dt wave. Artifacts were removed using MindWare Impedance Cardiography V. 3.1 software (MindWare Impedance Cardiography, 2008). 20% of cases were processed for artifact removal by 2 raters to establish inter-rater reliability ($k > 0.85$). There were no between-group differences in the rate of artifacts (all $p > .50$). PEP reactivity (i.e., change scores) from the 2-minute resting baseline period to the BART task was used to index SNS-based reward sensitivity (i.e., internal reward sensitivity).

Respiratory sinus arrhythmia (RSA; index of PNS-based regulation)—

RSA was derived in 60-second epochs via spectral analysis of the R-R time series derived from the ECG. Time series was detrended and submitted to a Fourier transformation and the high frequency band ($\ln(\text{ms}^2)$) was set over the respiratory frequency band of 0.24 to 1.040 Hz, derived from the impedance cardiograph signal (Z0). Artifacts in the R-R waves were removed using MindWare Heart Rate Variability V.3.1 software (MindWare, 2008). 20% of cases were processed for artifacts by 2 raters to ensure inter-rater reliability ($k > 0.93$). There were no between-group differences in artifacts, $p < 0.5$. RSA reactivity (i.e., change scores) from the 2-minute resting baseline period to the BART task was used to index PNS-based regulation.

Data Analysis Plan

Data analyses—Prior to all analyses missing data (less than 5% of total cases exhibited missing data) were addressed using multiple imputation using the maximum information likelihood approach in MPlus. Group comparisons were conducted using analysis of variance with covariates (ANCOVA) to examine group differences in task performance, PEP reactivity, and RSA reactivity. Bonferroni-adjusted pairwise comparisons were utilized as appropriate.

To examine ADHD, CD, and ODD symptomology continuously to detect subclinical comorbidity effects, as well as possible transdiagnostic associations, follow-up analyses were conducted using multiple linear regression models to examine the relationship between inattentive, hyperactive/impulsive, CD, and ODD symptom counts and task performance, PEP reactivity, and RSA reactivity.

Results

Preliminary Analyses

Demographic and diagnostic overview of sample—Demographic and diagnostic comparisons are reported in Table 1 for ADHD and typically developing youth. Groups did not differ with respect to age, ethnicity/race, or IQ (all $p > .17$; Table 1); inclusion of these variables did not affect the results of the primary analyses. Results are reported without these variables included. The ADHD group was more likely to be male and have a history of stimulant medication use ($p < .001$; Table 1); as such, child biological sex and previous stimulant medication use were treated as covariates in all results.

Clinical characteristics and comparisons are also provided in Table 1 for ADHD and typically developing youth. As expected, ODD and CD diagnosis were more common among the ADHD group (all $p < .02$; Table 1), as such ODD and CD diagnosis were examined in secondary analyses. Although group differences were not observed for anxiety disorders ($p = .11$), anxiety disorder diagnosis was included as covariate in all secondary analyses, due to the well-established influence of anxiety on the autonomic nervous system (Supplemental Table 1, includes all group-level analyses without anxiety disorder treated as a covariate; Online Supplemental materials Table 2, includes all continuous analyses without anxiety disorder treated as a covariate; Beauchaine, 2001; Boyce et al., 2001; El-Sheikh, Arsiwalla, Hinnant, & Erath, 2011).

Demographic and diagnostic comparisons among ADHD only, ADHD+ODD, ADHD+ODD+CD, and typically developing youth are also presented in Table 1. Each of the ADHD groups were more likely than the typically developing youth to be male and previously receive medication for behavioral, emotional or, other psychiatric problems (all $p < .02$; Table 1). However, no significant differences were observed in biological sex or medication history between the ADHD, ADHD+ODD and ADHD+ODD+CD groups (all $p > .29$). Consistent with prior research, the ADHD+ODD and the ADHD+ODD+CD group had greater numbers of hyperactive/impulsive and greater parent-rated impairment scores than the ADHD only group (all $p > .05$; Table 1; Frick and Nigg, 2012).

Primary Analyses: Reward Behavior, PEP, and RSA by ADHD Diagnosis

Reward task performance, PEP, and RSA for all task conditions and baselines are presented in Table 2 according to diagnostic group status.

Reward task performance according to ADHD diagnosis—No group-based differences were observed in total pops across trials, suggesting no differences in behaviorally based external reward sensitivity between the ADHD and typically developing groups, $F(1,113) = 2.06$, $p = .15$, partial $\eta^2 = .04$; Table 2.

Secondary analyses examined the effect of comorbid ODD and CD diagnosis on behavioral external reward sensitivity. When treated as separate groups, significant between-group differences were observed in external reward sensitivity (i.e., total pops; $F(3,110) = 5.96$, $p = .001$, partial $\eta^2 = .14$; Table 2). Specifically, children with ADHD+ODD+CD had significantly greater total pops compared to children with ADHD only, $t = 3.87$, $p = .001$, and compared to

children with ADHD+ODD, $t=3.56$, $p=.003$. No other significant group differences were observed (Table 2).

PEP reactivity according to ADHD diagnosis—ADHD diagnosis was associated with reduced SNS-based reward sensitivity compared to typically developing youth (i.e., PEP lengthening; $F(1,112)=4.01$, $p=.047$, partial $\eta^2=.04$; Table 2).

Secondary analyses examining ADHD, ADHD+ODD, ADHD+ODD+CD and typically developing youth, revealed marginally significant between-group differences in PEP reactivity, $F(3,109)=2.60$, $p=.056$, partial $\eta^2=.07$; Table 2. Children with ADHD+ODD exhibited marginally significant reduced SNS-based reward sensitivity when compared to typically developing youth (i.e., PEP lengthening; $t=2.54$, $p=.075$).

RSA reactivity according to ADHD diagnosis—ADHD diagnosis was associated with reduced PNS-based regulation compared to typically developing youth (i.e., reduced RSA augmentation; $F(1,112)=10.12$, $p=.002$, partial $\eta^2=.08$; Table 2).

Secondary analyses of ADHD, ADHD+ODD, ADHD+ODD+CD, and typically developing youth revealed significant between-group differences in RSA reactivity (i.e., reduced RSA augmentation; $F(3,109)=4.22$, $p=.007$, partial $\eta^2=.10$; Table 2). Children with ADHD+ODD exhibited significantly reduced PNS-based regulation in response to reward (i.e., reduced RSA augmentation) when compared to typically developing youth, $t=3.38$, $p=.006$. No other significant group differences were observed.

Follow-up Continuous Analyses

Evaluation of ADHD, ODD and CD symptomology—To examine ADHD symptom and comorbidity effects continuously, hyperactive/impulsive, inattention, CD, and ODD total symptom counts were indexed via the DBD parent rating scale. Anxiety symptom counts were indexed via parent endorsement of DISC-IV generalized, separation, and social anxiety disorder subscale items.

Using hierarchical linear regressions with covariates, the model predicting external reward sensitivity from continuous symptom counts of ADHD, CD and ODD, while covarying anxiety was not significant, $R^2=.05$, $p=.09$. However, in the model, CD total symptom count was significantly associated with total pops, $\beta=.32$, $t=2.56$, $p=.01$, with increased CD total symptoms associated with greater total pops across trials (i.e., increased external reward sensitivity); no other significant associations were observed with external reward sensitivity (all $p>.11$). With respect to PEP reactivity, the model predicting PEP reactivity from continuous symptom counts of ADHD, CD and ODD, while covarying anxiety was significant, $R^2=.43$, $p<.001$. Specifically, increased ODD symptoms were significantly associated with PEP lengthening (i.e., reduced SNS-based internal reward sensitivity; $\beta=.23$, $t=2.06$, $p=.04$); no other significant associations were observed with PEP reactivity (all $p>.05$). For RSA reactivity, the model predicting RSA reactivity from continuous symptom counts of ADHD, CD and ODD, while covarying anxiety was significant, $R^2=.46$, $p<.001$. Specifically, increased ODD symptoms were significantly associated with reduced PNS-

based regulation (i.e., reduced RSA augmentation; $\beta = -.26$, $t = -2.43$, $p = .017$); no other significant associations were observed with RSA reactivity (all $p > .07$).

Discussion

This study examined reward sensitivity and regulation as mechanisms underlying ADHD heterogeneity and comorbidity, using a multi-method approach. The hypotheses were designed to be in line with the dual pathway model (Sonuga-Barke, 2002, 2003), which proposes separate pathways in the development of ADHD, involving disruptions in reward and self-regulation (Nigg et al., 2004; Sonuga-Barke, 2002, 2003). Additionally, the dual pathway model proposes that these distinct pathways may account for the heterogeneity observed in ADHD presentations, as well as shared etiology with comorbid disorders (Sonuga-Barke, 2002, 2003).

The primary goal of this paper was to begin to explore ADHD heterogeneity with respect to both reward sensitivity and regulation. In contrast to our hypothesis, children with ADHD did not display increased external reward sensitivity, as indexed by performance (i.e., total pops) on the BART. However, when comorbid disruptive behavior diagnoses were considered, children with ADHD and comorbid CD/ODD were found to have greater external reward sensitivity. This association was corroborated when CD symptoms were examined at a continuous level. These results suggest that ADHD, in and of itself, is not directly associated with disruptions in external reward sensitivity, but rather these disruptions may be better accounted for by comorbid CD diagnosis and/or comorbid CD symptoms.

In contrast to the behavioral result, but in support of our hypotheses, children with ADHD differed significantly from healthy youth with respect to SNS-based internal reward sensitivity (indexed by cardiac pre-ejection period reactivity), as well as with respect to PNS-based regulation (indexed by respiratory sinus arrhythmia reactivity). These results are consistent with prior research (both in ADHD and other diagnoses, e.g., anxiety disorders) wherein no behavioral performance group differences were observed but wherein group-based differences in neural activation have been identified (Bunford et al., 2016b, 2016c; Klumpp et al., 2015; Wheaton et al., 2014). Thus, although there were no detectable behavioral group-based differences, disruptions in internal reward sensitivity and regulation appear to be associated with ADHD. Additionally, these results are largely consistent with prior research results regarding SNS and PNS-based reactivity according to ADHD diagnosis, which is mixed with regard to sympathetic differences (Beauchaine et al., 2007; Crowell et al., 2006; Musser et al., 2011), but relatively consistent with regard to parasympathetic differences in youth with ADHD (Beauchaine et al., 2012; Musser et al., 2011; Rash & Aguiere-Camacho, 2012). However, importantly, these results were also qualified by follow-up analyses examining ADHD and comorbid disruptive behavior disorders.

When comorbid disruptive behavior disorders were considered, children with increased ODD symptomology demonstrated reduced SNS-based internal reward sensitivity (i.e., PEP lengthening) in response to reward, while neither inattentive nor hyperactive/impulsive

symptoms were associated with SNS-based internal reward sensitivity. This is in line with prior research which has shown that preschoolers with ADHD and high levels of disruptive behavior symptoms, like ODD symptoms, exhibited reduced SNS reactivity compared to controls in the context of reward (Beauchaine et al., 2013). In contrast to prior findings, which have shown that adolescents with ADHD and comorbid CD diagnoses exhibit reduced SNS reactivity, CD symptoms were not associated with differences in SNS-based internal reward sensitivity (Beauchaine et al., 2001).

With respect to parasympathetic-based regulation, children with ADHD and comorbid ODD displayed parasympathetic-based dysregulation (i.e., reduced RSA augmentation) when compared to typically developing youth, and this was corroborated at the continuous level. These findings are in accordance with research demonstrating impaired RSA reactivity among individuals with externalizing symptoms, like ODD symptoms (Boyce et al., 2001).

When taken together, children with ADHD and increased ODD symptomology had both decreased SNS-based internal reward sensitivity and decreased parasympathetic-based dysregulation. In contrast, increased CD symptoms were associated with increased behaviorally-based external reward sensitivity. Thus, in identifying mechanisms underlying heterogeneity in ADHD, behaviorally-based external reward sensitivity appears to be uniquely associated with comorbid CD, while disruptions in parasympathetic-based regulation and internal reward sensitivity appear to be uniquely associated with comorbid ODD. Building upon these results may allow for a better understanding of the roles comorbid conditions, external and internal reward sensitivity, and parasympathetic-based regulation play in ADHD etiology and heterogeneity providing potential individualized treatment targets. For example, once replicated and extended, clinicians may treat children more specifically by targeting regulatory deficits in youth with both ADHD and ODD symptomology and/or determining more salient rewards for children with ADHD and CD symptomology.

While this study represents a first step in understanding reward sensitivity and parasympathetic-based regulation in ADHD and disruptive behavior disorders, there are several notable limitations. First, this study is cross-sectional, and longitudinal analyses of these constructs may serve to help understand etiology, differential trajectories, and predictions of prognosis among youth with ADHD. Second, although prior work has demonstrated an association between Body Mass Index and the autonomic indexes of interest in youth with ADHD, unfortunately, height and weight were not obtained in the full sample (Bunford et al., 2016a; Koenig et al., 2014; Molino et al., 2009). Third, the sample size and composition limited the examination of additional subgroups, including comorbid internalizing diagnoses, and future research should consider these distinct groups as well as children with subclinical ADHD symptoms. Fourth, a subset of the children in the ADHD sample were previously medicated prior to enrolling in the study (i.e., N=43 children receiving prior stimulant medication). Future work should replicate these findings in a medication-naïve sample of children with ADHD given the potential long term alterations observed at the neural level for children who have previously been treated with stimulant medication (Schlochtermeyer et al., 2011) and the fact that prior medication status was significantly associated with PEP reactivity in the present study. Finally, the magnitude of

effects observed should be considered when interpreting results, consistent with other physiological investigation, the effect sizes observed in this study were somewhat modest.

In conclusion, in line with the dual pathway model, this study revealed distinct patterns of both external and internal reward sensitivity, as well as parasympathetic-based regulation, among youth with ADHD. However, these associations appear to be accounted for, in part, by comorbid CD and ODD, highlighting the importance of accounting for these conditions when conceptualizing and evaluating ADHD. Future work is needed to evaluate these patterns longitudinally to determine whether these heterogeneous profiles serve as separate etiological pathways to ADHD and/or whether these dual pathways represent shared etiologies between ADHD and disruptive behavior disorders. If replicated these results may provide a starting point for identifying better-targeted mechanisms (i.e., use of reward processes and/or regulation to serve as mechanisms of change) via person-centered treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive and diagnostic statistics for ADHD and control groups

Variable	Control (n=48)	ADHD all (n=69)	F(1,115)/ χ^2 (1)	Control (n=48)	ADHD only (n=28)	ADHD+ODD (n=34)	ADHD+ODD+CD (n=7)	F(3,113)/ χ^2 (3)
Demographics								
Age mean (SD)	8.52(2.06)	8.11(1.69)	1.43	8.52(2.06)	7.96(1.84)	8.21(1.62)	8.14(1.57)	.56
Gender (%male)	56.3	84.1	11.0**	56.3 ^a	85.7 ^b	85.3 ^b	71.4 ^b	11.6**
Ethnicity (% Hispanic or Latino)	85.4	88.4	.27	85.4	89.3	91.2	71.4	2.39
WASI-II FSIQ, mean (SD)	99.38(11.86)	99.32(12.73)	.001	99.38(11.86)	99.57(14.85)	101.44(10.31)	88(9.26)	.01
Previously received Medication for behavior, emotional or psychiatric problems (%received)	0.0	62.3	47.3***	0.0 ^a	71.4 ^b	55.9 ^b	57.1 ^b	49.1***
Parent Rating Scales								
Impairment Rating ^e	–	4.94(1.06)	–	–	4.48(.92) ^a	5.09(1.0) ^b	5.86(.38) ^b	7.03**
Total ADHD symptoms ^f	1.17(1.86)	12.33(4.71)	242.9***	1.17(1.86) ^a	10.68(5.0) ^b	13.24(4.03) ^c	14.57(5.2) ^{b,c}	90.06***
Inattention Symptoms	.67(1.26)	6.77(2.76)	205.1***	.67(1.26) ^a	6.14(3.01) ^b	7.18(2.53) ^b	7.29(2.63) ^b	70.56***
Hyperactivity/Impulsivity Symptoms	.50(.97)	5.57(2.82)	142.8***	.50(.97) ^a	4.54(3.06) ^b	6.06(2.40) ^c	7.29(2.56) ^c	56.18***
ODD Symptoms	.10(.47)	3.06(2.63)	58.9***	.10(.47) ^a	1.14(1.50) ^b	3.82(2.30) ^c	7.0(.82) ^c	71.8***
CD Symptoms	.00(.00)	.65(1.01)	19.9***	.00(.00) ^a	.29(.71) ^{a,b}	.56(.66) ^b	2.57(1.40) ^c	39.6***
Teacher Rating Scales^g								
Impairment Rating	–	4.91(1.41)	–	–	4.59(1.65)	5.06(1.24)	5.50(.84)	1.41
Inattention Symptoms	–	6.91(2.66)	–	–	7.11(2.42)	6.70(2.90)	7.17(2.71)	.21
Hyperactivity/Impulsivity Symptoms	–	5.21(3.11)	–	–	4.07(3.10) ^a	5.97(2.90) ^b	6.17(3.25) ^{a,b}	3.27*
ODD Symptoms	–	2.98(3.02)	–	–	.93(1.47) ^a	4.15(3.03) ^b	5.83(2.64) ^b	17.03***
CD Symptoms	–	87(1.34)	–	–	.33(.73) ^a	.85(1.30) ^a	3.33(1.03) ^b	18.92***
Comorbid Disorders (% Diagnosis)								
ODD ^h	0	59.4	43.9***	–	–	–	–	–
CD ^h	0	10.1	5.18*	–	–	–	–	–
Anxiety ⁱ	10.4	21.7	2.56	10.4	21.4	20.6	28.6	2.83
Total Anxiety Symptoms/ ^j	1.69(3.22)	6.99(6.15)	26.5***	1.69(3.22) ^a	7.96(6.09) ^b	5.88(6.27) ^b	8.29(5.77) ^b	9.89***

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Note=

indicates $p < .001$;

**
indicates $p < .01$;

*
indicates $p < .05$; SD=Standard Deviation; WASI-II=Wechsler Abbreviated Scale of Intelligence- Second Edition; FSIQ=Full-Scale Intelligence Quotient (estimated); Parent Rating Scales=Disruptive Behavior Disorders Parent Rating Scale indexed total symptoms and The Impairment Rating Scale Overall Severity; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; DISC=Diagnostic Interview Schedule for Children-Parent Version.

a, b, c, d Differing subscripts indicates post hoc analyses that are significant after a modified Bonferroni correction for multiple group comparisons ($\alpha = .025$) for continuous variables, including age, estimates full-scale IQ, Disruptive Behavior Disorders Parent Rating Scale and The Impairment Rating Scale-Parent Version and total anxiety symptoms and χ^2 comparisons for categorical variables, including gender, ethnicity, previous medication status and presence of comorbid disorders.

e Severity rating comprises the overall severity rating from The Impairment Rating Scale Parent Report and is not available for control participants. $F(2,61)$.

f Total ADHD symptoms includes total ADHD symptoms endorsed on the Disruptive Behaviors Parent Rating Scale.

g Teacher Rating Scales not available for control participants, $F(2,65)$.

h Oppositional Defiant Disorder and Conduct Disorder for the ADHD group was diagnosed by the clinical diagnostic team and the DISC-IV parent report was used for the control group.

i Anxiety disorders; Generalized anxiety disorder, separation anxiety disorder and social anxiety disorder were diagnosed based off of endorsements of the DISC-IV parent report.

j Total anxiety symptoms include all generalized anxiety disorder, separation anxiety disorder and social anxiety disorder symptoms endorsed on the DISC-IV, $F(1, 108)$ and $F(3,106)$.

Table 2

Physiology and BART Task Data Controls and ADHD Groups

Variable Mean (SD)	Control (n=48)	ADHD all (n=69)	F(1,113)	Partial η^2	Control (n=48)	ADHD only (n=28)	ADHD+ODD (n=34)	ADHD+ODD+CD (n=7)	F(3, 110)	Partial η^2
Resting Baseline										
RSA	6.81(1.11)	6.27(1.22)	4.83*	.04	6.81 (1.11)	6.06(1.48)	6.31(.95)	6.86(1.23)	2.64	.07
PEP	96.46(13.27)	98.82(12.29)	.34	.003	96.46(13.27)	96.84(12.95)	101.04(12.13)	95.92(9.56)	.98	.03
BART Task Physiology ^c										
RSA	7.04(.87)	6.50(.93)	10.12**	.08	7.04(.87) ^a	6.59(1.12) ^{a,b}	6.40(.81) ^b	6.63(.63) ^{a,b}	4.22**	.10
PEP	97.73(12.69)	101.65(12.4)	4.02*	.04	97.73(12.69)	97.43(10.23)	105.47(13.86)	100(7.09)	2.60	.07
Physiology Change Scores										
RSA	.23(.96)	.24(.95)	.75	.007	.23(.96)	.53(.97)	.09(.88)	-.23(.90)	1.85	.05
PEP	1.27(11.75)	2.83(10.75)	2.41	.02	1.27(11.75)	.58(8.34)	4.43(13.02)	4.07(5.07)	1.17	.03
Task Data										
Total Pops	6.35(4.08)	5.84(4.06)	2.06	.02	6.35(4.08) ^{a,b}	5.00(3.20) ^a	5.47(3.70) ^a	11(5.54) ^b	5.96**	.14

Note: RSA=Respiratory Sinus Arrhythmia (ms^2); PEP=Pre-ejection period. All models include covariates (previous medication use and gender for primary analyses and previous medication use, gender and anxiety diagnosis for secondary analyses).

^{a,b} Differing subscripts indicates post hoc analyses that are significant after a modified Bonferroni correction for multiple group comparisons.

^c BART Task Physiology includes Resting Baseline as an additional covariate, $F(1,112)$ and $F(3,109)$