Sympathetic- and Parasympathetic-Linked Cardiac Function and Prediction of Externalizing Behavior, Emotion Regulation, and Prosocial Behavior Among Preschoolers Treated for ADHD

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Objective: To evaluate measures of cardiac activity and reactivity as prospective biomarkers of treatment response to an empirically supported behavioral intervention for attention-deficit/hyperactivity disorder (ADHD).

Method: Cardiac preejection period (PEP), an index of sympathetic-linked cardiac activity, and respiratory sinus arrhythmia (RSA), an index of parasympathetic-linked cardiac activity, were assessed among 99 preschool children (ages 4–6 years) with ADHD both at rest and in response to behavioral challenge, before participants and their parents completed 1 of 2 versions of the Incredible Years parent and child interventions.

Results: Main effects of PEP activity and reactivity and of RSA activity and reactivity were found. Although samplewide improvements in behavior were observed at posttreatment, those who exhibited lengthened cardiac PEP at rest and reduced PEP reactivity to incentives scored higher on measures of conduct problems and aggression both before and after treatment. In contrast, children who exhibited lower baseline RSA and greater RSA withdrawal scored lower on prosocial behavior before and after treatment. Finally, children who exhibited greater RSA withdrawal scored lower on emotion regulation before and after treatment.

Conclusions: We discuss these findings in terms of (a) individual differences in underlying neurobiological systems subserving appetitive (i.e., approach) motivation, emotion regulation, and social affiliation and (b) the need to develop more intensive interventions targeting neurobiologically vulnerable children.

Keywords: ADHD, intervention, PEP, RSA, treatment response.
who are impulsive often progress to more serious externalizing (Mannuzza et al., 2008; Piquero, Farrington, Welsh, Tremblay, & Jennings, 2009), identifying children with ADHD who are vulnerable to later delinquency and providing them with empirically supported treatments should be a national priority (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009).

Hyperactive/impulsive males—both with and without comorbid conduct problems—exhibit structural and functional compromises in the central and peripheral nervous systems (see, e.g., Beauchaine, Katkin, Strassberg, & Snarr, 2001; Castellanos et al., 2003; Crowell et al., 2006; Durston et al., 2003; Gatzke-Kopp et al., 2009; Nigg, in press; Sagvolden, Johansen, Aase, & Russell, 2005; Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012; Scheres, Milham, Knutson, & Castellanos, 2007; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009; Valera, Faraoe, Murray, & Seidman, 2007). Accumulating evidence suggests that these neurobiological vulnerabilities interact with high-risk and protective environments to either promote or inhibit progression along the externalizing trajectory outlined above (for reviews, see Beauchaine & Gatzke-Kopp, 2012; Beauchaine & McNulty, in press; Beauchaine et al., 2010, 2009; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007). As a result, children who are impulsive are more likely to progress toward and/or engage in delinquent behaviors when reared in environments characterized by hostile and inconsistent parenting (Drabick, Gadow, & Sprafkin, 2006), mal-treatment and neglect (De Sanctis et al., 2008), and/or neighborhood violence/criminality (Lynam et al., 2000; Meier, Slutske, Arndt, & Cadoret, 2008). Moreover, children who are impulsive are more likely than nonimpulsive children to evoke aversive reactions from their caregivers, which may exacerbate their pre-existing vulnerabilities (O’Connor, Deater-Deckard, Fulker, Rut-ter, & Plomin, 1998). Furthering our understanding of how biological vulnerabilities interact with high-risk environments to promote progression of externalizing conduct—and how prevention and intervention programs can inhibit such progression—has therefore received considerable research attention in recent years (see Burnett & Cicchetti, 2012). In this article, we examine whether cardiovascular biomarkers of trait impulsivity and emotion dysregulation predict response to an empirically supported treatment among 4- to 6-year-old children with ADHD.

Although full articulation of the neurobiological substrates of ADHD is well beyond the scope of this article, most theories of impulsivity focus at least in part on deficient responding in mesolimbic structures rich in dopamine (DA) neurons (see Volkow et al., 2009). The mesolimbic DA system comprises the nucleus accumbens, the caudate, and several other interconnected structures, which evolved to modulate appetitive (i.e., approach) behaviors. Midbrain DA neurons are less responsive to reward—including monetary incentives—among impulsive individuals than among controls (see Durston, 2003; Durston et al., 2003; Scheres et al., 2007). Consistent with theories of central and autonomic underarousal (e.g., Gatzke-Kopp, Raine, Loebber, Stoutamer, Loebber, & Steinhauser, 2002), we have argued that those with ADHD engage in excessive reward-seeking behaviors—expressed as hyperactivity/impulsivity—in part to upregulate a persistently underactive mesolimbic DA system, which is experienced psychologically as an aversive, irritable mood state (Laakso et al., 2003).

In high-risk environments such as those outlined above, children who are impulsive often progress to more serious externalizing conduct given many opportunities to engage in maladaptive reward-seeking behavior (see Lynam et al., 2000).

Despite research indicating consistent group differences between children with ADHD and controls in mesolimbic responding to incentives, no studies have examined whether individual variation in reward responding among children with ADHD prospectively predicts treatment response. Identifying biomarkers of treatment outcome can be important for several reasons in addition to those alluded to above (Beauchaine, 2009a). In the present case, current interventions for ADHD—both pharmacological and behavioral—do not benefit all children (MTA Cooperative Group, 1999). Discovering biomarkers of treatment response may help identify which children are more likely to respond to current treatments, which children need additional forms of treatment, and which children should be assigned to different types of treatment (see Beauchaine, Neuhaus, et al., 2008). Identifying biomarkers of treatment outcome may also advance our basic understanding of heterogeneity in the ADHD phenotype (Castellanos & Tannock, 2002).

Assessing midbrain DA responding is difficult in young children—particularly those with ADHD. As noted above, neuroimaging experiments consistently reveal blunted mesolimbic reactivity to incentives among older children with ADHD and other externalizing behaviors (e.g., Durston, 2003; Durston et al., 2003; Scheres et al., 2007). However, preschoolers have difficulty tolerating lengthy imaging protocols. In an effort to circumvent this problem, we have used sympathetic nervous system (SNS)-linked cardiac reactivity as a proxy for central DA responding to incentives (see Beauchaine & Gatzke-Kopp, 2012). As detailed elsewhere, several sources of evidence suggest that cardiac pre-ejection period (PEP)—an SNS-mediated systolic time interval spanning left ventricular depolarization to the onset of ejection of blood into the aorta—marks mesolimbic DA reactivity specifically during reward responding (Brenner & Beauchaine, 2011; Brenner, Beauchaine, & Sylvers, 2005).

Cardiac PEP shortens through β-adrenergic mechanisms when the SNS is activated.

The argument that PEP shortening marks central DA reactivity to incentives is based on several considerations. First, approach behaviors characteristic of reward responding require energy mobilization, a metabolic function served by the SNS. Second, increases in cardiac output required for behavioral approach are controlled by SNS-mediated changes in the contractile force of the left ventricle (Sherwood, Allen, Obrist, & Langer, 1986). Third, infusions of DA agonists into mesolimbic structures produce SNS-induced increases in cardiac output (van den Bussche, 1998), similar to those observed when normal volunteers participate in reward tasks (see Brenner et al., 2005). Finally, PEP shortening among normal controls is not observed during extinction or mood induction in well-controlled experiments and is therefore specific to reward (Brenner et al., 2005; Richter & Gendolla, 2009). Nevertheless, interpreting PEP reactivity as a biomarker of mesolimbic DA responding to incentives depends on careful selection of stimulus conditions (see Beauchaine, 2012; Beauchaine & Gatzke-Kopp, 2012). Some active coping tasks such as mental arithmetic also elicit PEP shortening (e.g., Kelsey, Soderlund, & Arthur, 2004). However, such tasks induce different motivational states, including fear and anxiety. As a result, β-adrenergic cardiac reactivity, the peripheral mechanism of PEP change (see Sherwood et al., 1986), is likely effected through other brain systems depending on task type (see, e.g., Pribram & McGuinness, 1975). This illustrates why stimulus conditions must be chosen carefully if one wishes to interpret the neural origin(s) of reactivity in any peripheral or central nervous system measure (Beauchaine, 2009b).
In a series of studies conducted over the past decade, we have found that PEP reactivity or no PEP reactivity to incentives among preschoolers with ADHD (Crowell et al., 2006), and among both middle schoolers and adolescents with ADHD and conduct problems (Beauchaine et al., 2007, 2001; Crowell et al., 2006, 2005; Hastings et al., 2008; Porges, 2007, 2001; Rottenberg, 2007; Rottenberg, Salomon, Gross, & Gotlib, 2005; Rottenberg, Wilhelm, Gross, & Gotlib, 2002; Thayer, Friedman, & Borkovec, 1996; Vasey, Crowell, Beauchaine, Mead, & Gatzke-Kopp, 2009). As reviewed elsewhere, low-baseline RSA and/or excessive RSA withdrawal in response to emotionally evocative stimuli have been linked to conduct problems, trait hostility, eating disorders, anxiety disorders, depression, and panic—among other adverse outcomes (see Beauchaine, 2001).

In our own work, we have found consistent reductions in resting RSA and excessive RSA reactivity (i.e., withdrawal) to various social and emotional challenges among children and adolescents with ADHD and other externalizing behaviors (Beauchaine, 2002; Beauchaine, Hong, & Marsh, 2008; Beauchaine et al., 2007, 2001; Marsh, Beauchaine, & Williams, 2008). In contrast, numerous studies indicate that high-resting RSA marks resilience to psychopathology in adverse rearing contexts, including those characterized by interparental conflict (Katz & Gottman, 1995), heavy parental drinking (El-Sheikh, 2005), divorce (El-Sheikh, Harger, & Whitson, 2001), and maternal depression (Shannon, Beauchaine, Brenner, Neuhau, & Gatzke-Kopp, 2007). Children with low-RSA and/or excessive RSA withdrawal might benefit less from treatment for at least three reasons. First, the experience of associated negative emotions such as anxiety and anger might interfere with learning and acquisition of alternative coping strategies. Second, low-baseline RSA and excessive RSA withdrawal to behavioral challenge—both of which predict poor ER—are associated with sustained attention difficulties (see Beauchaine, 2001; Sues, Porges, & Pflude, 1994), which might also interfere with learning and acquisition of alternative coping strategies. Third, low-RSA and excessive RSA reactivity are associated with deficiencies in social affiliation (see Beauchaine et al., 2007; Porges, 1995), which might interfere with acquisition of prosocial skills, a target of many interventions. Accordingly, we hypothesized that higher resting RSA and less RSA withdrawal in response to behavioral challenge would predict greater improvement in ER and social competence following treatment among preschoolers with ADHD.

Method

In this study, we describe links between patterns of cardiovascular responding and maternal reports of treatment outcome among 99 children, ages 4–6, who participated in a randomized controlled trial evaluating the effectiveness of the Incredible Years (IY) parent and child training programs for preschoolers with the hyperactive/impulsive and combined subtypes of ADHD. All study procedures were approved by the University of Washington Institutional Review Board, and parental consent was obtained. Immediate posttreatment and 1-year follow-up outcomes for the intervention have been reported elsewhere (Webster-Stratton, Reid, & Beauchaine, 2011, 2012). In brief, significant intervention effects were observed immediately posttreatment for both maternal and paternal reports of a wide range of externalizing behaviors, including hyperactivity, inattention, oppositionality, aggression, ER, and social competence. Improvements in externalizing behavior and social competence were also reported by teachers. Almost all of these effects were maintained at 1-year follow-up. Below we
evaluate whether baseline PEP, PEP reactivity to incentives, baseline RSA, and/or RSA reactivity during behavioral challenge—all collected prior to the intervention—predict improvements in mother reports of externalizing behavior, emotion regulation, inattention, and/or hyperactivity.

**Participants**

Children enrolled in the intervention included 99 preschoolers, ages 4–6 years, who were diagnosed with either the hyperactive/impulsive or combined subtype of ADHD. Participants were assigned randomly to either (a) an immediate intervention condition \((n = 49)\) or (b) a delayed (waitlist control) intervention condition \((n = 50)\), described below. For purposes of this study, participants were aggregated into a single group for analysis. Between-group comparisons of intervention and waitlist participants across 136 pre- to postoutcome measures yielded only 10 statistically significant differences \((7\%; \text{ about that expected by chance}), \) with an average effect size of \(d = .04\). Combining the groups was therefore justifiable.

Participants were recruited with the help of teachers and school counselors at local preschools and elementary schools, pediatricians, and mental health professionals, and through ads placed in family/parent-focused community publications. Parents were invited to call the lab if their child had been diagnosed with ADHD previously, or showed very high levels of hyperactive and/or impulsive behaviors. In an initial phone screen, a trained research assistant explained requirements of the study \((\text{e.g., random assignment to immediate treatment or waitlist condition, no medication for the duration of the study, length of intervention, no autism diagnosis, etc.})\). In total, 204 parents inquired. Among these, 156 felt their child might be eligible and elected to continue with a detailed phone screen. These parents completed a structured telephone interview with a trained clinician, which included portions of the Child Symptom Inventory \((\text{CSI}; \text{Gadow} \& \text{Sprafkin, 1997})\) and the Child Behavior Checklist \((\text{CBCL}; \text{Achenbach} \& \text{Edelbrock, 1991})\).

Among the 156 families who completed the phone screen, 103 had a child who met the following inclusion criteria: (a) scored \(\geq 95\)th percentile on the CBCL attention problems scale, \(\text{b) metDiagnostically and Statistical Information of Mental Disorders, fourth \text{Diagnosis and Statistical Information of Mental Disorders, fourth edition (DSM–IV) criteria for the hyperactive/impulsive or combined subtype of ADHD on the CSI, and (c) were not taking medication to treat ADHD. These families were scheduled for an initial clinic visit at which parents were administered the Diagnostic Interview Schedule for Children \((\text{DISC}; \text{Shaffer, Fisher, Lucas, Mina, \& Schwab-Stone, 2000})\), ADHD module. Of the 103 parents interviewed with the DISC, 99 had a child who met criteria for the hyperactive/impulsive or combined subtype of ADHD and were enrolled in the study. Among these children, 48 also met criteria for ODD. However, because no significant correlations were observed between continuous ODD symptom counts and any of the cardiac measures \((\text{all } r \leq .09, \text{ all } p s \geq .55)\), ODD was not included as a covariate in any of the analyses.

Eighty \((81\%)\) of the children provided scoreable psychophysiological data. Of the 19 participants who did not provide data, nine did not show up for their psychophysiological assessment \((\text{described below}), \) and 10 were lost due to problems with psychophysiological recording or excessive movement. These 19 participants did not differ at intake from the remainder of the sample on any of the psychopathology measures reported below \((\text{all } F_s \leq 0.47, \text{ all } p s \geq .50)\). Nevertheless, missing psychophysiological data were imputed in SPSS 20, following recommendations set forth by Graham \((2009)\).

**Interventions**

**Immediate intervention condition.** Those enrolled in the immediate intervention condition received the IY parent and child training programs directly following baseline assessment. The IY parent program has proved effective in reducing conduct problems among children, both in the United States and Europe \((\text{e.g., Beauchaine, Webster-Stratton, \& Reid, 2005; Drugli \& Larsson, 2006; Reid, Webster-Stratton, \& Beauchaine, 2001; Scott, Spender, Doolan, Jacobs, \& Aspland, 2001; Webster-Stratton \& Reid, 2010})\). The IY Dinosaur school child program is effective in increasing children’s conflict management and cognitive problem solving, and in reducing their aggression in the classroom \((\text{Webster-Stratton \& Hammond, 1997; Webster-Stratton, Reid, \& Hammond, 2004})\). In the current study, the IY parent intervention included 20 weekly 2-hr sessions conducted with six families per group. The newest versions of the IY preschool parent and child curricula \((2008 \text{ revision})\) were offered. This version includes new material focusing on academic persistence, social and emotional coaching, establishing predictable household routines and schedules, ER strategies, and teaching children to problem solve. The program includes vignettes showing children with ADHD in order to enhance parents’ understanding of (a) how to respond effectively to impulsive children and (b) children’s developmental levels and temperaments. Additional sessions from the IY advance parent curriculum included problem solving between adults and teachers and strategies to build family interpersonal support, reduce depression, and manage anger.

The IY Dinosaur training program was held concurrently with the parent program. Topics included following group rules, identifying/expressing feelings, problem solving, anger management, friendship skills, and teamwork. Each 2-hr session consisted of three short circle times and three to four planned activities to reinforce concepts. Therapists used coaching methods during unstructured play times to encourage appropriate peer interactions and targeted social and emotional skills. See Webster-Stratton \((2007), \text{Webster-Stratton and Reid (2008), and Webster-Stratton et al. (2011})\) for more detailed information regarding the use of these two interventions for children with ADHD, and for details about fidelity monitoring.

**Waitlist control condition.** All waitlist control families received the IY intervention following a postassessment comparison with the immediate treatment group. Parents in the waitlist condition received 10 sessions of treatment \((\text{about half the dose received by parents in the immediate condition})\). Children in both conditions received an equivalent treatment dose of about 40 hr \((\text{see Webster-Stratton et al., 2012})\). As noted above, IY and waitlist families were combined into a single group for all analyses. For both groups, baseline assessments were conducted before the immediate intervention condition. In contrast, posttreatment assessments were conducted immediately after each group received their intervention \((\text{as opposed to before and after the immediate treatment group received their intervention})\). Although questions regarding poten-
Psychopathology Measures

Psychopathology measures included in this study comprise a subset of those reported in our analysis of posttreatment behavioral outcomes (see Webster-Stratton et al., 2011). Our choice of measures was driven by four considerations. First, we selected constructs, including aggression, ER, prosocial behavior, and hyperactivity, for which pre- to posttreatment improvement was observed. It would make little sense to examine physiological predictors of treatment outcome for behaviors that did not change following treatment. Second, we chose constructs that were linked theoretically to traits underlying aberrant reward responding (e.g., problem behaviors) and emotion regulation/dysregulation (e.g., prosocial behavior), consistent with the literature review presented above. Third, we restricted our analyses to six outcome measures in order to control—at least in part—for inflation of familywise error. Finally, we included mother reports only given substantially lower availability of father report data (n = 58) and associated reduction in statistical power.

The CSI (Gadow & Sprafkin, 1997). The CSI yields dimensional scores and diagnostic cutoffs for most Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM–IV–TR; American Psychiatric Association, 2000) internalizing and externalizing disorders. Both the hyperactive/impulsive and inattentive subscales were administered. In the most recent validation sample (Sprafkin, Gadow, Salisbury, Schneider, & Loney, 2002), internal consistency (coefficient α) was .91 for ADHD. As outlined above, the CSI was used for screening purposes.

The CBCL (Achenbach & Edelbrock, 1991). The CBCL, which is validated for children ages 4–16, assesses broadband internalizing and externalizing symptoms, and a number of more specific behaviors. We used the Attention Problems subscale for screening purposes (see above) and the Aggression subscale as an outcome measure of severe externalizing conduct. The CBCL has well-established norms, with coefficient α of .91 and .84 for the Aggression and Attention Problems subscales, respectively.

Eyberg Child Behavior Inventory (ECBI; Robinson, Eyberg, & Ross, 1980). The ECBI is a commonly used measure for assessing conduct problems among children ages 2–16 years. We used the Problem Behavior subscale as a second measure of more severe externalizing symptoms. Coefficient α was .94.

Conners’ Parent Rating Scale—Revised (CPRS–R; Conners, Sitarenios, Parker, & Epstein, 1998). The CPRS–R is a widely used instrument for assessing ADHD and comorbid psychopathology. For the present study, summary scores for both inattention and hyperactivity were used as outcome measures. Coefficient α for both scales exceeded .90.

Social Competence Scale (SCS; Conduct Problems Prevention Research Group, 1999a, 1999b). The SCS consists of 12 items that assess children’s prosocial behaviors (e.g., resolves peer problems, understands others, shares, is helpful, listens; α = .81) and ER (e.g., accepts things, copes with failure, thinks before acting, can calm down, controls temper; α = .80). We used the SCS as a broad index of ER capabilities.2

Cardiovascular Assessments

The psychophysiological protocol was similar to that used in our previous research assessing cardiovascular activity and reactivity among preschool children with ADHD (Crowell et al., 2006). This protocol is effective in eliciting both PEP reactivity to incentives and RSA reactivity to behavioral challenge in normal controls, and in eliciting group differences in baseline PEP and PEP reactivity among preschoolers with ADHD. Participant children and a parent (mothers in all but one case) visited the lab for a psychophysiological assessment roughly 1 week after their diagnostic interview (see above). Assessments were conducted in a separate lab session, before the intervention was delivered. The 30-min protocol was administered in a sound-attenuated room, which was monitored via microphone and closed-circuit video. Patterns of cardiac activity and reactivity were measured during a 5-min baseline, after which children played a simple matching game in which they viewed a shape (e.g., square, circle, star) projected on a large screen and pressed a corresponding button (among five) on a keyboard made specifically for preschool children. Correct responses were followed by an image of a smiley face and a tone, whereas incorrect responses were followed by a blank screen and contrasting tone. To increase the reward value of the game, we showed children a large container of toys valued at about $10 each and told them that they could choose their favorite toy if they earned enough smiley faces during the course of the game. Following completion of the task, all were given their chosen toy for “trying hard.” Parents waited in the adjacent room with the experimenter.

Next, children and their parent engaged in (a) 7 min of free play followed by (b) 7 min of a challenging block-building task that required parent–child cooperation and attentional focus. During free play, children and their parent were seated on the floor in the same room where the incentive task took place, and given a tub of assorted toys. This unstructured time was designed to encourage acclimation to the surroundings prior to block building. After the free-play session, parents were instructed to (a) retrieve a box containing 32 large foam geometric shapes, which was stored in a corner of the room; (b) dump the contents of the box on the floor; and (c) have their child to build a series of four layers of blocks, in order, one on top of the other. Each layer required that multiple blocks of various shapes be arranged exactly as shown on a figure provided to the parent. Difficulty increased with each layer. Par-

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2 As pointed out by an anonymous reviewer, the SCS is multifaceted and includes items that assess impulsivity and compliance as well as those related more directly to ER. Nevertheless, the scale was conceptualized initially as a broad index of emotion regulation. Given our previous reports using the full SCS with this sample (Webster-Stratton et al., 2011, 2012), we continue to use all items to maintain consistency.
ents were told that they could provide only instructions and that their child had to do the hands-on work. This task is difficult for 4- to 6-year-olds, and pulls for both parental and child frustration, as assessed by dyadic conflict, negative affective expression, and coercive parent–child exchanges (Beauchaine, Strassberg, Kees, & Drabick, 2002).

Cardiovascular Measures

Cardiac PEP. Sympathetic-linked (β-adrenergic) cardiac function was assessed by measuring PEP—the interval between the onset of left ventricular depolarization and ejection of blood into the aorta. Shorter intervals represent greater SNS effects (Sherwood et al., 1990; Sherwood, Allen, Obrist, & Langer, 1986). Electro- and impedance-cardiographic signals were obtained from an HIC 2004 impedance cardiograph (Chapel Hill, NC). Both waveforms were sampled at 1 kHz using the spot electrode configuration described by Qu, Zhang, Webster, and Tompkins (1986). Preecision period values were extracted by ensemble-averaging data in 30-s epochs (see Kelsey & Guethlein, 1990) using Bio-Impedance Technology’s CopWin software system, version 5.06 (Bio-Impedance Technology, Inc., 2001). All ensemble-averaged waveforms were inspected visually by trained research assistants to correctly locate the dZ/dt B-wave in cases in which the computer algorithm failed to do so.

RSA. Parasympathetic-linked cardiac function was assessed using spectral analysis, which decomposes the heart rate time series into component frequencies through Fast Fourier transformation. High-frequency heart rate variability (≥0.15 Hz) was extracted to measure RSA. Spectral densities were calculated in 30-s epochs, roughly the minimum length required for reliable assessment (Bernetson et al., 1997). As is customary, these values were normalized via natural log transformations using Nevrokard ionization 5.06 (Bio-Impedance Technology, Inc., 2001). All ensemble-averaged waveforms were sampled at 1 kHz using the spot electrode configuration described by Qu, Zhang, Webster, and Tompkins (1986). Preecision period values were extracted by ensemble-averaging data in 30-s epochs (see Kelsey & Guethlein, 1990) using Bio-Impedance Technology’s CopWin software system, version 5.06 (Bio-Impedance Technology, Inc., 2001). All ensemble-averaged waveforms were inspected visually by trained research assistants to correctly locate the dZ/dt B-wave in cases in which the computer algorithm failed to do so.

For purposes of this study, both PEP and RSA values were averaged across 30-s epochs within each condition (i.e., baseline, reward task, block building). Reactivity was computed by subtracting baseline averages from reward task and block-building averages. Thus, negative values were associated with (a) PEP shortening, indicative of increased SNS activity, and (b) RSA withdrawal, indicative of reduced PNS activity.

Results

The average age of children, 76% of whom were male, was 64.3 months (SD = 11.0). Pre- and postintervention scores on measures of psychopathology are presented in Table 1. For outcomes reported in this study, pre–post effect sizes were generally large. Further details about the sample, including information about parental education, parental marital satisfaction, parents’ contacts with the criminal justice system, and so forth, are reported in Webster-Stratton et al. (2011). Mean PEP scores at baseline were 80.5 ms (SD = 13.3), and mean PEP reactivity scores during the incentive condition were −0.8 ms (SD = 6.9). Mean RSA scores at baseline were 6.6 ms² (SD = 1.0), and mean RSA reactivity scores during block building were 1.0 ms² (SD = 1.0). Intercorrelations among variables are reported in Table 2.

Cardiac PEP

To assess prediction of treatment outcome from baseline PEP and PEP reactivity to incentives, analyses of variance (ANOVAs) were conducted in which pre–post scores on the behavioral outcome measures (e.g., CBCL aggression) served as repeated measures, and cardiovascular variables and age in months served as covariates. Including age as a covariate was necessary given normative developmental lengthening of PEP from ages 4 to 6. Missing psychophysiological data were imputed using SPSS 20. Fully conditional specification was used across 30 imputations. In these models, differential prediction of treatment response by cardiac function is carried in Behavioral Outcome × PEP interaction terms. These interactions are reported along with main effects in Table 3. Contrary to our hypotheses, significant interactions were not found for either PEP activity or reactivity in predicting aggression or problem behaviors. However, main effects of both PEP activity and reactivity on CBCL aggression and ECBI problem behavior were found (all Fs ≥ 5.87, all ps ≤ .05, all ηp² ≥ .07). Thus, although all children tended to show improvement from pre- to posttreatment, those who exhibited lengthened cardiac PEP at rest and reduced PEP reactivity to incentives scored higher on measures of conduct problems and aggression both before and

Table 1

Descriptive Statistics

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<th>Variable</th>
<th>Pre</th>
<th>Post</th>
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<th>ηp²</th>
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<td>Severe conduct</td>
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<tr>
<td>CBCL aggression (T)</td>
<td>66.6 (9.7)</td>
<td>61.9 (9.4)</td>
<td>29.1</td>
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<td>ECBI problem behavior</td>
<td>21.7 (6.6)</td>
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<td>.50</td>
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<td>SCS emotion regulation</td>
<td>1.9 (0.5)</td>
<td>2.4 (0.6)</td>
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<td>&lt;.001</td>
<td>.44</td>
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<tr>
<td>SCS prosocial</td>
<td>2.7 (0.6)</td>
<td>3.2 (0.7)</td>
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<td>.42</td>
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<td>CPRS–R inattention (T)</td>
<td>69.3 (13.1)</td>
<td>64.9 (12.3)</td>
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<td>CPRS–R hyperactive (T)</td>
<td>74.5 (8.4)</td>
<td>67.8 (10.7)</td>
<td>39.7</td>
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<td>.32</td>
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after treatment. The latter finding is illustrated in Figure 1, where
we plot Eyberg problem behavior scores at pretreatment and posttreatment for those who scored > 1.0 SD above the sample mean on PEP reactivity, and those who scored > 1.0 SD below the sample mean on PEP reactivity.

**RSA**

To assess prediction of treatment outcome from baseline RSA and RSA during block building, ANOVAs were conducted in which pre–post scores on the behavioral outcome measures (e.g., prosocial behavior) served as repeated measures, and cardiovascular variables and age in months served as covariates. Including age as a covariate was necessary given normative developmental increases in RSA from ages 4 to 6. In these models, differential prediction of treatment response by cardiac function is carried in Behavioral Outcome × RSA interaction terms. These interactions are reported along with main effects in Table 3. Contrary to our hypotheses, significant interactions were not found for either RSA activity or reactivity in predicting ER or prosocial behavior. However, main effects of both RSA activity and reactivity on SCS prosocial behavior, and of RSA reactivity on ER, were found (all F's ≥ 4.16, all ps ≤ .05, all η² ≥ .05). These main effects indicate that despite samplewide improvement in ER and prosocial behavior, (a) children who exhibited lower baseline RSA and greater RSA withdrawal scored lower on prosocial behavior both before and after treatment and (b) children who exhibited greater RSA withdrawal scored lower on ER both before and after treatment.

Finally, a significant RSA Reactivity × CPRS-R Inattention interaction was observed. As depicted in Figure 2, although greater RSA withdrawal during block building was associated with more

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<tbody>
<tr>
<td>1. RSA baseline</td>
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<td>2. RSA change</td>
<td>.31**</td>
<td>—</td>
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<td>3. PEP baseline</td>
<td>.19</td>
<td>.17</td>
<td>—</td>
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<td>4. PEP change</td>
<td>.14</td>
<td>.22</td>
<td>.54**</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>5. CBCL aggression</td>
<td>— .04</td>
<td>— .16</td>
<td>— .12</td>
<td>— .20</td>
<td>—</td>
<td>—</td>
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<td>6. ECBI problem behavior</td>
<td>— .03</td>
<td>— .06</td>
<td>— .25</td>
<td>— .26</td>
<td>.45**</td>
<td>—</td>
<td>—</td>
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<tr>
<td>7. SCS emotion regulation</td>
<td>— .29**</td>
<td>— .11</td>
<td>— .00</td>
<td>— .02</td>
<td>— .37**</td>
<td>— .33**</td>
<td>—</td>
<td>—</td>
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<tr>
<td>8. SCS prosocial</td>
<td>.19</td>
<td>.07</td>
<td>.11</td>
<td>— .01</td>
<td>— .32**</td>
<td>— .28**</td>
<td>.52**</td>
<td>—</td>
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<tr>
<td>9. CPRS-R inattentive</td>
<td>.01</td>
<td>— .07</td>
<td>— .01</td>
<td>— .03</td>
<td>.19</td>
<td>.24*</td>
<td>— .13</td>
<td>— .20*</td>
<td>—</td>
<td>—</td>
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<tr>
<td>10. CPRS-R hyperactive</td>
<td>.03</td>
<td>.03</td>
<td>— .06</td>
<td>— .11</td>
<td>.40**</td>
<td>.32**</td>
<td>— .12</td>
<td>— .17</td>
<td>.40**</td>
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</table>

*Note.* RSA = respiratory sinus arrhythmia; PEP = preejection period; CBCL = Child Behavior Checklist (Achenbach & Edelbrock, 1991); ECBI = Eyberg Child Behavior Inventory (Robinson, Eyberg, & Ross, 1980); SCS = Social Competence Scale–Parent Report (Conduct Problems Prevention Research Group, 1999a, 1999b); CPRS–R = Conners’ Parent Rating Scale—Revised (Conners, 1998; Conners, Sitarenios, Parker, & Epstein, 1998). "p ≤ .05. **p ≤ .01.
attention problems at pretreatment, this difference disappeared by posttreatment, when samplewide improvement was observed.

Discussion

In this study, we evaluated SNS- and PNS-linked cardiac activity and reactivity as predictors of improvement in conduct problems and ER, respectively, among preschoolers who were treated for ADHD with an empirically supported behavioral intervention. Contrary to our expectations, neither PEP at rest nor PEP reactivity to incentives predicted improvements in aggression or conduct problems. However, main effects of both PEP activity and reactivity indicated that children with lengthened PEP at baseline and less PEP reactivity to incentives scored higher on measures of aggression and problem behavior both at pretreatment and posttreatment, even though they improved as much as their peers. On the one hand, this finding is encouraging because it indicates that current interventions are effective in reducing problem behaviors among preschool children who may be vulnerable to developing especially severe externalizing behaviors as they mature (see Beauchaine & Gatzke-Kopp, 2012). On the other hand, our findings present a treatment development challenge. As Brestan and Eyberg (1998) noted 15 years ago, we must address questions such as: “For whom does this treatment work?” and “When is this treatment not enough?” In the present case, the intervention we provided may not be enough for children with aberrant PEP responding, who continue to suffer from more behavioral difficulties than their peers following treatment.

Although individual differences in baseline PEP can arise from many sources (e.g., preload, afterload, total peripheral resistance) and are therefore difficult to interpret, PEP reactivity to behavioral challenge is effected almost exclusively through the SNS (Sherwood et al., 1990). As outlined above, reduced SNS reactivity to incentives likely marks deficient mesolimbic DA responding, which is observed consistently among older children with ADHD and other externalizing behaviors (Durston, 2003; Durston et al., 2003; Scheres et al., 2007). Children in our study were required to remain medication free throughout the intervention, which enabled us to attribute treatment effects—which were generally large—to the parent and child programs (see Webster-Stratton et al., 2011). However, despite these large effect sizes, individual variation in treatment response was observed. One question that emerges is whether children low in PEP activity and/or reactivity might have benefitted more from combined behavioral and medication management than from behavioral management alone. Psychostimulants normalize deficiencies in midbrain DA responding among children with ADHD (e.g., Rubia et al., 2011; Vaidya et al., 1998) and increase cardiac output through SNS mechanisms (see, e.g., Gilden, 2012). Future research is required to test whether children with ADHD who are low in PEP and/or PEP reactivity may benefit more from combined forms of treatment.

We are the first research group to evaluate associations between treatment response and SNS-linked cardiac function among children at any age. Importantly, however, PEP reactivity to incentives also predicts initiation and escalation of alcohol and other substance use among middle schoolers with conduct problems (Brenner & Beauchaine, 2011). Taken together, these findings suggest that PEP responding to reward may mark vulnerability to progression along the externalizing spectrum among children with ADHD, and may therefore be a useful biomarker in future research.

In addition to the PEP findings summarized above, children with low-baseline RSA scored lower on prosocial behavior at both pre- and posttreatment, and children who exhibited RSA withdrawal...
during block building exhibited poorer ER and scored lower on prosocial behavior than their peers at both pre- and posttreatment. As with the PEP data, this occurred despite sample-wide improvements from pre- to posttreatment in prosocial behavior and ER. These findings add to a large body of research linking individual differences in RSA to competent ER and social affiliation (e.g., Beauchaine, 2001; Beauchaine et al., 2007, in press; Porges, 1995, 2007). As outlined above, high-baseline RSA marks resilience to psychopathology in adverse rearing contexts, including those characterized by interparental conflict (Katz & Gottman, 1995), heavy parental drinking (El-Sheikh, 2005), divorce (El-Sheikh et al., 2001), and maternal depression (Shannon et al., 2007). Children with higher resting RSA are also more empathic toward others and more socially competent than their peers (Eisenberg et al., 1995; Fabes, Eisenberg, Karbon, Troyer, & Switzer, 1994). Once again, however, the issue of “When is this treatment not enough?” arises.

In considering this question, several findings are worth noting. First, behavioral genetics studies indicate that ER is affected considerably by environmental influences (e.g., Kupper et al., 2004). Second, excessive RSA reactivity is usually observed among externalizing children who have progressed further along the externalizing spectrum than children in the current sample (e.g., Beauchaine et al., 2001; Beauchaine & McNulty, in press). Third, RSA reactivity appears to develop over time as emotional lability and associated ER deficiencies are socialized through repeated negative reinforcement processes within families that occur thousands of times across development (see Beauchaine et al., 2007, 2009; Crowell et al., 2006, in press). This set of observations suggests that increasing the dose of ER training in our intervention might improve ER capabilities among children who exhibit low RSA and excessive RSA withdrawal while interacting with their parents, as they did in the block-building task. Future research should address this question.

As in our previous research (see Beauchaine & Gatzke-Kopp, 2012; Beauchaine et al., 2007), associations of outcomes with PEP and RSA were specific to aggression/conduct problems and ER/prosocial behavior, respectively. Even though predictive effects were not found, this is consistent with theoretical expectations given the CNS and peripheral nervous system functions marked by each measure. Nevertheless, one limitation of our study is that we did not control for the inflated probability of Type I error associated with multiple statistical tests. Had we applied such a correction, none of our findings would have been significant. Yet, if our findings were attributable to chance, it is highly unlikely that significant PEP and RSA effects would be specific to theoretically relevant outcomes.

The only other significant finding was an interaction between RSA withdrawal and the intervention in predicting inattention scores. Although children who exhibited greater RSA withdrawal scored higher on inattention at pretest, no such difference was observed at posttest. Interestingly, both resting RSA and RSA withdrawal have been linked to attentional capacity in previous studies (see Beauchaine 2001; Suess et al., 1994). Our findings suggest that the intervention was especially helpful in improving inattention among more vulnerable children. However, we are reluctant to interpret the interaction further given that it was not predicted.

PEP and RSA were unrelated to any other changes in hyperactivity or inattention. For RSA, this is not surprising, because ER and impulsivity are separate constructs with distinct neural substrates, as reviewed above (see Beauchaine & Gatzke-Kopp, 2012; Beauchaine & McNulty, in press). In contrast, given our hypothesis that PEP reactivity to incentives marks central DA responding—a neural substrate of trait impulsivity—we might have expected to find links between PEP reactivity and improvements in hyperactivity/impulsivity. However, three considerations should be noted. First, previous studies have revealed stronger associations between deficient PEP responding and conduct problems than between deficient PEP responding and hyperactivity/impulsivity (Beauchaine et al., 2001). Second, participants were selected on the basis of a very restricted range of hyperactivity/impulsivity scores, whereas aggression and conduct problem scores were free to vary. Thus, the sample was more homogeneous on hyperactivity/impulsivity than on aggression/conduct problems, which may have affected statistical power for tests involving the latter. Indeed, effect sizes for most measures of change in aggression/conduct problems were larger than effect sizes for hyperactivity/impulsivity (Webster-Stratton et al., 2011). Thus, there was a larger range of difference scores in aggression/conduct problems for the PEP variables to map onto. Smaller effect sizes for changes in hyperactivity/impulsivity are unsurprising given that ADHD is largely heritable (e.g., Willcutt, in press), whereas aggression and conduct problems are affected more by socialization mechanisms (see, e.g., Beauchaine et al., 2010, 2009; Lynam et al., 2000), and may therefore be more responsive to behavioral interventions.

In addition, all effect sizes for PEP and RSA in predicting treatment outcome were modest. Here, it is important to note that all children in the sample met full criteria for the hyperactive/impulsive or combined subtype of ADHD on the DISC, and scored at or above the 95th percentile on attention problems on the CBCL. Such children consistently show reduced tonic PEP at baseline, lower PEP reactivity to incentives, and attenuated resting RSA compared with normal controls (e.g., Beauchaine et al., 2001; Beauchaine, Hong, & Marsh, 2008; Crowell et al., 2006). Thus, even among a group of children likely characterized by restricted ranges on all cardiovascular measures, individual differences were related to theoretically relevant and important functional outcomes. Yet another limitation concerns the role of parental behavior in affecting children’s physiological responses to the block-building task. Coercive exchanges, for example, may have affected children’s autonomic functioning; yet, we did not assess such exchanges in this article.

We did not examine whether the intervention altered posttreatment cardiac function. Following from the rationale presented in the introduction of this article, such a finding might be especially plausible for RSA, which shows sizable environmental effects in behavioral genetics studies (Kupper et al., 2004). Future research should determine whether relatively brief behavioral interventions are sufficient to effect such change—with associated improvements in ER—or whether parasympathetic functioning requires longer time intervals to be altered by familial and extrafamilial influences.

Finally, our analyses were restricted to mother reports. As noted above, the number of fathers who participated was much smaller than the number of mothers, so power was low. We did, however, collect teacher report data across a number of outcomes. We did not include these data because teacher reports on variables that are linked theoretically to the PEP (severe conduct) and RSA (ER,
prosocial behavior) either did not show significant treatment effects in the original RCT (Webster-Stratton et al., 2011) or were not assessed. For example, we did not have teacher report measures of ER or prosocial behavior that paralleled the SCS. Including variables for which treatment effects were not found or variables that are not linked theoretically to psychophysiological responding makes little sense in the context of examining physiological predictors of treatment response. Notably, however, data from multiple informants are especially important when there is reason to suspect that reporting bias among one or more informants is affecting the validity of results. In the present case, mothers could not observe their child’s psychophysiological response patterns, so links between maternal reports of child behavior and psychophysiology cannot be attributable to response bias. This course of doing things does not explain the discrepant results observed. Nonetheless, a lurking reason to suspect that reporting bias among one or more informants is affecting the validity of results. In the present case, mothers could not observe their child’s psychophysiological response patterns, so links between maternal reports of child behavior and psychophysiology cannot be attributable to response bias. This course of doing things does not explain the discrepant results observed. Nonetheless, a lurking reason to suspect that reporting bias among one or more informants is affecting the validity of results.

Limitations aside, this is the first study to evaluate associations between treatment outcome and cardiovascular measures among preschool children with ADHD. Our findings indicate that children who are hyperactive/impulsive and demonstrate heightened PEP at rest, PEP nonreactivity to incentives, and/or low-resting RSA score higher on several measures of psychopathology at pretreatment, PEP nonreactivity to incentives, and/or low-resting RSA score higher on several measures of psychopathology at pretreatment, and that even though they improve as much as their peers, they still score higher at posttreatment. As noted elsewhere (Beachaine et al., 2005; Breslan & Eyberg, 1998; Nock, 2003; Owens et al., 2003), developing effective treatments is not the only objective of intervention research. Once the efficacy of an intervention is established, mechanisms through which treatment effects are exerted must be elucidated, and factors that alter efficiency of the intervention within different subsamples must be identified if we wish to help the greatest number of children (see also Beachaine, Neuhaus, et al., 2008). The research presented in this article represents a small step forward in identifying child-level variables that are associated with treatment outcome. We hope future treatment–outcome research will extend our findings by developing interventions that target children who appear to be neurobiologically vulnerable to continued behavioral difficulties following treatment.

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PHYSIOLOGICAL MARKERS OF ADHD TREATMENT RESPONSE

491


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