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Comorbid Depression and Heart Rate Variability as Predictors of Aggressive and Hyperactive Symptom Responsiveness During Inpatient Treatment of Conduct-Disordered, ADHD Boys

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The primary objective of the present study was to assess the utility of (1) comorbid depression and (2) parasympathetic influence on cardiac function as markers for treatment response among aggressive preadolescent males. Inpatient records of 53 patients with conduct disorder and attention deficit hyperactivity disorder (17 with a comorbid depressive disorder) were examined, including an intake electrocardiogram and daily tallies of several indices of aggressive behavior across 3 weeks of stay. The relations of comorbid depression, heart rate variability, and residualized heart rate (primarily of sympathetic origin) to treatment response were assessed through analyses of linear growth functions. Significant vagal tone by diagnostic status interactions were obtained for both frequency and duration indices of aggression, whereby nondepressed patients with high vagal tone deteriorated and depressed patients with high vagal tone improved during hospitalization. No such relation was found for attention deficit hyperactivity disorder symptoms. Patients in the comorbid group also exhibited greater heart rate variability than their nondepressed counterparts. Furthermore, residualized heart rate was predictive of maternal substance use and paternal incarcerations. These findings suggest complex relations among treatment response, comorbid depression, and emotion regulation in male preadolescents with severe behavior disorders. Additionally, the differen-

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tial prediction afforded by vagal tone and residualized heart rate underscores the importance of assessing both parasympathetic and sympathetic indices of cardiac function as distinct physiological markers. Aggr. Behav. 26:425–441, 2000.

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INTRODUCTION

The stability and resistance to treatment of antisocial behavior are well documented. When conduct-disordered (CD) boys become adults, they are arrested and imprisoned more often, experience more marital and occupational difficulties, and abuse alcohol and drugs more frequently than do controls [Robins, 1966; 1978]. Cases accompanied by attention deficit hyperactivity disorder (ADHD) are particularly refractory to treatment and may represent a more virulent subtype of CD characterized by a strong genetic loading and maximal risk for future antisocial behavior and psychopathy [Edelbrock et al., 1995; Faraone et al., 1997; Lynam, 1996].

In clinical samples, the proportion of CD cases characterized by comorbid ADHD often approaches 70% [Klein et al., 1997; Stewart et al., 1981]. This is particularly likely at inpatient settings, where referrals are often made after alternative intervention strategies have failed. Thus, many boys presenting for inpatient treatment of aggression have a particularly poor prognosis. Nevertheless, some cases do respond, implying that current intervention strategies are adequate for a subset of patients. Identifying trait or state markers that differentiate responders from nonresponders is thus an important line of inquiry toward formulating more effective treatment protocols and because it may ultimately provide for a better understanding of subtypes of CD [Vitiello and Stoff, 1997].

One potential indicator of positive short-term treatment response is a comorbid depressive disorder, which may suggest a level of emotional responsiveness that is not characteristic of many CD cases. Evolutionary theorists have suggested that emotions provide motivation for behavioral coping in response to both short- and long-term challenges and to organize cognitive resources toward facilitating coping efforts [Clark and Watson, 1994; Levenson, 1994]. Thus, patients who experience a more variable range of emotions might also be expected to exhibit a broader repertoire of behavioral responses to intervention efforts.

Consistent with this interpretation, research on undersocialized aggressive conduct disorder (UACD), as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, third edition* (*DSM-III*) [American Psychiatric Association, 1980], has suggested that this subgroup, characterized by a lack of emotional responsiveness and empathy, is particularly recalcitrant [Quay, 1993]. Moreover, undersocialized aggressive CD samples are more behaviorally disinhibited [Daugherty and Quay, 1991; Shapiro et al., 1988] and less socially competent [Henn et al., 1980] and exhibit delinquent characteristics across a greater variety of situations [see Moffitt, 1993] than do other CD groups. Indeed, CD children selected for the callous and unemotional traits characteristic of adult psychopathy exhibit a greater variety and frequency of delinquent behaviors than do CD children without such traits [Christian et al., 1997]. Furthermore, nonanxious CD children are more likely to ignore punishment cues than are those with comorbid anxiety symptoms [O'Brien and Frick, 1996]. Thus, restricted emotional responsiveness seems to be a negative prognostic indicator for children presenting with CD.

Empirical support for a treatment response-depression relation has been offered by Puig-Antich [1982], who reported reductions in CD symptoms in a sample of prepubertal males with comorbid depressive disorders. These results should be interpreted cautiously, however, because no pure CD control group was included, and because contrary results have been reported elsewhere, albeit in older samples [Harrington et al., 1991]. Thus, further inquiry into the relation between comorbid depression and treatment response is warranted, particularly given the finding that the incidence of depression is higher in delinquent samples than in the population at large [e.g., Kashani et al., 1980].

Differences in emotional responsiveness may also be reflected in measures of peripheral autonomic nervous system activity. Heart rate variability (HRV), an index of parasympathetic influence on cardiac functioning [Hayano et al., 1991; Katona and Jih, 1975], is typically reduced in CD cases [Mezzacappa et al., 1996; Pine et al., 1996a]. Moreover, HRV is positively correlated with empathy [Fabes et al., 1993], emotional expressiveness [Fabes et al., 1994], social competence [Eisenberg et al., 1995], and sustained attention [Suess et al., 1994] in normative samples. Although no studies have been reported comparing groups with and without affective disorders, shifts in mood state toward sadness have been associated with increased HRV [Miller and Wood, 1997]. Taken together, these findings suggest the possibility that reductions in HRV characteristic of CD may be attenuated in patients with a comorbid depression.

Thus, the primary objective of the present study was to explore the relations among treatment response, comorbid depression, and HRV in a sample of mixed CD and ADHD inpatient males. As previously noted, this group represents most inpatient CD referrals [Klein et al., 1997; Stewart et al., 1981] and is at particular risk for negative treatment outcome [Edelbrock et al., 1995; Faraone et al., 1997; Lynam, 1996]. Nevertheless, it was hypothesized that both comorbid depression and HRV would predict positive treatment response during the course of an inpatient stay and that comorbid depression would be associated with increased HRV.

A secondary objective was to examine the relation between sympathetic nervous system (SNS) activity in the inpatient participants and variables indicative of parental disinhibition (i.e., antisocial behavior and substance use) that are known to predict CD and ADHD [Cadoret et al., 1983, 1995; Slutske et al., 1997]. These parental characteristics contribute common genetic risk for CD [Slutske et al., 1998] and exert considerable environmental influence on child behavior [Cadoret et al., 1997]. Furthermore, evidence suggests that both sources of influence affect noradrenergic and serotonergic functioning [Ciaranello and Boehme, 1981; Pine et al., 1996b; Rogeness, 1991; Rogeness et al., 1987], resulting in reduced behavioral inhibition [Gray, 1987a; Rogeness et al., 1992].

According to Gray [1982a, b, 1987a, b], such disinhibition results from an imbalance between two actively opposed motivational subsystems, the behavioral activation system (BAS) and the behavioral inhibition system (BIS). The BAS subserves appetitive motivational functions, governing approach and active avoidance. Thus, the system is responsible for maximizing rewards (approach behavior) and for minimizing punishments in situations where behavioral responses are required (active avoidance). Gray [1987a] hypothesized that neural mediation of the BAS is rooted in the dopaminergic pathway, including the ventral tegmental area, the nucleus accumbens, and the ventral striatum.

The BIS subserves an aversive motivational function, controlling passive avoidance and extinction. Through the production of fear and anxiety, the system actively inhibits appetitive behaviors when aversive consequences are anticipated. Gray suggested that neural mediation of the BIS is rooted in both the serotonergic projections of the raphe nucleus and the noradrenergic projections of the locus ceruleus. Note that this conceptualization is consistent with findings of serotonergic dysfunction in CD [Birmaher et al., 1990; Kruesi et al., 1990] and with findings of noradrenergic dysfunction in both CD [Rogeness et al., 1982, 1986, 1988] and ADHD [Shekim et al., 1982, 1987; Yu-cun and Yu-feng, 1984]. Disinhibition in both of these disorders is proposed to result from a BAS/BIS profile favoring behavioral activation [Fowles, 1980, 1988; Quay, 1993; Rogeness et al., 1992]. Thus, impulsivity occurs because the BAS operates relatively unopposed.

Psychophysiological evidence suggests that BAS and BIS activity are reflected in the periphery in measures of SNS functioning. Findings reported by Fowles [1980, 1988], e.g., suggest that BAS activity is reflected in heart rate changes.[1] Furthermore, the increases in cardiac output required of behavioral activation are facilitated in large part by changes in the contractile force of the left ventricle, which are mediated exclusively by the sympathetic branch of the autonomic nervous system [see Sherwood et al., 1990].

To summarize, both genetic and environmental effects of parental antisocial behavior and substance abuse have been consistently tied to CD and to dysregulation in neurochemical systems that are reputed substrates of disinhibited behavior. Psychophysiological evidence suggests that this dysregulation is mediated at the peripheral level by the SNS. Following from these findings, an additional hypothesis of this study was that parental substance use and antisocial behavior would be related to measures of sympathetic influence on cardiac activity in their offspring.

METHODS

Participants

Institutional review board approval was obtained for examining the charts of patients admitted to an inpatient child psychiatry unit between 1987 and 1994. These children had been referred to the inpatient facility from county clinics and social service agencies and by private providers within the community. Because HRV-behavioral competence relations have not been consistently demonstrated in female samples [Eisenberg et al., 1995, 1996], and because only three females met the inclusion criteria outlined below, only the charts of males were retained. Male patients were selected who were 12 years or younger at admission (range, 4.8–12.0 years), who remained on the inpatient unit for a minimum of 21 days, and who met *DSM-III-R* criteria for both ADHD and CD. Age 12 years was used as a cutoff point to reduce the impact of potential developmental differences in cardiac activity between child and adolescent participants. Because potential participants were drawn from a child inpatient facility, few were rejected from the study based on this age criterion. Current diagnoses were rendered within the

[1]Fowles [1980, 1988] also asserted that BIS functioning can be indexed directly by assessing electrodermal responding, which is mediated peripherally by cholinergic fibers of the SNS [see Fowles, 1986]. Although the assessment of electrodermal responding was of interest given the hypotheses set forth in this paper, the retrospective nature of our investigation precluded us from including the index.

first week of treatment through consensus of the attending psychiatrist and unit psychologist using a validated checklist of *DSM-III-R* symptoms (the Child Symptom Inventory) [Grayson and Carlson, 1991]. Children who met criteria for both disorders (n = 53) were included in the study.[2] Sources of information used to assess symptoms included behavioral observation during the first week of stay, interviews with parents, and relevant items from two validated rating scales completed daily by unit nurses and school teachers. Rating scales included were the Teacher Self Control Rating Scale [Humphrey, 1982], which assesses impulsivity, and the Attention Deficit Disorder-Hyperactivity Comprehensive Teacher Rating Scale (ACTeRS) [Ullmann et al., 1984], which assesses attention problems and hyperactivity. Additionally, charts were screened for the presence or absence of a current major depressive episode or major depressive disorder. As with CD and ADHD, diagnoses were rendered within the first week of treatment through consensus of the attending psychiatrist and unit psychologist based on *DSM-III-R* criteria, using the Child Symptom Inventory. Sources of information used to assess symptoms of depression included behavioral observation during the first week of stay, interviews with parents, and items from the Children's Depression Rating Scale [Poznanski et al., 1983].[3] Of the 53 CD/ADHD participants, 17 also met *DSM-III-R* criteria for depression and were assigned to the depressed group. Those who reported symptoms of a psychotic disorder or schizophrenia were excluded from the study. Because many of the children were administered either a tricyclic antidepressant (3 nondepressed, 4 depressed) or a stimulant (26 nondepressed, 8 depressed) during the course of their stay, this information was also extracted, providing for statistical control of medication effects on treatment response. Demographic and descriptive characteristics of the sample are reported in Table I.

Treatment

Each participant received the standard multidisciplinary treatment in place on the inpatient unit. Included were (1) 6 hr of school led by state-certified teachers and teacher assistants, at a 5:1:1 ratio (children:teacher:teacher aide); (2) 1 hr of recreational therapy twice per week led by a unit psychologist; (3) 1 hr of gym time twice per week com-

[2]Although depression-treatment response relations in pure CD and ADHD groups were of potential interest, group sizes were not sufficient for statistical analyses. In total, 22 patients met criteria for CD without ADHD, and 25 met criteria for ADHD without CD. Among these subgroups, 7 patients met criteria for depression in the CD only group, and 8 met criteria for depression in the ADHD only group. These subgroup sizes offered insufficient power for testing HRV-depression interaction effects and were most likely inadequate for assessing main effects as well. Because the depression-treatment response relation was central to the hypotheses set forth in this paper, only those patients (n = 53) who met criteria for both CD and ADHD were included, since the number presenting with a comorbid depression was greater (n = 17).

[3]Although the ACTeRS and the Children's Depression Rating Scale yield cutoff scores for hyperactivity and depression, respectively, these scores were not used directly for diagnostic purposes. Rather, scale items bearing directly on *DSM-III-R* criteria were used as one of several inputs toward formulating diagnoses. This approach was used to maximize reliability, since each instrument was completed by only one informant. Nevertheless, during the first week of treatment, 94% of the sample scored within the clinical range on the ACTeRS attention scale, 87% scored within the clinical range on the ACTeRS hyperactivity scale, and 100% scored within the clinical range on one scale or the other. Additionally, all of the participants assigned to the comorbid group were classified as at least mildly depressed by the Children's Depression Rating Scale.

TABLE I. Sample Descriptive Statistics*

	CD/ADHD group (n = 36)		Comorbid group (n = 17)	
Characteristic	No.	%	No.	%
Race[a]				
African-American	9	27.3	1	5.9
Caucasian	20	60.6	15	88.2
Other	4	12.1	1	5.9
	Mean	SD	Mean	SD
Age[b]	8.9	2.0	8.7	1.8
Household income (in thousands)	22.4	21.4	26.9	12.8

*No statistically significant differences were evidenced on any of the presented measures. CD/ADHD - conduct disorder/attention deficit hyperactivity disorder.
[a]Race data were missing for three patients in the CD/ADHD group and one patient in the comorbid group.

prised of a variety of team sports; (4) 1 hr of group social skills training once per week led by unit nurses or clinical psychology interns, including instruction on making friends, initiating conversations, problem solving in conflict situations, recognizing anger cues, and developing effecting coping strategies for anger; (5) 1 hr of individualized cognitive behavioral treatment led by a unit psychologist; (6) 1 hr of parent training one to two times per week led by unit nurses, focused on altering behavioral contingencies in the home (depending on parent availability); and (7) a 1-hr family meeting each week led by a psychiatry (attending or resident) or psychology (Ph.D. or intern) staff member addressing issues of conflict among family members. Child and parent sessions followed closely the protocol described in detail by Frankel and colleagues [see Frankel et al., 1995, 1997].

Measures

Cardiac function. As part of the intake procedure to the inpatient unit, a registered nurse administered a standard 12-lead plus rhythm strip electrocardiogram (EKG) to each child to screen for abnormalities in cardiac functioning within 48 hours of arrival. Patients were medication free for a minimum of 24 hours (medications were discontinued on admission to observe native symptom levels) and were placed in a quiet room in a recumbent position. A 10-sec recording was obtained for each participant at a paper speed of 25 mm/sec. These recordings were transcribed into a series of R-R intervals to the nearest .02 sec by a trained research assistant who was blind to the experimental hypotheses. HRV was indexed by calculating the absolute mean successive difference in R-R intervals [Hayano et al., 1991].

Sympathetic influence on cardiac functioning was estimated through two related procedures. For analyses in which both the criterion and predictor variables were continuous, and multiple regressions were employed, sympathetic activity was estimated for each patient as the residual of heart rate when predicted by HRV in a bivariate regression. In other words, the component of heart rate attributable to HRV was statistically removed, leaving a remainder, or residual. These residuals, which represent both independent SNS and nonneural influences on heart rate [Grossman and Svebak, 1987], were then used to predict treatment outcome in the analyses described below. For analyses involving group comparisons, analyses of covariance (ANCOVAs) were employed in

which heart rate served as the criterion and HRV as a covariate. Thus, group differences in heart rate were examined after statistically removing HRV effects. This approach is mathematically similar to the residual analysis described above, yet suited for categorical comparisons.

Parental substance use and antisocial behavior. As part of the admission procedure to the inpatient unit, each primary guardian (the mother in most cases) received a family history interview, including global questions about maternal and paternal incarcerations, alcohol use, and drug use. In each case, an intake nurse queried the primary guardian regarding the presence or absence of symptoms of interest (e.g., "have you or the patient's father ever served jail time?" "have you or the patient's father ever experienced problems related to the use of alcohol?"), yielding a dichotomous rating. Alcohol and drug use were combined to form a single substance use scale.

Behavioral measures of aggression. Aggressive behaviors were assessed directly from the standardized behavioral management plan (BMP) in effect on the inpatient unit. The BMP is a response-cost contingency system in which each child earns points for appropriate behaviors and loses points for inappropriate behaviors. Daily tallies of point gains and losses are retained as part of each patient's record and were used to derive the number of discrete incidents of behavioral transgression. Of central interest for this study was the class of behaviors including physical aggression (e.g., hitting, pushing a peer or staff member) and verbal aggression (e.g., swearing at, threatening a peer or staff member). In addition, children were subjected to a seclusion procedure for (1) aggressive acts deemed by staff to be so severe as to warrant solitary confinement in a padded room and (2) refusal to comply with staff-initiated time-outs. Counts of seclusions thus served as an index of particularly serious aggression and defiance. Finally, the time in minutes required for patients to calm while in seclusion was recorded and served as an index of self-regulation.

Ratings of attention and hyperactivity. Because the ACTeRS was completed by unit school teachers at the end of every week, the Attention and Hyperactivity factor scores were available toward assessing change in ADHD symptoms across the treatment period. Each factor score was comprised of a series of statements related to attention (e.g., persists with task for a reasonable amount of time) and hyperactivity (e.g., fidgety), which are rated on 5-point Likert scales. Because low scores on the ACTeRS Attention factor represent problem behavior, items were reverse coded to render the direction of the scale consistent with the other indices used in the study.

Statistical Analyses

Data analyses proceeded in three phases. First, initial group differences in cardiac functioning, attention problems, physical aggression, and behavioral regulation were examined. Because the hypothesis of greater HRV in the depressed group was directional and specified a priori, it was assessed with a one-tailed t-test [see Hays, 1988]. SNS differences were assessed with an ANCOVA in which diagnostic status (depressed vs. not depressed) served as the predictor, heart rate served as the criterion, and HRV served as a covariate. For the BMP comparisons, each category was summed across the first week of treatment, and group differences were assessed in a series of two-tailed t-tests.

Phase two assessed the hypotheses that comorbid depression and HRV would predict improvement. The ACTeRS scales and each BMP category were summed for the sec-

ond and third weeks of hospitalization.[4] Treatment response was then assessed through analyses of linear growth functions [Rogosa et al., 1982]. This approach involved calculating least-squares regression lines through scores on each index (e.g., point losses for aggression), at each measurement point (i.e., weeks 1, 2, and 3), for each patient. The slopes of the regression lines, or growth functions, were used as indices of improvement in a series of simultaneous multiple regressions. For each ACTeRS and BMP index, slope was predicted by diagnostic status, medication status, week 1 symptoms, HRV, and the HRV × diagnostic status interaction. Simultaneous multiple regression yields F-ratios testing the independent contribution of each effect to outcome, over and above all other variables in the equation. This is a conservative approach because any shared variance among predictor variables is removed before the significance of any specific effect is tested [see Pedhazer, 1982]. Thus, the effects of comorbid depression and HRV on improvement were examined after removing the contributions of baseline behavior scores and medication status, the latter of which was represented by creating dummy-coded stimulant and tricyclic administration vectors. To determine if effects were specific to parasympathetic functioning, a parallel set of analyses was conducted in which the SNS residuals replaced HRV in the regression analyses.

In the third and final phase, the hypothesis that sympathetic activity is related to parental substance use and antisocial behavior was assessed. Comparisons of SNS differences were conducted in a series of one-way ANCOVAs in which heart rate was compared across levels of each dichotomous parent variable (e.g., father antisocial vs. father not antisocial), controlling for HRV. Thus, the variance in heart rate attributable to parasympathetic functioning was removed before testing for group differences in parental characteristics. To determine if such differences were specific to the SNS residuals, two-tailed t-tests were also performed assessing HRV differences across the parent variables.

RESULTS

Table II summarizes the cardiac variables and outlines the behavioral characteristics of the sample at week 1. The hypothesis of higher HRV in the depressed group was confirmed ($t_{(52)} = 1.79$, $P = .04$). Additionally, when adjusted for the effect of HRV, no significant difference in resting heart rate was found ($F_{(1, 51)} = 1.40$, $P = .24$). Thus, the independent SNS contribution to heart rate did not differ across groups. Significant group differences at week 1 were not evident on any ACTeRS indices or the BMP categories either (all Ps > .05). Thus, the depressed and nondepressed groups were roughly equivalent on measures of baseline functioning. Because the aggression measures were positively skewed, a parallel set of *t*-tests was performed in which variables were normalized through square root transformations. Results were unaffected, so only raw scores are reported.

Regression analyses testing the hypothesis of an HRV-treatment response relation

[4]Although many subjects remained on the inpatient unit for longer than 21 days (range = 21-427; M = 71.84; SD = 61.22), only those data derived from their first 3 weeks of stay were entered into the growth curves. This approach was employed because attrition thereafter rendered the sample size too small for statistical analyses. Moreover, those who remained on the unit for a longer time period might be expected to exhibit greater improvement by the end of their stay. Restricting all analyses to the first 3 weeks of treatment for all patients also avoided this potential confound.

TABLE II. Cardiac Indices and Week 1 Behavioral Characteristics of Patients by Diagnostic Status*

	CD/ADHD group (n = 36)		Depressed group (n = 17)		
	Mean	SD	Mean	SD	Range
Vagal tone (ms)[a]	48.26	29.17	63.76	30.04	7.3–133.3
Mean resting heart rate (bpm)	62.64	9.77	57.37	7.20	44.9–87.7
Adjusted heart rate[b]	60.89	—	58.96	—	—
ACTeRS scores					
Attention problems	16.56	5.35	17.11	4.82	9–29
Hyperactivity	17.18	5.51	17.24	5.59	5–25
Behavior Management Plan					
Verbal aggression episodes	.41	.72	.29	.47	0–2
Physical aggression episodes	2.64	2.35	2.41	1.97	0–12
Seclusions	1.30	3.00	.61	1.54	0–17
Time to calm in seclusion (min.)	11.01	17.85	5.93	12.54	0–65

*CD/ADHD = conduct disorder/attention deficit hyperactivity disorder; ACTeRS = Attention Deficit Disorder-Hyperactivity Comprehensive Teacher Rating Scale.
[a]One-tailed $t_{(52)} = 1.79$, $P = .04$; all other *t*-statistics were nonsignificant.
[b]Heart rate after removing the contribution of vagal tone in an analysis of covariance.

are presented in Table III. Betas and F-ratios refer to the independent contribution of each effect, over and above all others. The most potent predictor of treatment response was the number of symptoms during the first week of admission. The negative betas suggest greatest improvement (i.e., reduced symptoms across the treatment period) for patients who were more symptomatic during week 1.[5] In addition, tricyclic administration was related to improvement in aggressive symptoms, as indexed by both the number and duration of seclusions. Stimulant administration, on the other hand, was related to improvement in ACTeRS-rated hyperactivity, but to increased ACTeRS-rated attention problems across the treatment period.

Of greater interest for this study are the relations between HRV and treatment response. As indicated, interactions between HRV and diagnostic status were obtained for physical aggression, number of seclusions, and time to calm while in seclusion. Thus, the relations of these measures to HRV differed depending on whether patients were in the depressed or nondepressed groups. For this reason, main effects of HRV and diagnostic status are not interpreted. Figure 1 depicts the significant interactions of HRV and treatment response for physical aggression. As indicated, HRV above the

[5]Readers familiar with growth curve analysis will notice two departures from common practice. First, growth curve analyses are typically conducted using intercepts to control for baseline functioning. In the analyses reported here, however, symptom counts at week 1 were employed rather than intercepts because they represent observed scores rather than estimates. A parallel analysis in which intercepts were employed yielded similar results, with no changes in the significance levels of parameter estimates using an alpha error rate of .05. Second, in the interest of conserving space, confidence intervals are not presented for the growth functions of each dependent variable. However, when the slopes of growth functions are entered into regression analyses, the null hypothesis significance test compares those slopes across groups. Thus, when the confidence intervals around growth curve slopes overlapped for the depressed and nondepressed groups, differences in improvement or decline across the treatment period were not significant. Conversely, when the confidence intervals did not overlap, the groups did differ significantly.

TABLE III. Regression Summaries of the Relations of Vagal Tone and SNS Residuals to Treatment Response[†]

	Behavioral Management Plan (BMP) measure[a]											
	ACTeRS attention problems		ACTeRS hyperactivity		Verbal aggression		Physical aggression		Seclusions		Time to calm	
Effect	β	*F*	β	*F*	β	*F*	β	*F*	β	*F*	β	*F*
Vagal tone analyses												
DS[b]	.02	.01	.03	.02	–.07	.18	.46	2.72	.25	5.15*	.32	2.34
Stimulant medication[c]	.27	5.62*	–.24	4.28*	–.11	1.85	–.05	.15	–.05	.81	.12	1.21
Tricyclic medication[d]	.16	2.04	.01	.01	–.02	.05	–.23	3.10	–.13	5.86*	–.20	4.20*
Week 1 symptoms[e]	–.67	50.69***	–.78	61.47***	–.88	160.02***	–.49	17.31***	–.90	360.62***	–.75	68.23***
HRV	.23	.65	.01	.01	–.03	.02	.91	5.81*	.40	7.02**	.79	7.78**
DS × HRV interaction	–.25	.52	–.23	.41	.09	.12	–1.05	4.67*	–.49	6.50**	–.86	5.52*
Multiple R^2		.63		.79		.79		.37		.90		.65
SNS residual analyses												
DS[b]	.08	.20	.05	.07	.00	.00	–.05	.36	.07	.56	–.08	.47
Stimulant medications[c]	.23	4.33*	–.22	3.64	–.10	1.96	–.07	.44	–.14	1.82	.06	.27
Tricyclic medication[d]	.16	2.22	.03	.07	–.02	.08	–.17	2.92	.03	.09	–.14	1.30
Week 1 symptoms[e]	–.69	54.91***	–.71	45.70***	–.89	166.41***	–.72	65.12***	–.74	67.40***	–.65	36.05***
SNS residual	.05	.26	–.12	1.14	–.11	.25	.31	1.12	–.37	1.59	.28	.60
DS × SNS interaction	–.23	1.51	–.20	1.02	.09	.14	–.33	1.23	.35	1.37	–.19	.27
Multiple R^2		.63		.59		.79		.63		.61		.45

[†]SNS = sympathetic nervous system; ACTeRS = Attention Deficit Disorder-Hyperactivity Comprehensive Teacher Rating Scale; DS = diagnostic status; HRV = heart rate variability; CD/ADHD = conduct disorder/attention deficit hyperactivity disorder.

[a]Betas and *F*-ratios refer to improvement or decline in the BMP measures as indexed by the slope of individual growth functions.

[b]Dummy-coded vector in which 1 = CD/ADHD with depression and 0 = CD/ADHD without depression.

[c]Dummy-coded vector in which 1 = stimulant treatment and 0 = no stimulant treatment.

[d]Dummy-coded vector in which 1 = tricyclic antidepressant treatment and 0 = no tricyclic treatment.

[e]Indicates the effect of the BMP week 1 sum for respective columns.

*$P \leq .05$.

**$P \leq .01$.

***$P \leq .001$.

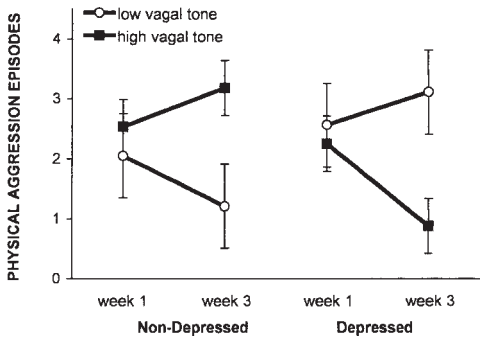

Fig. 1. Episodes of physical aggression (±1 standard error) at weeks 1 and 3 for patients above (n=17 nondepressed; n = 9 depressed) and below (n = 19 nondepressed; n = 8 depressed) the overall mean (54.5) on vagal tone.

overall sample mean of 54.5 was related to an increasing number of physical aggression episodes across the treatment period for nondepressed patients but to a decreasing number of such episodes for patients who were depressed. HRV below the sample mean, on the other hand, was related to improvement for the nondepressed group, but to deterioration for the depressed group. Similar patterns were observed for both seclusion indices. As indicated in Figure 2, high HRV was related to deterioration for nondepressed patients but to improvement for depressed patients, who were not subjected to any seclusions during the third week of treatment.

Two additional points are suggested by the regressions presented in Table III. First, neither HRV nor diagnostic status predicted improvement or decline in frequency of verbal aggression or in ADHD symptoms. Thus, HRV prediction in treatment response was restricted to more serious acts of aggression and defiance. Second, the SNS residuals did not predict treatment response on any of the ACTeRS or BMP measures.

ANCOVAs addressing the hypothesis of an SNS residual relation to parental substance use and incarcerations are presented in Table IV. Because only two mothers reported a history of jail time, no analyses were conducted with maternal incarcerations as a predictor. Both maternal substance use and paternal incarcerations were significantly related to heart rate, controlling for HRV. Patients whose mothers reported problems related to substance use evidenced lower resting heart rates than did patients whose mothers reported no such problems. This pattern was reversed for patients whose fathers reported incarcerations. Furthermore, these relations were specific to sympathetic functioning; no effects were found in t-tests assessing HRV differences (all *P*s > .20).

DISCUSSION

There are several points to be made about these findings. As predicted, HRV was significantly higher in the depressed group, which is consistent with theories implicating it in the experience of emotion. Results regarding treatment response suggest that this relation is more complex than anticipated. For those without depression, HRV was related to deterioration across 3 weeks, whereas for those with depression, it was related to improvement. This pattern was evident for both the frequency and duration of

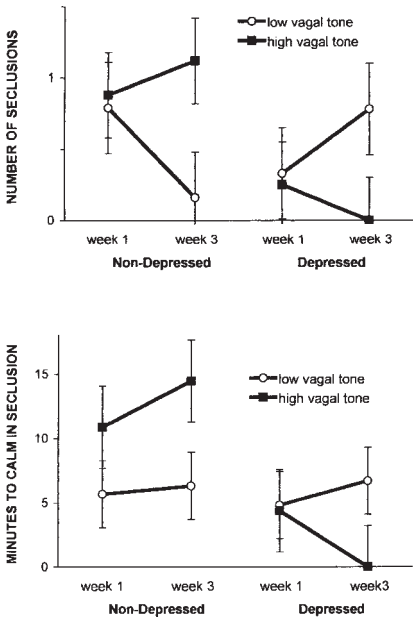

Fig. 2. Number of seclusions and minutes to calm in seclusion (±1 standard error) at weeks 1 and 3 for patients above (n = 17 nondepressed; n = 9 depressed) and below (n =19 nondepressed; n = 8 depressed) the overall mean (54.5) on vagal tone.

aggressive outbursts. Although no group differences were evident at the onset of treatment, by week 3 members of the depressed group high in HRV were aggressive less often, and their outbursts were less severe, requiring no seclusions. Members of the nondepressed group high in HRV, on the other hand, were more likely to be aggressive, and less able to regulate their arousal when placed in seclusion. Thus, the effect of HRV differed depending on whether patients were in the depressed or nondepressed group. Moreover, these effects were independent of the significant contributions of both tricyclic administration and symptom severity at intake.

TABLE IV. Summary of ANCOVAs Assessing Relations Among the SNS Residuals, Parental Substance Use, and Paternal Incarcerations*

	Diagnostic status of parent							
	Negative			Positive				
Parental characteristic	N	Mean HR	Adjusted HR[a]	N	Mean HR	Adjusted HR[a]	$F_{(1,49)}$ [b,c]	*P*
Substance use[d]								
Maternal	27	65.2	63.8	25	57.3	58.6	5.98	.02
Paternal	16	64.1	63.9	36	60.1	60.3	2.54	.12
Paternal incarcerations	45	60.0	61.8	7	70.1	68.3	4.28	.04

*ANCOVA = analysis of covariance; SNS = sympathetic nervous system; HR = heart rate.
[a]Adjusted for vagal tone in ANCOVAs.
[b]Parent data were missing for one patient in the comorbid group.
[c]Note that the *F*-statistic corresponds to a two-tailed *t*-statistic through the relation $F = t^2$.
[d]Includes alcohol and/or drug use.

Studies of infants have revealed that HRV predicts negative behavioral reactivity, as well as maternal ratings of temperamental difficulty [Bazhenova and Porges, 1997; Porges, et al., 1994]. When combined with reports that HRV also predicts positive emotional expression and social competence [Eisenberg et al., 1995; Fabes et al., 1993, 1994], a complicated picture emerges. One interpretation of these findings is that HRV serves as an index of emotionality, which is undifferentiated from behavioral reactivity in infancy. Through normal developmental processes, behavioral reactivity becomes actively inhibited in the face of emotional experience. If such differentiation does not take place, HRV may become a marker for impulsivity. Conversely, if differentiation does take place, HRV may serve as a marker for competence in the face of challenge. Although no patients in the current study would be placed in the latter category, the depressed group may exhibit some differentiation of behavior from emotion, which may help explain the observed pattern of results. Interpretive issues aside, it is noteworthy that HRV at intake accounted for variance in treatment response over and above that accounted for by medication and baseline rates of aggression.

Additionally, parental incarcerations and problems related to substance use were significant predictors of the SNS contribution to heart rate. This finding is consistent with the theory of dysregulated BAS/BIS functioning set forth in the introduction of this manuscript. However, the difference in the direction of effects when patients had a substance-using mother vs. an incarcerated father was not expected and cannot be readily interpreted. Moreover, because this result was not specified a priori, and because of the large number of comparisons performed within this study, it should be considered preliminary, pending future replication.

Nevertheless, this is the first report that we are aware of demonstrating differential prediction by indices of sympathetic and parasympathetic influence on cardiac functioning in a sample of CD/ADHD boys. These results suggest that inpatient treatment response among this population may be less dependent on differences in SNS activity than on differences in HRV. The relation of HRV to treatment response was further dependent on diagnosis, suggesting that comorbid depression may confer improved short-term prognosis to high HRV patients. In fact, by the third week of hospitalization, incidents of physical aggression were reduced to one, and seclusions administered to zero for members of this subgroup.

Independent SNS influence on heart, rate on the other hand, although not related to treatment response, may be predictive of risk factors specific to the parent and the home environment. Because these risk factors are somewhat stable, an important relation may exist between SNS influence and long-term course, which we know to be similar in CD cases with and without depression [Harrington et al., 1991].

Limitations and Directions for Future Research

Perhaps the most important caveat regarding this study is that the results may be difficult to replicate. As mentioned previously, the large number of comparisons carries a significant probability of Type I error. Moreover, the interactions obtained for the frequency and duration indices of aggression do not follow from theory. Thus, one possibility is that the reported results represent chance findings. It is therefore imperative that these results be interpreted tentatively until either replicated or refuted by future research efforts.

In addition, the retrospective nature of this study resulted in several limitations. Of

potentially greatest concern is the use of coarse cardiac measures. Indices of heart period variability are typically derived from EKG data collected over significantly longer time periods. This enables researchers to separate baseline levels of cardiac functioning (trait measures) from changes resulting from reactions to environmental events (state measures). Because the EKG procedure may elicit state-related changes in cardiac functioning, it is unclear whether the differences reported in this study are state or trait specific.

Additionally, modern EKG measures are typically more precise, with peak deflections in heart beats measured to the nearest millisecond. Thus, the procedure employed in this study includes unwanted measurement error. Because this influence is apt to reduce rather than inflate the likelihood of detecting effects, however, and because patients were selected for poor prognosis, findings of differential treatment response are noteworthy. Nevertheless, replication is required before conclusions are drawn. The prediction of parental substance use and incarcerations by independent SNS effects on heart rate should be confirmed using impedance cardiography, which directly assesses preejection period, and thus the SNS component of cardiac functioning [McCubbin et al., 1983].

In addition, the washout period before EKG administration was relatively short. This is troublesome because certain medications, particularly tricyclics, require weeks rather than days to clear. Although reliable records of pretreatment medication status were not available, it is likely that many members of the depressed group were taking such medication prior to admission. However, tricyclics and other antidepressants typically attenuate rather than enhance HRV [Jakobsen et al., 1984; Mezzacappa et al., 1998; Rissanen et al., 1998; Yeragani et al., 1992]. Thus, the observed group difference, with comorbid participants exhibiting higher HRV than controls, is not likely attributable to a residual antidepressant effect.

Also of potential concern are reports that comorbid mood disorders indicate greater severity of both CD and ADHD symptoms [Jensen et al., 1988; Zoccolillo, 1992], thereby conferring greater opportunity for improvement on depressed patients. Although this possibility cannot be ruled out with certainty, it is an unlikely explanation for the present findings for two reasons. First, group differences between depressed and nondepressed patients were not evidenced on any of the behavioral outcome measures at baseline. Second, the impact of baseline symptom levels was statistically removed before significance tests of the effects of diagnostic status and HRV were conducted.

Finally, several questions could not be addressed with the available measures. Onset age, for instance, may be an important mediator of the relation between depression and treatment response. Consistent with the theory set forth in this paper, depressive symptoms developing in reaction to institutionalization may imply greater emotional responsiveness than long-standing depressions. Unfortunately, no reliable estimates of onset age were available. Moreover, symptoms of depression were not formally assessed throughout the treatment period. Thus, the course of depression in the sample is unknown, as is the relation between changes in depression and aggression, which might be expected to covary. Clarifying both of these issues may provide additional insights into the differential treatment responses uncovered in these subgroups of aggressive preadolescent males. It is our hope that these questions and others will be addressed in future prospective studies directed at the complex relations among autonomic nervous system activity, emotion regulation, and treatment response in behavior-disordered youth.

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