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Intervening to enhance cortisol regulation among children at risk for neglect: Results of a randomized clinical trial

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Abstract

The hypothalamus–pituitary–adrenal axis is particularly sensitive to conditions of maltreatment. In particular, neglected children have shown a flatter slope with lower wake-up values relative to nonneglected children. An intervention, the Attachment and Biobehavioral Catch-Up (ABC), was developed to enhance biological and behavioral regulation in young children at risk for neglect. The effectiveness of the intervention was assessed in a randomized clinical trial for children with involvement with Child Protective Services. Following the intervention, children receiving the ABC intervention ($n = 49$) showed more typical cortisol production, with higher wake-up cortisol values and a steeper diurnal slope, than children receiving the control intervention ($n = 51$). These results suggest that the ABC intervention is effective in enhancing biological regulation.

When infants face chronic stress in childhood, such as neglect and poverty, their behavioral and biological regulation is compromised (Gunnar & Vazquez, 2001). The hypothalamus–pituitary–adrenal (HPA) axis is especially vulnerable to the effects of early adversity and nonoptimal caregiving (e.g., Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010; Gunnar & Vazquez, 2001). Among humans and other primates, cortisol represents an end product of the HPA system. Cortisol typically follows a diurnal pattern, characterized by high wake-up values and low bedtime values. Early adversity has been associated with a blunting of this diurnal pattern, with children living under high-risk conditions showing a blunted pattern of cortisol production across the day (Bernard et al., 2010; Kroupina et al., 2012). These findings, as well as experimental studies with animals (Mirescu, Peters, & Gould, 2004; Sanchez, Ladd, & Plotsky, 2001), suggest that significant stress experienced in early life may disrupt children's developing regulation of the HPA system. An intervention, the Attachment and Biobehavioral Catch-Up (ABC), was designed to support children's development of regulatory capabilities. Through a randomized clinical trial, the current study assessed whether children who received the ABC intervention showed more normative diurnal production of cortisol than children who received a control intervention.

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HPA Axis Functioning

There are two relatively orthogonal functions of the HPA axis: mounting a stress response and maintaining a circadian rhythm.

Stress reactivity

The HPA axis is perhaps best known for its role in mounting a stress response. At the moment of stress, as the result of other limbic system input, the hypothalamus secretes corticotrophin-releasing hormone, which signals the pituitary to release adrenocorticotropin hormone (ACTH). ACTH is released into the blood stream, which then signals the adrenal cortex to release cortisol. Cortisol is an end product of this system and has a negative feedback function of signaling the shutdown of ACTH and corticotrophin-releasing hormone production.

Whereas most older children and adults reliably show a cortisol response under some types of stressful experiences, there is evidence that young children undergo a stress hyporesponsive period, during which cortisol is not elevated in response to stressors. Such a period parallels that seen among rodents (Gunnar & Quevado, 2007; Sapolsky & Meaney, 1986), and it may function to protect the developing brain from high levels of circulating glucocorticoids (Gunnar & Cheatham, 2003). Among rodents and humans, the availability of a sensitive mother is necessary to maintain this stress hyporesponsive period (Levine, 2001). For example, human infants with organized attachments do not show an increase in cortisol to the Strange Situation, a procedure involving maternal separations, whereas infants with disorganized attachments do show a cortisol response (Bernard & Dozier, 2010; Gunnar, Broderson, Nachmias, Buss, & Rigatuso, 1996). Because differences in reactivity can be difficult to

interpret among young children, much of the work on intervention effects has focused instead on diurnal patterns of cortisol production (e.g., Dozier, Peloso, et al., 2006; Fisher, Stoolmiller, Gunnar, & Burraston, 2007).

Diurnal production

Among humans and other diurnal creatures, cortisol has a diurnal pattern, with high morning values and low evening levels. Cortisol begins to rise prior to wake-up and is relatively high at wake-up. It increases to a peak 30 min post-wake-up, then decreases quickly (typically by midmorning), and is flat to decreasing across the day to near zero levels at the bedtime nadir. This diurnal pattern serves to mobilize energy in the morning and prepare the organism for sleep at night, among other things. The system is important in promoting similar sleep–wake cycles among members of a species.

At birth, human infants do not show an established diurnal rhythm but instead exhibit two cortisol peaks within a 24-hr period (Sippell, Becker, Versmold, Bidlingmaier, & Knorr, 1978). By 3 months of age, a single diurnal peak and evening nadir is seen (Gunnar & White, 2001; Larson, White, Cochran, Donzella, & Gunnar, 1998; Price, Close, & Fielding, 1983), with the pattern gradually approximating the adult pattern over the first 2 years of life among typically developing children (Gunnar & Donzella, 2002).

Perturbations in diurnal cortisol production have been observed across a variety of conditions of early adversity, including maltreatment, placement into foster care, and extreme institutional deprivation (Bernard et al., 2010; Bruce, Fisher, Pears, & Levine, 2009; Carlson et al., 1995; Gunnar & Vazquez, 2001). The specific experience of neglect, especially early in life, has been associated with a blunting of the HPA axis across a variety of settings and populations. Children reared in extremely depriving institutional settings have shown blunting of diurnal HPA activity relative to children raised with their biological parents (Carlson et al., 1995; Carlson & Earls, 1997; Gunnar & Vazquez, 2001; Kroupina et al., 2012). Lower morning values and atypically flat cortisol production have been observed among foster children removed from their biological caregivers primarily due to the experience of neglect (Bruce et al., 2009; Dozier, Manni, et al., 2006). Bernard et al. (2010) found that children living with their high-risk birth parents who were identified by Child Protective Services (CPS) due to risk of neglect showed more blunted patterns than even foster children. It has been theorized that the neglecting environments may lead to a downregulation of the HPA axis in response to chronic stress, as reflected in the atypically flat diurnal cortisol rhythms among neglected children (Bruce et al., 2009). Although it is not yet clear whether these blunted cortisol rhythms predict problematic long-term outcomes, there is evidence that low, flat diurnal cortisol patterns are associated with increased risk for mood disorders (Gunnar & Vazquez, 2001), aggression (McBurnett, Lahey, Rathouz, & Loeber, 2000), and conduct problems (Pajer, Gardner, Rubin, Perel, & Neal, 2001).

Taken together, recent research suggests that a blunted diurnal cortisol rhythm, as opposed to an overall heightened production of cortisol, reflects the characteristic pattern of HPA axis dysregulation among children who experience early adversity. It is important to note, however, that the literature is mixed, with some studies finding higher cortisol levels among subgroups of children who experience early life stress relative to comparison children. The patterns of cortisol dysregulation (i.e., hyper- vs. hypocortisolism) among maltreated children have been found to vary depending on gender, concurrent psychopathology (e.g., internalizing problems), and characteristics of the experienced maltreatment (Bruce et al., 2009; Cicchetti & Rogosch, 2001; Doom, Cicchetti, Rogosh, & Dackis, 2013). In addition to these between-individual factors, the pattern of cortisol dysregulation *within* maltreated individuals may change over time (e.g., Cicchetti & Rogosch, 2001; Tricket, Noll, Susman, Shenk, & Putnam, 2010). For example, Trickett et al. (2010) found that females who experienced childhood abuse showed a different developmental trajectory in basal cortisol production from childhood through adulthood (assessed 6 times from 6 to 30 years old), compared to nonabused females. In childhood, abused females showed higher cortisol levels relative to control females, whereas the same group of abused females showed lower cortisol levels relative to control females in adulthood. This downregulation or attenuation of cortisol production over time suggests that both hypo- and hyperactivation of the HPA axis can follow maltreatment. Thus, although we focus our attention here on cortisol dysregulation characterized by blunted diurnal patterns, it is possible that young children experience high cortisol levels at earlier points of development.

Intervening to support children's regulation of diurnal cortisol production

There is evidence that therapeutic, nurturing environments can normalize cortisol production among previously maltreated children (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Dozier, Peloso, et al., 2006; Fisher et al., 2007). In an exploratory study, Dozier, Peloso, et al. (2006) found that foster infants whose caregivers completed the ABC intervention showed a more normative pattern of cortisol production following the intervention than did foster infants in a control intervention condition. More specifically, foster infants who received the ABC intervention showed lower levels of cortisol that were comparable to a low-risk comparison group, as contrasted with foster infants in the control condition. Fisher et al. (2007) found that preschoolers (the majority with prior experiences of neglect) assigned to an experimental condition (multidimensional treatment foster care) showed steeper slopes from morning to evening than those receiving regular foster care. Those assigned to the control intervention continued to show a persisting pattern of blunted cortisol reactivity typical of neglected children (Fisher et al., 2007). Improvements among children adopted from orphanage care suggest the robustness of these effects. Once removed from the neglecting environment, previously institutionalized children

eventually no longer exhibit the flattened patterns across the day, but instead develop more normative diurnal rhythms (Gunnar & Donzella, 2002; Kertes, Gunnar, Madsen, & Long, 2008).

Cicchetti et al. (2011) examined midmorning cortisol of maltreated infants longitudinally across 2 years. Maltreating parents were randomly assigned to receive an intervention (either child–parent psychotherapy or a psychoeducational parenting intervention) or community services as usual, and morning cortisol was assessed at preintervention, midintervention, postintervention, and at a long-term follow-up (1 year postintervention). Whereas maltreated infants receiving care as usual showed progressively lower levels of morning cortisol across the 2-year period, cortisol levels of maltreated infants who received either of the early parenting interventions remained similar to children in a nonmaltreated comparison group. Thus, the parenting interventions essentially prevented biological dysregulation among maltreated children. However, it is notable that this study only examined cortisol collected at midmorning prior to laboratory-based assessments; thus, findings do not speak to intervention effects on the diurnal pattern of cortisol production from wake-up to bedtime.

Although results have varied somewhat from one study to another, it seems that blunted cortisol production is the most consistent pattern seen among children exposed to adversity (Bernard et al., 2010; Cicchetti & Rogosch, 2001; Kroupina et al., 2012). Thus, consistent with other findings (Fisher et al., 2007; Kroupina et al., 2012), we were interested in assessing whether an early intervention for the parents of young children referred for risk of neglect resulted in a steeper diurnal cortisol pattern relative to the slope of young children whose parents received a control intervention.

The ABC intervention was developed to enhance children's self-regulatory capabilities. The objective of the ABC intervention in this study was to intervene with neglecting biological parents and their young children prior to the point at which a foster care intervention might be necessary. Bernard et al. (2012) have previously shown that the ABC intervention was effective in enhancing attachment security. The current study investigated whether the intervention effectively promoted children's diurnal cortisol regulation. We expected that children who received the ABC intervention would show enhanced physiological regulation, as indexed by higher wake-up levels of cortisol and a steeper wake-up to bedtime decline in cortisol, compared with children who received the control intervention.

Method

Participants

Primary analyses included 101 children receiving services as part of a diversion from foster care program who were assessed by CPS as being at risk for neglect. In this sample, there were three sets of siblings (with both children within the targeted age range at the time of referral; data were analyzed with full sample, and with reduced sample removing one sibling). Parents were referred to this randomized clinical trial as one of the services provided. Among the conditions most often noted for these parents were maltreating other children, domestic violence, parental substance abuse, homelessness, and mental disorders. We did not have access to formal records, however, and we were limited to reports of referring agencies and parent report.

At the time of postintervention assessment of cortisol, children ranged in age from 5.0 to 34.2 months ($M = 17.6$, $SD = 7.8$). Most (62%) of the children were African American, with 17% biracial, 13% Hispanic, and 8% White/non-Hispanic. All of the primary parents were female, with the exception of two males. Parents ranged in age from 15.1 to 46.6 years ($M = 26.9$, $SD = 7.6$); eight parents did not provide information about their age. Most (65%) of the parents were African American, 6% were biracial, 13% were Hispanic, and 16% were White/non-Hispanic. Table 1 presents demographic characteristics of the two groups.

Table 1. *Child demographic characteristics*

	ABC Intervention ($n = 49$)		DEF Control Intervention ($n = 52$)	
Variable	*n*	%	*n*	%
Gender				
Male	29	59	29	56
Female	20	41	23	44
Ethnicity				
White	5	10	3	6
African American	29	59	34	65
Hispanic	2	4	11	21
Biracial	13	27	4	8
	Mean (*SD*)	Min–Max	Mean (*SD*)	Min–Max
Child age (months)	17.7 (7.6)	5.0–33.8	17.2 (7.8)	5.8–34.2
Months postintervention	2.75 (2.49)	0.20–10.9	2.59 (2.19)	0.37–10.0

Note: ABC, Attachment and Biobehavioral Catch-up; DEF, Developmental Education for Families.

Procedures

Figure 1 displays the Consolidated Standards of Reporting Trials flow diagram, which includes information about participant referral, enrollment/randomization, and follow-up. We report more detailed information about participants included in the analyses for the current sample below.

Participant recruitment. Parents were recruited through a foster care diversion program in a large Mid-Atlantic city. Besides enrollment in the city's diversion program (following involvement with CPS), the only criterion for inclusion was the child being under 2 years old at the time of referral. Thus, families demonstrated a broad range of experiences that led to CPS involvement, from homelessness to a history of neglect. Referrals were received directly from agency staff, and parents were contacted individually by phone. When parents expressed initial interest in the program, research staff met with families individually to describe participation fully and to obtain consent. Given the study's lack of exclusionary

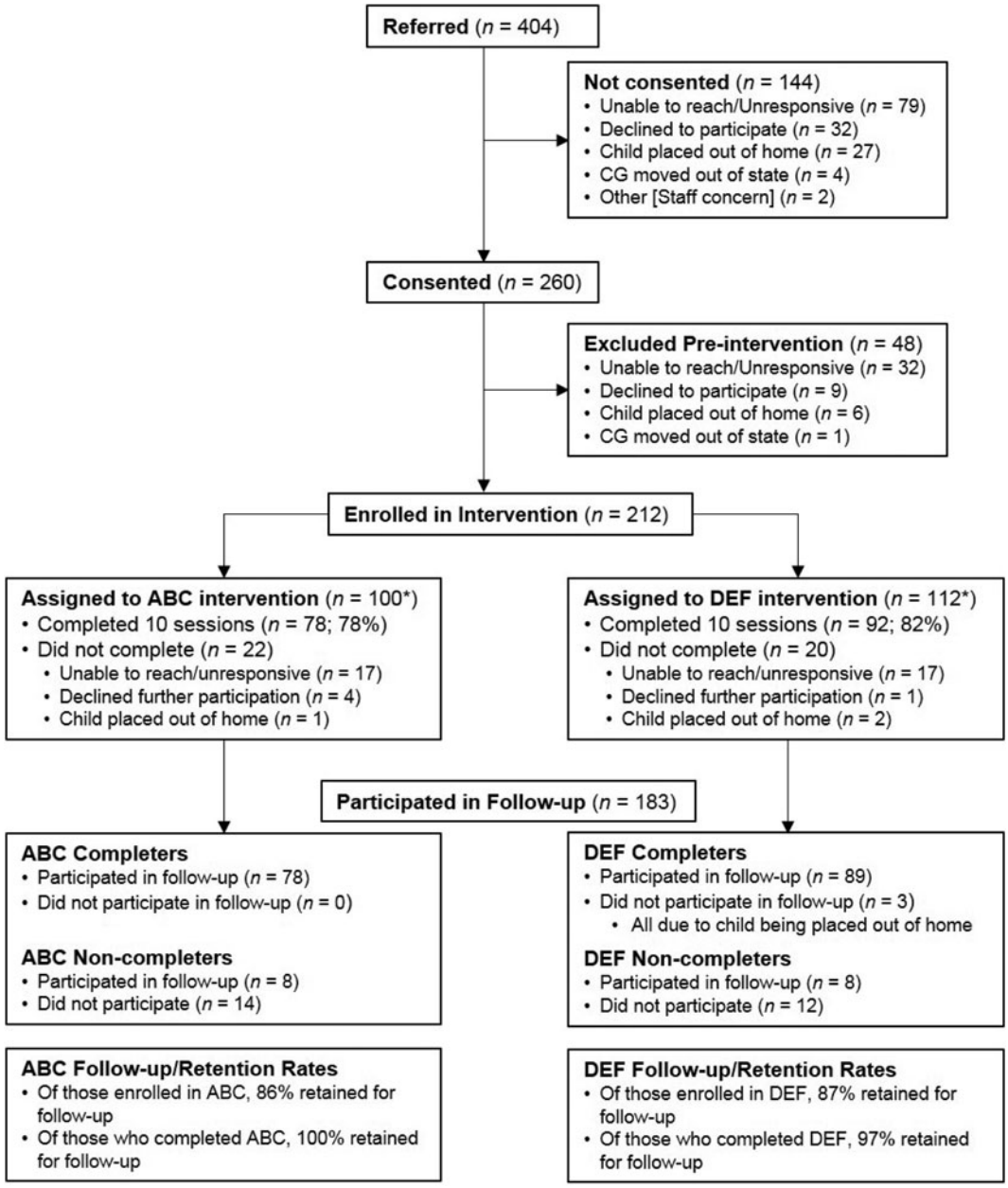

Figure 1. Consolidated standards of reporting trials flow diagram. *We report numbers of children enrolled in the Attachment and Biobehavioral Catch-Up intervention ($n = 100$) and the Developmental Education for Families intervention ($n = 112$) groups following completion of preintervention baseline visits. However, participants were randomly assigned to group upon consenting ($N = 260$; Attachment and Biobehavioral Catch-Up, $n = 129$; Developmental Education for Families, $n = 131$), at which time the intervention group sample sizes were more similar. Follow-up numbers include participants seen for any postintervention visits. More specific information is provided in the Method Section.

criteria, the sample may best be described as a diverse, high-risk, community sample. All components of this research study were approved by an internal review board at the University of Delaware.

Preintervention and postintervention assessments. After consenting, parents were randomly assigned to receive either the ABC (experimental) intervention or the Developmental Education for Families (DEF; control) intervention. Randomization occurred immediately after a parent provided consent. Of the 260 children who were consented, 129 were randomly assigned to receive the ABC intervention and 131 were randomly assigned to receive the DEF intervention. We did not consider children "enrolled" in the intervention until they completed preintervention research visits and had their first intervention session scheduled. Of the 212 children enrolled in the intervention phase, 100 were in the ABC group and 112 were in the DEF group. All pre- and postintervention assessments were the same for the two groups, and the two interventions were of the same duration (i.e., 10 1-hr sessions) and frequency (i.e., weekly). All intervention sessions and the assessment of cortisol production were conducted in families' homes.

The intended follow-up schedule included one visit a month after the last intervention session, and then annual follow-up visits around the time of the child's birthday. For the present study, cortisol was assessed as part of the first follow-up visit. Although efforts were made to collect data approximately 1 month after the last session, there was considerable variability in the timing of this assessment, with some of these visits ranging up to a year postintervention. The mean time between the last session and the cortisol assessment from the first follow-up visit was 2.67 months ($SD = 2.33$), with the majority (88%) collected within the first 6 months following the last session.

As can be seen from Figure 1, 183 participants were retained during the postintervention phase of the study (representing 86% of the 212 children enrolled in the intervention). Of these participants, cortisol data were collected from 120 children within the time window of the first follow-up visit. Of these 120 children, 19 provided samples that were not useable (15 children had insufficient volumes of saliva for all samples, 2 had insufficient volumes of saliva for two samples and other samples were excluded as outliers, and 2 had all samples excluded as outliers), resulting in a sample size for the present study of 101 children. For the remaining 63 children, cortisol data were not available because parents did not collect or did not return the samples ($n = 48$) or because parents could not be reached to schedule a follow-up visit at that time ($n = 15$).

Interventions. Parent coaches with extensive experience working with children and with strong clinical skills were selected to implement both the ABC and DEF interventions. All sessions were videotaped, which allowed supervision and fidelity monitoring. Sessions were typically conducted in parents' homes, or in shelters or other facilities as needed.

Experimental intervention: ABC. The ABC intervention was designed to help parents become more synchronous and nurturing, and less frightening, in their interactions with their children. The first two sessions provide an assessment of parents' beliefs and behaviors, and begin to emphasize the importance of nurturing behavior. During these sessions, parent coaches help parents to recognize that children need them even when they fail to signal their need clearly. Sessions 3 and 4 focus on synchrony, helping the parents recognize the importance of following the child's lead. Sessions 5 and 6 focus on helping parents behave in ways that are not intrusive or frightening, respectively. Sessions 7 and 8 introduce consideration of how parents' own issues can affect their ability to behave in synchronous, nurturing, and nonfrightening ways. In particular, the parent coach helps the parents identify "voices from the past" (i.e., influences from the past that influence parenting) and consider how these "voices" affect parenting. The final two sessions of the ABC intervention help consolidate gains made through the prior sessions and celebrate change.

Throughout all 10 sessions, parent coaches observe the parent's behavior and make comments on behaviors that relate to the intervention targets. This "in the moment" feedback is used to focus attention on intervention targets, promoting behavioral change during the intervention sessions. Along with "in the moment" comments, parent coaches provide video feedback to highlight parents' strengths, challenge weaknesses, and celebrate changes in behaviors.

Control intervention: DEF. The DEF intervention is designed to enhance motor, cognitive, and language skills. It was adapted from a home-visiting program that was previously shown to be effective in enhancing intellectual functioning (Brooks-Gunn, Klebanov, Liaw, & Spiker, 1993; Ramey, McGinness, Cross, Collier, & Barrie-Blackley, 1982; Ramey, Yeates & Short, 1984). Components that targeted maternal sensitivity were removed to keep the interventions distinct. The DEF intervention followed a manual, with sessions tailored to the developmental level of the child. During each session, DEF parent coaches provided general psychoeducation about developmental milestones, presented age-appropriate activities for parents to use to support their children's learning, and used video feedback to review session activities. During discussions, activities, and video feedback, DEF parent coaches focused on the child's abilities with respect to the targeted areas of development (i.e., motor, cognitive, or language). DEF parent coaches did not provide information, guidance, or feedback to parents about parenting behaviors or how to interact with their children during the activities.

Saliva sampling. The procedures used for collecting and assaying cortisol followed established protocol (e.g., Gunnar

& White, 2001). Research staff trained parents to collect and store saliva samples in their homes. In addition, step-by-step pictorial directions of the sampling procedure were given to parents along with the sampling materials. Parents collected saliva samples from children twice per day over a 2- or 3-day period. Initially, parents were asked to collect saliva samples for 2 days, but this was increased to 3 days later in data collection in order to increase the number of samples for analyses. Each day, parents collected one sample when the child first woke up and one sample at bedtime. Parents were asked to complete data collection on "typical" days, and to collect samples at least 30 min prior to or following mealtime or eating. Parents completed daily questionnaires about infant health status variables such as whether children were teething, were sick, or had eaten prior to sampling. If children were sick, parents were asked to delay sampling until the children were healthy again.

Samples were obtained by placing the end of the cotton roll in the child's mouth. Flavored sugar-free beverage crystals (cherry-flavored drink mix) were provided to facilitate sampling. Parents were instructed to first wet the cotton in the child's mouth, then dip the cotton in a cup containing 0.8 g of the flavored crystals and place it back in the child's mouth until the cotton was soaking wet. Controlled studies have reported that flavored crystals only minimally affect cortisol levels when radioimmunoassay is used (Gordon, Peloso, Auker, & Dozier, 2005; Talge, Donzella, Kryzer, Gierens, & Gunnar, 2005). The saturated cotton roll was returned to a prelabeled vial and stored in the freezer until it was collected by a research assistant.

The saliva samples were stored in a freezer at −20 °C prior to assay procedures. Samples were assayed using a high-sensitivity salivary cortisol enzyme immunoassay kit (Salimetrics, LLC, State College, Pennsylvania). All samples from a child were assayed in duplicate on the same plate to minimize variability. The intraassay and interassay coefficients of variation fell below 3.7% and 6.4%, respectively.

Primary analyses focused on postintervention cortisol data collected within the year following the completion of the intervention. There were no intervention group differences in the time between the last session and the time of saliva sample data collection. Wake-up samples were collected between 4:20 a.m. and 11:46 a.m. (M = 8:45 a.m.), and bedtime samples were collected between 5:45 p.m. and 12:45 a.m. (M = 9:11 p.m.). Table 2 shows descriptive statistics of sampling times. Although it is important to also consider the actual time of waking with respect to the sample collection time, this information was not consistently available across participants.

Of the participants with postintervention data included in the present study, 59 (28 ABC and 31 DEF) had preintervention cortisol data available for preliminary analyses. Preliminary analyses were conducted to ensure that there were no group differences in cortisol at baseline. There were multiple reasons that data were not available for the full sample of participants, including children were considered too young at the time of the preintervention assessment to provide valid physiological data (excluded children under 4 months), samples were not returned prior to beginning the intervention (thus not representing a true baseline), and not enough saliva was collected by parents.

Cortisol data preparation

Following procedures commonly used in previous studies (e.g., Fisher et al., 2007), biologically implausible cortisol values (i.e., defined as values greater than 2.0) were deleted. In addition, cortisol values greater than 3 *SD* above the mean were considered outliers and excluded from analyses. Each

Table 2. *Descriptive statistics*

		Time of Sample			Cortisol Value (μg/dl)			Log-Transformed Cortisol Value		
	N	*M* (*SD*)	Min	Max	*M* (*SD*)	Min	Max	*M* (*SD*)	Min	Max
ABC Intervention (n = 49)										
Wake, Day 1	39	8:08 (1:33)	4:20	11:17	0.24 (0.20)	0.033	1.03	−0.75 (0.35)	−1.48	0.01
Wake, Day 2	42	8:21 (1:18)	5:25	11:46	0.23 (0.17)	0.023	0.61	−0.79 (0.39)	−1.64	−0.21
Wake, Day 3	17	8:28 (1:16)	6:00	11:00	0.27 (0.17)	0.055	0.79	−0.64 (0.27)	−1.26	−0.31
Bed, Day 1	44	8:58 (1:04)	6:15	11:25	0.16 (0.16)	0.019	0.63	−1.01 (0.46)	−1.72	−0.20
Bed, Day 2	39	9:23 (1:12)	6:18	12:00	0.16 (0.16)	0.019	0.66	−0.98 (0.42)	−1.72	−0.18
Bed, Day 3	15	9:22 (1:09)	7:19	12:30	0.18 (0.14)	0.020	0.50	−0.93 (0.45)	−1.70	−0.31
DEF Control Intervention (n = 52)										
Wake, Day 1	44	8:12 (1:28)	4:20	11:45	0.18 (0.13)	0.006	0.60	−0.92 (0.45)	−2.22	−0.22
Wake, Day 2	39	8:23 (1:16)	5:25	11:46	0.19 (0.17)	0.010	0.61	−0.90 (0.43)	−2.00	−0.19
Wake, Day 3	21	8:39 (1:11)	6:00	11:25	0.14 (0.14)	0.004	0.53	−1.09 (0.57)	−2.40	−0.28
Bed, Day 1	45	8:58 (1:07)	6:15	11:32	0.15 (0.13)	0.010	0.65	−1.04 (0.46)	−2.00	−0.19
Bed, Day 2	42	9:16 (1:08)	5:45	12:00	0.15 (0.16)	0.004	0.62	−1.11 (0.55)	−2.40	−0.28
Bed, Day 3	19	9:33 (1:22)	7:00	12:45	0.13 (0.11)	0.010	0.42	−1.09 (0.46)	−2.00	−0.38

Note: ABC, Attachment and Biobehavioral Catch-up; DEF, Developmental Education for Families.

child could have up to 4 or 6 cortisol values (i.e., 2 wake-up and 2 bedtime samples for the 59 children with 2 days of data collection, or 3 wake-up and 3 bedtime samples for the 42 children with 3 days of data collection). Of 488 possible samples, 406 were included in analyses, with 3.7% removed as outliers and 13.1% missing due to an inadequate volume of saliva or because no sample was collected. Missing data patterns were comparable for the two groups, with children from the ABC group missing 15.5% and children in the DEF group missing 18.0%. Of the 49 ABC children, 31 had cortisol collected across 2 days (18 with 4 samples included in analyses, 6 with 3 samples, 6 with 2 samples, and 1 with 1 sample), and 18 had cortisol collected across 3 days (9 with 6 samples included in analyses, 5 with 5 samples, 2 with 4 samples, and 2 with 3 samples). Of the 52 DEF children, 28 had cortisol collected across 2 days (16 with 4 samples included in analyses, 4 with 3 samples, 4 with 2 samples, and 4 with 1 sample), and 24 had cortisol collected across 3 days (14 with 6 samples included in analyses, 4 with 5 samples, 1 with 4 samples, 4 with 3 samples, and 1 with 2 samples). Patterns of missingness of cortisol samples were examined in multiple ways to determine whether data could be considered missing at random. First, we conducted *t* tests for each sampling time point, with missingness for a particular sample (i.e., missing vs. not missing) as the independent variable and cortisol value for all other samples as the dependent variables. All of these were nonsignificant ($ps > .05$), indicating that there was no association between whether a particular cortisol sample was missing and cortisol level based on available observed measurements. Second, we examined whether missingness was associated with demographic information or group assignment, using chi-square tests for categorical variables (i.e., minority, gender, and intervention group) and *t* tests for continuous variables (i.e., child age). Missingness was not associated with child demographic variables or intervention group ($ps > .05$). Based on these analyses, the data meet criteria for missing at random (Schafer & Graham, 2002). Finally, there were 7 samples that had cortisol levels below the detectable limit of the assay; these samples were replaced with a value of .004 μg/dl. Log10 transformation was used to normalize the distribution of cortisol values due to a positive skew. See Table 2 for descriptive statistics regarding cortisol values (raw and log-transformed) and sampling times.

Results

Preliminary analyses

Preintervention cortisol data for the subset of participants were analyzed using the data analytic approach described in detail below. At preintervention, children randomly assigned to receive the ABC intervention or the control (DEF) intervention did not differ with regard to wake-up cortisol levels ($\beta_{01} = 0.10$, $p > .05$), bedtime cortisol levels ($\beta_{01} = 0.09$, $p > .05$), or wake-up to bedtime slope in cortisol production ($\beta_{11} = -0.01$, $p > .05$). There were no preintervention differences between the ABC and DEF groups in child or caregiver age and percentage of minority versus nonminority participants ($ps > .05$). Demographic variables were examined to determine whether child characteristics were associated with log-transformed postintervention cortisol values. Child gender and minority status were not associated with cortisol values at any of the time points ($ps > .05$). Child age was negatively correlated with log-transformed bedtime cortisol levels on Day 1 ($r = -.36$, $p = .001$) and Day 2 ($r = -.24$, $p < .05$), and with log-transformed wake-up cortisol levels on Day 3 ($r = -.38$, $p < .05$). Given these associations and findings from previous studies (e.g., Larson et al., 1998; Watamura, Donzella, Kertes, & Gunnar, 2004), child age was included as a covariate in primary analyses. Although time of sample collection was not associated with cortisol values at any of the time points (p values $> .05$), it was included as a covariate in primary analyses based on previous studies.

Data analytic strategy

Intervention group differences in cortisol levels at wake-up and bedtime as well as change in cortisol levels across the day were analyzed using hierarchical linear modeling (HLM; Raudenbush & Bryk, 2002). HLM accounts for the nonindependence of repeated measures by modeling multiple data points as nested within individuals. This approach allows for separate estimates of within-subject and between-subject variation. Whereas other approaches collapse across samples to create an average wake-up level and an average bedtime level, HLM models all samples individually and accounts for measurement error associated with each sample (Raudenbush, Brennan, & Barnett, 1995). Thus, this approach is considered more appropriate than aggregating all wake-up samples or all bedtime samples together, because it accounts for the error associated with each measurement occasion. Given that HLM allows for variability in the timing and number of repeated data points, participants can be included even if they are missing one or more points of data.

The dependent variable was the log-transformed cortisol value, measured in micrograms per deciliter (μg/dl). Cortisol sample collection time (in hours since the average wake-up sample collection time) was included as a time-varying covariate at Level 1. The following Level 1 within-individual model was specified:

$$\log \text{cort}_{ti} = \pi_{0i} + \pi_{1i}(\text{SAMPLE}) + \pi_{2i}(\text{TIME}) + e_{ti},$$

where $\log \text{cort}_{ti}$ represents the log-transformed cortisol value for child i at time t, π_{0i} represents child i's estimated log-transformed cortisol value at wake-up when controlling sampling time, π_{1i} is the estimated slope of cortisol change from wake-up to bedtime, π_{2i} is the regression coefficient representing the effect of the time-varying covariate (i.e., sample collection time), SAMPLE represents whether the sample was collected at wake-up or bedtime (with 0 = wake-up and 1 = bedtime), TIME represents the collection time of

the sample in hours from the mean time for wake-up sample collection (i.e., 8:45 a.m.), and e_{ti} is the within-individual error in child i's log-transformed cortisol value.

Level 2 (i.e., between-subject) variables were included to examine whether there were intervention group effects on cortisol levels at wake-up or bedtime and in change across the day. Child age was included as a covariate given that it was associated with cortisol levels in preliminary analyses. The following Level 2 model was specified:

$$\pi_{0i} = \beta_{00} + \beta_{01}(\text{ABC}) + \beta_{02}(\text{ChAGE}) + r_{0i},$$
$$\pi_{1i} = \beta_{10} + \beta_{11}(\text{ABC}) + \beta_{12}(\text{ChAGE}) + r_{1i},$$
$$\pi_{2i} = \beta_{20} + \beta_{21}(\text{ABC}) + \beta_{22}(\text{ChAGE}) + r_{2i},$$

where π_{0i} represents the wake-up log-transformed cortisol value (intercept) for an individual; π_{1i} represents the linear change (slope) in log-transformed cortisol across the day for an individual; β_{00} represents the average estimated log-transformed cortisol level at wake-up for children in the DEF group, controlling for child's age; β_{01} represents the difference between the wake-up log-transformed cortisol value between the children in the DEF group and the ABC; β_{02} is the regression coefficient representing the effect of the child's age (grand centered at the mean); ABC represents the intervention group (with 0 = DEF and 1 = ABC); ChAGE represents the child's age (months); and r_{0i} is the between-subject differences left unexplained by the Level 2 predictors The equations for linear change (i.e., β_{1i}) contain the same predictors, allowing for examination of intervention group effects on cortisol change across the day.

Primary analyses

In order to test intervention effects on the diurnal pattern of cortisol production, we examined whether intervention group predicted the wake-up level of cortisol (intercept) and the change in cortisol level from waking to bedtime (slope). The log-transformed cortisol value at wake-up differed significantly between children in the ABC group and children the DEF group, controlling for time of sample collection and age ($\beta_{01} = 0.21$, $p < .01$). Specifically, children in the ABC group showed a higher wake-up level of cortisol, relative to children in the DEF group (Table 3). Intervention effects on bedtime cortisol levels were examined by rerunning the model with the bedtime sample as the intercept (by recoding the SAMPLE variable with 0 = bedtime and 1 = wake-up). Log-transformed cortisol values at bedtime did not differ significantly between the intervention groups ($\beta_{01} = 0.06$, $p > .05$). There was a significant effect of intervention group on the change in cortisol across the day, with children in the ABC group showing a steeper wake-up to bedtime pattern (i.e., more negative slope) than children in the DEF intervention group ($\beta_{11} = –0.15$, $p = 0.051$). Thus, children in the DEF intervention group showed a more blunted diurnal cortisol pattern, relative to children in the ABC intervention group. Figure 2 presents the model estimates of the wake-up and bedtime values for each intervention group.

Table 3. *Multilevel modeling coefficients of intervention effects on diurnal cortisol production*

	Log-Transformed Cortisol				
Effect	Coefficient	*SE*	*t*	*df*	*p*
Intercept, β_{00}	−.95	.05	−17.37	98	.000
ABC, β_{01}	.21	.08	2.67	98	.009
ChAGE, β_{02}	−.01	.00	−1.89	98	.061
SAMPLE slope, β_{10}	−.09	.05	−1.75	98	.083
ABC, β_{11}	−.15	.08	−1.98	98	.051
ChAGE, β_{12}	−.00	.00	−1.60	98	.114
TIME slope, β_{20}	.02	.03	0.73	98	.469
ABC, β_{21}	−.04	.04	−1.03	98	.304
ChAGE, β_{22}	−.00	.00	−0.16	98	.875

Note: ABC, Attachment and Biobehavioral Catch-up; ChAGE, child's age (months); β_{00} and β_{10}, the wake-up level of cortisol and the slope of cortisol production across the day, respectively, for Developmental Education for Families (control) children; β_{01} and β_{11}, the difference in the wake-up level of cortisol and slope of cortisol production across the day, respectively, between Developmental Education for Families children and ABC children.

Effect sizes were computed to determine the magnitude of the intervention effect on wake-up cortisol level and the diurnal slope following procedures recommended for clinical trials (Feingold, 2009; Karna et al., 2011). Specifically, the Cohen *d* was computed by dividing the unstandardized estimate of the intervention effect (taking into account Level 1 and Level 2 covariates) by the pooled within-group standard deviation. Estimates of standard deviation for each group were computed using the raw data for wake-up cortisol (to examine the intervention effect on the intercept) and raw data for wake-up to bedtime change in cortisol (to examine the

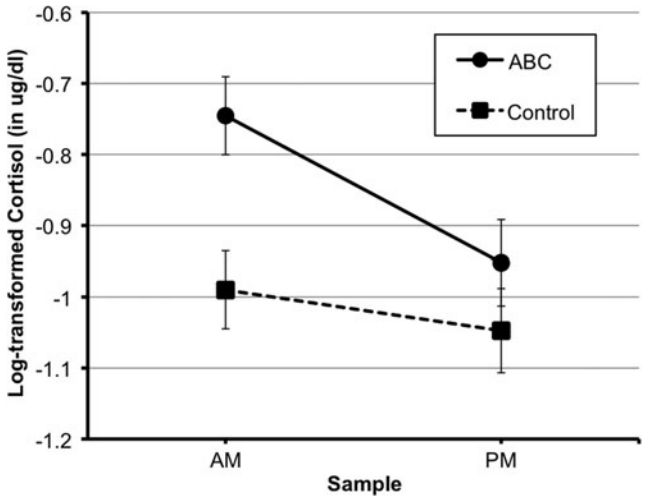

Figure 2. Cortisol patterns for neglected children who received the Attachment and Biobehavioral Catch-Up intervention versus neglected children who received the control (Developmental Education for Families) intervention. Error bars represent standard errors.

intervention effect on the slope). Based on conventions for small (0.2), medium (0.5), and large (0.8) effect sizes, the effect size for group difference in wake-up cortisol was approximately medium ($d = 0.48$), and the effect size for the group difference in the diurnal slope of cortisol was small to medium ($d = –0.38$).

Additional analyses were conducted to determine whether findings held if children who did not complete the interventions as intended were excluded and if children who were part of a sibling pair were excluded. Whereas all ABC children included in the present study completed the full 10 sessions, there were 4 DEF children who provided follow-up cortisol data who did not complete the full 10 sessions (considered "noncompleters" but retained for follow-up visits). When these 4 noncompleters were excluded from analyses, findings held for the effect of the ABC intervention on wake-up cortisol ($\beta_{01} = 0.19$, $p < .05$), and the diurnal slope ($\beta_{11} = –0.16$, $p < 0.05$). There were three sets of siblings in the sample (2 in ABC and 1 in DEF). When one sibling from each pair was excluded from analyses, the intervention effect held for wake-up cortisol ($\beta_{01} = 0.20$, $p < .05$) and was marginally significant for the diurnal slope ($\beta_{11} = –0.14$, $p = 0.07$).

Discussion

This study assessed the effectiveness of a 10-session attachment-based parenting program in supporting the regulation of diurnal production of cortisol among neglected children who were living with their birth parents. Results showed differences in the postintervention diurnal cortisol patterns of children assigned to the ABC intervention when compared to those assigned to the control intervention. Children randomly assigned to the ABC intervention showed higher wake-up values of cortisol and a steeper wake-up to bedtime decline in cortisol than did children randomly assigned to the control intervention. This pattern is an important index of the intervention's effectiveness, because it suggests that the intervention serves to support children's cortisol regulation.

Among humans and animals, cortisol (or corticosterone in rodents) is an integral component of the HPA axis, necessary for adaptation to chronic and immediate stress, and maintenance of circadian rhythms and homeostasis (Sapolsky, Romero, & Munck, 2000). Children exposed to chronic neglect are especially prone to low morning cortisol values (Bruce, Kroupina, Parker, & Gunnar, 2000; Dozier, Manni, et al., 2006; Fisher et al., 2007), perhaps due to a downregulation of the HPA axis in response to elevated glucocorticoid production in a chronically stressful environment. Such flat or blunted diurnal patterns, characterized primarily by low wake-up cortisol values, represent dysfunction in this important regulatory system (Gunnar & Vazquez, 2001). Low wake-up cortisol represents a biomarker for clinical, social, and physical maladjustment (Finsterward, Selig, Schieche, Wurmser, & Papousek, 2000; Pruessner, Hellmammer, & Kirschbaum, 1999; White, Gunnar, Larson, Donzella, & Barr, 2000). Given these risks and consequences of low morning cortisol values and associated blunted diurnal patterns, we find our results especially promising.

An important remaining question concerns the mechanism by which the ABC intervention leads to more typical cortisol regulation. The ABC intervention was designed to target parenting behaviors that were expected to promote biological regulation among young children at risk for neglect. Specifically, parents were supported to behave in synchronous ways to children's signals, respond with nurturance when children were distressed, and not engage in frightening behaviors. Synchronous interactions, in particular, may help children develop a sense of control over their environment, and thus support biological and behavioral regulation (Feldman, Greenbaum, & Yirmiya, 1999; Raver, 1996). Thus, a critical next step is to identify mechanisms of intervention effectiveness, by examining the specific ways in which parenting behaviors change, and how these changes in parenting behaviors contribute to changes in child outcome. Though important, demonstrating that specific changes to parent behavior mediate the effect of the intervention on cortisol regulation (or other outcomes) may be challenging. Meta-analyses indicate that maternal sensitivity often underperforms in predicting child attachment, relative to its expected role based on attachment theory (De Wolff & van IJzendoorn, 1997; van IJzendoorn, 1995). These modest effect sizes may be partially due to variable or even inadequate procedures for measuring maternal sensitivity (Cassidy et al., 2005; Lindhiem, Bernard, & Dozier, 2011). Given that the primary purpose of the present study was to examine the effect of the intervention on children's cortisol regulation, we did not aim to test the mediating role of changes in parenting in this paper. However, testing mediation in future studies will help us clarify mechanisms of intervention effectiveness, as well as inform our understanding of basic processes within developmental psychopathology.

The ABC intervention is similar to other short-term interventions that emphasize the importance of synchrony and nurturance for at-risk parent–infant populations in general (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003; Hoffman, Marvin, Cooper, & Powell, 2006; Lieberman & van Horn, 2009; van den Boom, 1994). Enhancing these behaviors among parents of young children has strong support in the literature, with effects primarily tested and seen with regard to children's quality of attachment relationships. Thus, we are excited to extend this work by showing that the intervention, designed to increase synchrony and nurturance among high-risk birth parents, can also have effects on children's diurnal cortisol regulation. Given that the effectiveness of the ABC intervention has now been demonstrated on both behavioral outcomes (i.e., attachment organization, Bernard et al., 2012; cognitive flexibility, Lewis-Morrarty, Dozier, Bernard, Terracciano, & Moore, 2012) and biological outcomes, it is important to consider potential models for how such changes influence each other and other outcomes. As we suggest above, changes to parenting behavior, such as

enhanced synchrony, may serve a direct role in helping children develop typical biological regulation. Similarly, changes to parenting behavior, such as enhanced nurturance, may serve a direct role in supporting the development of organized, secure attachment relationships. Whether changes to specific parenting behaviors (e.g., synchrony vs. nurturance) uniquely predict changes to specific child outcomes (e.g., cortisol regulation vs. attachment quality) remains to be tested. It may also be the case that enhancing attachment organization leads to more normative cortisol regulation or vice versa. Multiple studies report associations between attachment quality and cortisol responses (e.g., Bernard & Dozier, 2010; Hertsgaard, Gunnar, Erickson, Farrell, & Nachmias, 1995). Further, these more immediate targets (i.e., attachment organization and cortisol regulation) may serve as mediators to later outcomes, such as emotion regulation, attention/behavioral regulation, and physical health.

In a previous study of infants in foster care (Dozier, Peloso, et al., 2006), the ABC intervention was shown to be effective in leading to more typical cortisol regulation. However, the pattern of findings differs between that previous study and the current study. In the Dozier, Peloso, et al. (2006) study, infants whose foster parents received the ABC intervention showed lower wake-up and bedtime levels than did infants whose foster parents received the control intervention. Foster infants in the ABC group showed cortisol levels that were similar to a low-risk comparison group of similar age. Whereas lower cortisol values were seen as reflective of a more normative diurnal pattern among infants in foster care, we suggest here that a steeper slope and higher wake-up cortisol values may reflect a more normative diurnal pattern among young children living with their high-risk birth parents. The reason for the discrepancy across studies is unclear, but it may reflect differences between young children who remain in care with their high-risk birth parents and young children who are placed in foster care. Fisher et al. (2007) showed that preschoolers in foster care who received a psychosocial parenting intervention had steeper wake-up to bedtime slopes of cortisol production relative to children in a control condition. Given that the Fisher et al. (2007) findings parallel those of the current study, we cannot attribute discrepancies between the findings of Dozier, Peloso, et al. (2006) and our current findings solely to differences between children in foster care and children living with high-risk birth parents. However, it is possible that infants and toddlers in foster care represent a unique group in terms of cortisol regulation, compared to preschool-aged children in foster care or to infants and toddlers living with high-risk birth parents. In addition to infants in foster care (Dozier, Peloso, et al., 2006), high levels of cortisol have also been observed among other subsets of maltreated children, including foster children who experience severe emotional maltreatment (Bruce et al., 2009), as well as in postinstitutionalized children with significant growth delays (Kertes et al., 2008). Both atypically high and atypically low values of cortisol are considered problematic, and future research is needed to better understand what early experiences differentially predict these profiles. It will be critical to replicate and extend findings from these studies by examining diurnal cortisol regulation longitudinally among neglected children living in foster care and children living with their neglecting birth parents.

Unlike the Fisher et al. (2007) and the Dozier, Peloso, et al. (2006) studies, which examined interventions that target children *after* they had been removed from their neglecting parents and placed into foster care, the current study focused on improving children's neuroendocrine regulation in an environment of ongoing, chronic adversity. Cicchetti et al. (2011) intervened with a similar population of infants who were living with their maltreating parents, but they examined a laboratory assessment of cortisol, rather than the diurnal pattern. Here, we show that an intervention designed to enhance synchronous and nurturing parenting, even under chronically challenging conditions, may support children's cortisol regulation. The ABC intervention is intended to help parents serve a buffering role, in protecting their children from the negative effects of a chronically stressful environment. Thus, findings of the effectiveness of this short-term parenting intervention for highly vulnerable children have significant implications for prevention, which can be explored in future research. In addition to preventing short-term risk indicators (e.g., cortisol dysregulation and attachment disorganization) that are linked to later mental and physical health problems, the ABC intervention may have effects on child welfare system involvement.

Certain limitations to the current design must be recognized. We had limited information to children's experiences of neglect. This sample of parents and children was being monitored for neglect by child welfare services. In general, the experiences of neglect were likely not as severe as those that warrant removal of a child from a parent's care. However, families in the current study varied with regard to histories of neglect. Given this variability, it will be important for future research to consider whether different experiences of maltreatment are associated with treatment outcomes, ideally characterizing the type, severity, and frequency of maltreatment experiences and other stressors. In addition, we were unable to characterize change in cortisol patterns from pre- to postintervention. Thus, it is unclear whether cortisol patterns became more typical over time for children in the ABC group, whether cortisol patterns became more atypical (i.e., blunted) over time for children in the DEF group, or both. Future longitudinal analyses can further examine whether the ABC intervention serves to normalize cortisol patterns following early dyregulation or prevent later dysregulation. Further, although we established between-group comparability in cortisol profiles for a subset of children at preintervention, we did not have cortisol data from a low-risk comparison group. A low-risk age-matched comparison group would also help clarify the degree of dysregulation that was observed pre- and postintervention. Finally, we did not test whether changes to parenting behavior mediate the association between the intervention and children's cortisol regulation. This leaves the question about the mechanism by which the intervention is

effective unanswered. Although we have previously demonstrated that the ABC intervention leads to changes in parent sensitivity among foster parents (Bick & Dozier, 2013), it will be important to examine whether such improvements to parenting then explain changes in child functioning, such as cortisol regulation.

The results from the current study offer several directions for future research. The sustainability of ABC intervention effects on diurnal cortisol regulation and long-term advantages of children's improved cortisol regulation are currently unknown. Thus, it will be important to examine whether changes in cortisol regulation are maintained over time and whether changes contribute to improvements in other physical or mental health outcomes. As mentioned above, future research should test the mediating role of specific changes in parenting behavior that may drive effects of the intervention on child outcomes. Furthermore, it will be important to examine factors (i.e., moderators) that enhance or interfere with intervention effects. For example, variability in children's experiences of neglect may be associated with the effectiveness of the ABC intervention on influencing cortisol outcomes, because both the severity and the chronicity of neglect have been associated with the degree to which diurnal HPA patterns are blunted (Gunnar, Fisher, & the Early Experience, Stress, and Prevention Network, 2006; Gunnar & Vazquez, 2001). In line with a differential susceptibility model, Bakermans-Kranenburg, van IJzendoorn, Mesman, Alink, and Juffer (2008) demonstrated that the dopamine receptor D4 (*DRD4*) gene moderated the effectiveness of an attachment-based parenting program on basal cortisol levels among children with elevated externalizing behavior problems. More specifically, children with the *DRD4* 7-repeat allele, which has been associated with increased externalizing problems, were responsive to the intervention, whereas children without the *DRD4* 7-repeat allele were not. Future research examining genetic and environmental factors that moderate the effectiveness of interventions can enhance our ability to match particular treatment approaches to the individuals in need.

In conclusion, the ABC intervention, designed to enhance synchronous and nurturing responses among parents at-risk for neglecting their children, supports young children's diurnal cortisol regulation. In addition to supporting the efficacy of the ABC intervention, this study highlights the need to better understand associations between responsive caregiving and biological regulation. Among young children living in chronically challenging environments, responsive caregiving characterized by synchronous and nurturing interactions may be especially important for the development of basic biological regulation.

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