Family environment is associated with HPA-axis activity in adolescents. The TRAILS study

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The purpose of the present study was to investigate the developmental programming part of the theory of biological sensitivity to context using family environmental factors and hypothalamus–pituitary–adrenal (HPA) axis functioning. Specifically, we investigated whether perceived parenting (Rejection and Emotional Warmth) and socio-economic status (SES) predicted basal cortisol levels and the cortisol awakening response (CAR). In a population-based cohort of 1594 adolescents (mean age = 11.08, SD = 0.54) we assessed salivary cortisol, SES and perceived parenting. Perceived parental Emotional Warmth showed an inverse, linear association with basal cortisol levels. In addition, there was a curvilinear relationship between SES and both basal cortisol levels and the CAR. Our findings with regard to basal cortisol levels confirmed our hypothesis: lower basal HPA-axis activity in both high and low SES families compared to intermediate SES families.

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1. Introduction

The evolutionary–developmental theory of biological sensitivity to context (BSC) (Boyce and Ellis, 2005) offers a conceptual framework for understanding individual differences in biological sensitivity to the environment. Basicly, this theory consists of two parts. According to the first part of the theory, both children who, in early life, experience high-stress environments and children who experience supportive, low-stress environments tend to develop a highly reactive stress response system. In addition, children who experience moderate stress environments tend to develop a low reactive stress response system. We refer to this part of BSC theory as the developmental programming part. As a result, one expects a U-shaped association between environmental factors and reactivity of the stress response system. The developmental programming part of BSC theory was tested in two studies of children (3- to 5-year old and 5- to 7-year old). It was found that family stressors and socio-economic status (SES) predicted a U-shaped association in cardiovascular (i.e. heart rate) and adrenocortical (i.e. cortisol) stress reactivity, consistent with the theory (Ellis et al., 2005). According to the second part of the theory, specific beneficial aspects of individual differences are predicted in biological sensitivity to the environment. In a negative environment a highly reactive stress response system is helpful, because one is vigilant to threats and dangers, and in a positive environment one benefits from a highly reactive stress response system, because one is sensitive to social resources and support (Boyce and Ellis, 2005). In addition, a low reactive stress system serves a beneficial function for children in moderate environments, because increased passing of the emotional signals from chronic stressors leads to greater resilience under difficult conditions (Boyce and Ellis, 2005). This part of the theory has been tested and confirmed quite extensively by now (Boyce et al., 2006; Ellis et al., 2011; Essex et al., 2011; Obrović et al., 2010, 2011). The purpose of the present study is to test the developmental programming part of BSC theory on activity of the hypothalamus–pituitary–adrenal (HPA) axis.

The HPA-axis is a central component of the body’s neuroendocrine response to stress, with cortisol as its major end product (Tsigos and Chrousos, 2002). Three different aspects of HPA-axis activity are distinguished. Firstly, basal cortisol levels follow a circadian rhythm in healthy humans. We believe it is important to investigate basal cortisol levels since there is evidence that psychopathology in children and adolescents is associated with dysregulations in basal cortisol levels (Lopez-Duran et al., 2009), thus representing trait characteristics of HPA-axis functioning (Hellhammer et al., 2007). Secondly, the increase in cortisol
levels in about half an hour after awakening is another important aspect of HPA-axis activity (Wüst et al., 2000). This cortisol awakening response (CAR) is a specific response to awakening which is distinct from the basal circadian rhythm of cortisol secretion (Wilhelm et al., 2007). In a recent review several lines of results are presented that support the hypothesis that the magnitude of the CAR is dependent on the anticipation of demands of the upcoming day (Fries et al., 2009). Thirdly, challenge-induced cortisol secretion is called stress reactivity. The three measures of HPA-axis functioning are weakly correlated in our dataset (Bouma et al., 2009), indicating that they reflect different mechanisms (Fries et al., 2009).

Although initial formulation of BSC theory mainly seemed to apply to stress reactivity, the developmental programming part of BSC theory has recently been described in much greater detail, now also involving basal cortisol levels (Del Giudice et al., 2011). In the present study, we will examine how the early environment relates to two aspects of HPA-axis functioning: basal cortisol levels and the CAR.

As said before, the developmental programming part of BSC theory predicts high HPA-axis stress reactivity to develop both in unsupportive, high-stress environments as well as in supportive, low-stress environments (Boyce and Ellis, 2005; Del Giudice et al., 2011). Contrary to developmental programming of HPA-axis reactivity, Del Giudice et al. (2011) predicted that basal cortisol levels are similar between individuals who developed in different environments, while no prediction is done regarding the CAR.

Regarding basal cortisol levels, evidence points in the direction of lower basal cortisol levels in individuals who grew up in stressful family environments, which is inconsistent with Del Giudice et al.’s (2011) predictions. From many reviews written on this topic we conclude that, whereas a high-stress environment leads to increases in children’s basal cortisol levels in the short-term (De Bellis, 2001; Grassi-Oliveira et al., 2008; Gunnar, 1992), in the long-term decreases in basal cortisol levels are observed (Chrousos and Gold, 1992; De Bellis, 2001; Fries et al., 2005; Grassi-Oliveira et al., 2008; Gunnar and Vazquez, 2001; McEwen and Stellar, 1993; Miller et al., 2007). That is, persistent adversity over time may lead to lower basal cortisol levels in the long-term, and might have beneficial effects for the organism (Fries et al., 2005).

Relatively few studies investigated the association between positive aspects of the family environment and basal HPA-axis activity. Most studies focused on the potential modifying or buffering effect of positive aspects of family climate on HPA-axis reactivity in infants and young children (Albers et al., 2008; Gunnar, 1998; Gunnar and Donzella, 2002; Gunnar et al., 1992). Although the association between positive affect and low basal cortisol levels is well established (Dockray and Steptoe, 2010), to our knowledge, only one study investigated the direct association between a positive (family) environment and basal cortisol levels. That is, a recent study by Engert et al. (2011) carried out in young adults suggests that high perceived parental care was related to low basal cortisol levels and CAR, whereas those with low perceived parental care showed high basal cortisol levels and CAR. Regarding low perceived parental care, this finding contradicts our hypothesis that individuals who grew up in stressful environments have lower basal cortisol levels. Although evidence for the association between positive aspects of the environment and low basal cortisol levels is sparse, we hypothesize that low basal cortisol levels develop in both low-stress and high-stress environments as compared to moderate stress environments (inverse U-shape). This hypothesis is consistent with the idea that a strong reaction to stimuli from the environment is possible in a system with low basal cortisol levels, due to the lack of a ceiling effect.

Probably, Del Giudice et al. (2011) did not formulate any predictions regarding the developmental programming of the CAR, because of the lack of consistency among studies on the relationship between family environment and the CAR (Fries et al., 2009). One possible explanation for inconsistencies is that the CAR reflects state characteristics of the HPA-axis or, in other words, reflects the anticipated stress of the coming day (Hellhammer et al., 2007). In a study with ballroom dancers a much lower cortisol increase from awakening to 30 min after awakening was found on a competition day compared to a day without competition (Rohleder et al., 2007). In another study, it was found that feelings of loneliness and sadness on a specific day were related to a higher CAR, whereas feelings of tension and anger were not related to the CAR (Adam et al., 2006). In this respect, it is hard to formulate clear hypotheses regarding developmental programming of the CAR.

As far as we know, no study investigated the potential curvilinear relationship between family environment and basal cortisol levels or the CAR. In general, the vast majority of studies focused on linear relationships between negative aspects of the environment in relation to aspects of HPA-axis activity. In this paper, family environment is defined by positive and negative aspects of parenting on the one hand, that is, perceived parental Warmth and perceived parental Rejection, respectively, and socio-economic status (SES) on the other hand. We tested the hypothesis that the association between family environment and basal cortisol levels is inversely U-shaped; investigations with the CAR were largely exploratory.

2. Methods

2.1. Sample

The Tracking Adolescents’ Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch (early) adolescents, with the aim to chart and explain the development of mental health from early adolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk. Adolescents will be measured biennially at least until they are 25 years old. The present study involves data from the first (T1) assessment wave of TRAILS, which ran from March 2001 to July 2002. If both parents and adolescents agreed to participate, parental written informed consent was obtained after the procedures had been fully explained. Of all adolescents approached for enrollment in the study (N = 3145), 2230 (70.6%) adolescents participated in the study. Responders and non-responders did not differ with respect to the prevalence of teacher-rated behavior problems, nor regarding associations between sociodemographic variables and mental health outcomes. Detailed information about sample selection and analyses of non-response bias has been reported elsewhere (de Winter et al., 2005; Huisman et al., 2008). We received at least one saliva sample of 1768 adolescents (79%) of TRAILS participants. Non-responders differed to those who returned saliva samples in terms of gender (48.4% male vs. 49.4% male for non-responders vs. responders, respectively, x² (df = 1) = 0.132; p = 0.716), mean severity scores of behavioral problems (−0.0030 vs. −0.0001, t = −0.056; p = 0.955), mean directionality scores of behavioral problems (−0.0050 vs. 0.0018, t = −0.226; p = 0.821), perceived parental Rejection (1.40 vs. 1.42, t = 1.369, p = 0.171), and perceived parental Emotional Warmth (3.21 vs. 3.22, t = −0.322, p = 0.748). There was a slight difference in SES between non-responders and responders (t = −0.34 vs. 0.02, t = −8.350, p < 0.001).

We excluded 22 adolescents because they used corticosteroid-containing medication. For each time point, single cortisol samples with values that were above 3 SD of the mean of the particular time point were excluded from the analysis to reduce the impact of outliers (Cortmax, 21 excluded; 59 missing values; 1666 valid measurements in the final dataset; Cortmax 11 excluded; 52 missing values; 1683 valid measurements in the final dataset). From 1615 adolescents we received both morning saliva samples, and from 1594 adolescents we received data on SES and parenting (see Section 2.3) as well. Therefore, 71.5% (N = 1594, mean age = 11.08, SD = 0.54, 50.3% girls) of the adolescents who participated in the TRAILS study were included in the final dataset. The study was approved by the National Dutch Medical Ethics Committee, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Procedure

Well-trained interviewers visited one of the parents or guardians (preferably the mother, 95.6%) at their homes to administer an interview covering a wide range of topics, including developmental history and somatic health, parental psychopathology and care utilization. In addition to the interview, the parent was asked to fill out some questionnaires concerning the adolescent’s mental health and behavior. The adolescents filled out questionnaires at school, in the classroom, under the supervision of one or more TRAILS assistants. Besides, intelligence and a number of biological and neurocognitive parameters were assessed individually (at school,
except for saliva samples, which were collected at home). Teachers were asked to fill out a brief questionnaire for all TRAILS-participants in their class. Measures that were used in the present study are described more extensively below.

2.3. Measures

2.3.1. Socio-economic status (SES)

SES was based on income level, educational level of both parents, and occupational level of both parents, assessed by a parental questionnaire. These five variables were standardized and combined into one scale with an internal consistency of .84 (Veenstra et al., 2005). Several TRAILS studies used this SES-measure (Amoné-POikälä et al., 2009; Herba et al., 2008; Veenstra et al., 2008).

2.3.2. Perceived parenting

Adolescent’s perception of parental rearing practices was assessed with the EMBU-C (Markus et al., 2003), a child version of the EMBU (a Swedish acronym for My Memories of Upbringing). This questionnaire contains a list of 47 items on the factors Rejection, Overprotection and Emotional Warmth. For the present study, we will only use the factors Rejection and Emotional Warmth, because it is difficult to place overprotection on a dimension of positive and negative environment. That is, on the one hand overprotection may be characterized by parents being highly supervising, discouraging independent behavior, and acting in a highly controlling manner, while on the other hand parents may be showing high warmth and emotional involvement (Masia and Morris, 1998). Each item could be rated as 1 = no, never, 2 = yes, sometimes, 3 = yes, often or 4 = yes, almost always; and was asked for both the father and the mother. Rejection is characterized by hostility, punishment, derogation, and blaming of the child. Emotional Warmth refers to giving special attention, praising for approved behavior, unconditional love, and being supportive and affectionately demonstrative. Five items of the Rejection scale were excluded due to low loadings (Oldeninkel et al., 2006). After exclusion of these items, the Rejection scale contains 12 items with Cronbach’s α = .84 for fathers and .83 for mothers; and the Emotional Warmth scale contains 18 items with Cronbach’s α = .91 for both fathers and mothers. The answers for both parents were highly correlated (r = .67 for Rejection and r = .79 for Emotional Warmth), so we combined them into a single measure as in previous TRAILS papers (Bouma et al., 2008; Oldeninkel et al., 2006; Veenstra et al., 2006). The test-retest stability of a shortened version of the EMBU-C (10-item scales) over a 2-month period has been found to be satisfactory (r = .78 or higher) (Muris et al., 2003). There is sufficient support for the factorial and construct validity of this instrument (Dekovic et al., 2006).

2.3.3. Cortisol

TRAILS participants collected cortisol samples (saliva) at home, using the Salivette sampling device (Sarstedt, Rommelsdorfer Str., D-51588 Nümbrecht, Germany), which was handed to the parent at the parent interview, accompanied by a verbal and a written instruction. The Salivette tube consists of a plastic sampling vessel with a suspended insert containing a sterile neutral cotton wool swab that has to be chewed for about 45 s and then returned to the insert. Participants were instructed to collect three saliva samples; the first sample shortly after waking up (Cort0700), the second sample 30 min later, and the third sample at 2000 h. Both the sampling and the preceding day should be normal (school) days, without special events or stressful circumstances. Since all schools participating in TRAILS started at approximately the same time, the sampling-time variation of the morning samples among the adolescents is limited and the estimated corresponding times of the second and third sample (Cort0700 and 07:30 h for the first sample (Cort0730) and 07:30 h for the second sample (Cort0730)). In this cohort, 1141 (70.7%) showed a rise in cortisol levels between the awakening sample and the sample 30 min later, in 934 adolescents (57.8%) this awakening response was at least 2.5 nmol/l above individual baseline. Exact procedures and other requirements are described more extensively elsewhere (Rosmalen et al., 2005). Saliva samples were stored by the participants in their freezer directly after sampling and mailed to the institute as soon as possible. The saliva samples were stored at –20 °C until analysis. Previous studies suggest that salivary cortisol levels are stable for prolonged periods of time at –20 °C (Aardal and Holm, 1995). After completion of the data collection, all samples were sent in one batch (frozen, by courier) to the laboratory (Department of Clinical and Theoretical Psychobiology, University of Trier, Germany) for analysis. Procedures of determination of cortisol levels are described more extensively elsewhere (Rosmalen et al., 2005).

2.3.4. Behavioral problems

Behavioral problems were assessed with the Child Behavior Checklist (CBCL) (Achenbach, 1991a; Verhulst et al., 1996) and the Youth Self-Report (YSR) (Achenbach, 1991b; Verhulst et al., 1997). The CBCL is a measure of parent-reported emotional and behavioral problems in 4- to 18-year-old children and the YSR is a self-reported questionnaire that was modeled on the CBCL. The CBCL and the YSR contain 113 and 112 items, respectively. These items are rated as 0 (not true), 1 (somewhat or sometimes true) or 2 (very true or often true). Both the CBCL and the YSR contain two broadband scales: one for internalizing behavior problems and the other for externalizing behavior problems. For each of the two broadband scales, we used the mean of the standardized CBCL and YSR scores. In our previous study, we adopted the framework described by Essex et al. (2006) and used a Severity measure (Severity = [E + l]/2) as an index for comorbidity and a Directionality measure (Directionality = [E – l]/2) for determining whether the possible behavioral problems are mainly externalizing or internalizing, where E indicates the mean of the standardized externalizing behavior problems and l indicates the mean of the standardized internalizing behavior problems (Masman et al., 2008).

2.4. Statistical analyses

The cortisol levels followed a normal distribution (Cort0700 skewness = 0.70, kurtosis = 0.63; Cort0730 skewness = 0.43, kurtosis = 0.24). The computation of the Area Under the Curve (AUC) is a frequently used method in endocrinological research to assess basal cortisol levels (Area Under the Curve with respect to ground, AUCGR, and to CAR=Area Under the Curve with respect to increase, AUCI) (Pruessner et al., 2003; Pruessner et al., 2003) recommend employing both formulas when analyzing data sets with repeated measures. We used the following formulas for calculating: (1) basal cortisol levels: AUCGR = (Cort0730– Cort0700) × 0.5/2+ Cort0700 × 0.5 (in which 0.5 refers to 0.5 h), and (2) the increase in cortisol levels after awaken- ing or the CAR: AUCI = (Cort0730– Cort0700) × 0.5/2 (in which 0.5 refers to 0.5 h). AUC measures are given in h × nmol/l.

Pearson correlation coefficients (r) were used to assess the relationship between the family environmental factors (perceived parental Rejection, perceived parental Emotional Warmth, and SES) and the severity and directionality of behavioral problems. Prior to analyses, we standardized our predictor variables to be able to interpret our findings in terms of standard deviation units. Multicollinearity of these predictors was assessed using tolerance statistics and the variation inflation factor (VIF). Tolerance statistics less than 20 and/or VIF of 5 and above indicate a multi- collinearity problem (O’Brien, 2007). In the present study, the tolerance statistics ranged from .459 to .994, and the variance inflation factor (VIF) ranged from 1.001 to 1.911. These values indicate that there are no problems with multicollinearity.

In a previous study on the present sample, gender and the quadratic effect of age per month were identified as significant predictors of HPA-axis activity (Rosmalen et al., 2005). Only gender may be a potential confounder in our analyses since gender may also be related to differential susceptibility to parenting (Oldeninkel et al., 2006). Age, pubertal development, and BMI appeared not to be related to AUCGR levels and AUCI levels in the total group (Rosmalen et al., 2005).

Hierarchical regression analyses were conducted on AUCGR and AUCI levels. Gender was entered at Step 1 (0 = girls; 1 = boys). Behavioral problems may also be a potential confounder since behavior problems of the adolescents may be associated with the family environmental factors and HPA-axis activity. In a recent review it was found that there is an inverse association between an externalizing behavior problems and HPA-axis activity in elementary school-aged children (5–12 years old) (Alink et al., 2008). In addition, positive associations between behavioral problems, whether or not in interaction with gender, and HPA-axis activity were demonstrated in a previous study on the present sample (Marxan et al., 2008). However, the direction of the potential associations between family environmental factors and HPA-axis activity may also be reversed, leading to over-correction when adjusting for behavioral problems. For this reason, we chose to perform our analyses with and without adjusting for severity of behavioral problems, directionality of behavioral problems, and their interactions with gender at Step 1. Perceived parental Rejection, perceived parental Emotional Warmth, and SES were entered at Step 2. The variables perceived parental Emotional Warmth and SES were reversed, so that beta indicates the strength of the positive relationship between environmental adversity and cortisol measures. Perceived parental Rejection, perceived parental Emotional Warmth, and SES quadratic terms were entered at Step 3. Quadratic terms were calculated by squaring the standardized scores.

3. Results

3.1. Correlations

Table 1 shows several significant correlations between family environmental factors and behavioral problems. Firstly, we see that perceived parental Emotional Warmth was weakly and negatively
correlated with perceived parental Rejection. Secondly, severity of behavioral problems was moderately correlated with perceived parental rejection and weakly and negatively correlated with perceived parental warmth. Albeit significant, all other correlations were very weak to negligible (between 0.0 and 0.2).

3.2. Testing for curvilinear effects

Table 2 shows the results of the hierarchical regression analyses with adjustment for gender on AUCG levels and AUCI levels. Concerning AUCG levels, Step 1 revealed that girls have higher AUCG levels than boys. In addition, Step 2 revealed that the more perceived parental Emotional Warmth was observed, the lower AUCG levels were. In Step 3, the quadratic effect of SES was a significant predictor of AUCG levels. This means that both low and high SES was associated with lower AUCG levels. Together, the effects of gender, perceived parental Emotional Warmth, and the quadratic effect of SES accounted for 1.9% of the adjusted variance in AUCG levels. The quadratic effect of SES was also a significant predictor of AUCI levels, indicating that both low and high SES was associated with lower AUCI levels. The quadratic effect of SES accounted for 0.6% of the adjusted variance in AUCI levels. The quadratic effects of perceived parental Emotional Warmth and perceived parental Rejection did not predict AUCI levels or AUCG levels.

In the hierarchical regression analyses with adjustment for behavioral problems, we found again that the more perceived parental Emotional Warmth was observed, the lower AUCG levels ($\beta = 0.089, p < .01$) were. Again, the quadratic effect of SES was a significant predictor of AUCG levels ($\beta = 0.054, p < .05$) and AUCI levels ($\beta = -0.082, p < .01$), indicating that both low and high SES were associated with lower AUCG levels and AUCI levels. To illustrate our findings, we divided the SES measure into three groups, below the 25th percentile, 25–75 percentile, and above the 75th percentile, representing a low, middle, and high SES group, respectively. Fig. 1 shows that both curvilinear effects represent an inverse U-shaped curvilinear association. Table 3 shows the corresponding cortisol levels at waking up and 30 min later.

4. Discussion

Inspired by the hardly ever tested developmental programming part of the evolutionary-developmental theory of BSC (Boyce and Ellis, 2005), the present study tested the potential inverse U-shaped association between three family environmental factors (i.e. perceived parental Emotional Warmth, perceived parental Rejection, and SES) and two measures of HPA-axis functioning (i.e. basal cortisol levels, AUCG, and the cortisol awakening response, CAR, or AUCI). An inverse U-shaped association was observed between SES and both HPA-axis measures. Perceived parental Emotional Warmth in childhood was linearly associated with decreased basal cortisol levels, whereas perceived parental Rejection was not related to HPA-axis activity at all. An explanation for not finding an association between perceived parental Rejection and HPA-axis activity may be that in our population-based sample perceived parental Rejection does not represent a very high-stress environment, while the absence of parental Rejection does not necessarily represent a low-stress environment.

Concerning perceived parental Emotional Warmth, we did provide evidence that a supportive environment in the form of perceived parental Emotional Warmth was associated with low basal cortisol levels (AUCG levels). The association found is consistent with the right part of the inverse U-shape and fits with prior research showing an association between positive aspects of family climate and hypoactivity of the HPA-axis (Albers et al., 2008; Engert et al., 2011; Gunnar, 1992, 1998; Gunnar and Donzella, 2002). Moreover, whereas most previous studies considered a positive climate as a moderator of HPA-axis reactivity to a stressor (Albers et al., 2008; Gunnar et al., 1992; Gunnar, 1998; Gunnar and Donzella, 2002), the present study found a direct association.
between a positive family climate and HPA-axis functioning. The direct association is in line with studies that suggest an association between positive affect and low basal cortisol levels (Dockray and Steptoe, 2010) and the study by Engert et al. (2011), who demonstrated that high perceived parental care is directly associated with decreased basal cortisol levels in young adults. This finding does not rule out the possibility that perceived parental Emotional Warmth may also act as a modifier in the relationship between stress and HPA-axis reactivity. In contrast to our predictions, low perceived parental Emotional Warmth was not associated with low basal cortisol levels. Again, it could be that the absence of perceived parental Emotional Warmth does not necessarily represent a high-stress environment.

In line with our hypothesis, we found evidence for an inverse U-shaped relationship between SES and basal cortisol levels (AUC\textsubscript{C}) levels. SES is often used as a ‘container variable’ representing several aspects of the family context, and thus may be a more useful index representing a supportive and adverse environment on both sides of the continuum. In addition, it could be that SES is a more persistent and chronic factor in the life of a young adolescent. Belsky et al. (2007) suggested that parenting may be a mediating factor between SES and a child’s health, indirectly indicating that SES is a more stable and persistent factor than parenting.

In the present study, we chose to consider the three family environmental factors separately, and not all together. The fact that the three family environmental factors are (weakly) correlated with each other may provide support for combining them into a single measure. However, factors should not be combined unless there is reasonable evidence from prior research to combine them (Larose, 2005). For example, high perceived parental Rejection does not necessarily mean that there is no perceived parental Emotional Warmth and vice versa. For that reason, we decided to look at the family environmental factors separately. Furthermore, testing the effects of those three factors in the same model reveals the effect of each factor controlled for the other two factors. We can therefore safely conclude that SES has a quadratic association with basal cortisol levels over and above the linear association of perceived Emotional Warmth.

A curvilinear association was also found between SES and the CAR. It must be noted, however, that the amount of explained variance in the model with the CAR was small. The small but significant correlation between basal cortisol levels (AUC\textsubscript{C}) and the CAR (AUC\textsubscript{CAR}) (Rosmalen et al., 2005) makes it even more difficult to interpret this finding. The significant association between the CAR and SES squared might very well be ascribed to trait characteristics of HPA-axis functioning present in this measure of state characteristics (Hellhammer et al., 2007). Acknowledging the exploratory nature of studying associations with the CAR, this finding should be replicated in order to confirm the existence of an inverse curvilinear relationship between SES and the CAR.

As this is one of the first studies investigating the developmental programming part of BSC (Ellis et al., 2005), confirmation of our findings with respect to basal cortisol levels is also needed before firm conclusions can be drawn. Another question that needs to be addressed in future studies is whether individual differences in basal cortisol levels and CAR reflect differences in biological sensitivity to context. Although different measures of stress-reactivity have been shown to reflect differences in sensitivity in young children (Boyle et al., 2006; Ellis et al., 2011; Essex et al., 2011; Obradović et al., 2010, 2011), for as far as we know, individual differences in basal cortisol levels and the CAR have not been subjected to investigation in light of BSC theory. In the present study we investigated possible programming effects in 11-year-olds. However, increasing evidence suggests that developmental programming might continue into adolescence (Laceulle et al., 2011; Romeo, 2010; Schmidt et al., 2007). Another step would therefore be to investigate at what stage of development programming of basal cortisol levels and the CAR are finished.

A limitation of the present study is that we collected only two cortisol samples after awakening (which are part of the CAR), and used the aggregate measure (AUC\textsubscript{C}) as a measure of basal HPA-axis activity. Although the fact that the AUC\textsubscript{C} and AUC\textsubscript{CAR} are only weakly correlated (r = 32; Rosmalen et al., 2005) underlines that these are distinct measures, and several other studies used the AUC\textsubscript{C} as an indication of basal HPA-axis activity (Bonfazi et al., 2006; Boschloo et al., 2011; Marsman et al., 2008; Vedhara et al., 2006), we see that it would have been better to determine this AUC\textsubscript{C} measure on more measures than just the two measures after awakening. Del Giudice et al. (2011) did not specify at which time basal cortisol samples should be collected. According to the meta-analysis by Miller et al. (2007), exposure to chronic stress is associated with significantly lower concentrations of morning cortisol. In addition, many reviews on this topic show that a high-stress environment leads to decreases in basal cortisol levels in the long-term (Chrousos and Gold, 1992; De Bellis, 2001; Fries et al., 2005; Grassi-Oliveira et al., 2008; Gunnar and Vazquez, 2001; McEwen and Stellar, 1993). Since the results with morning cortisol samples (i.e. stress related with decreased levels) fit with these reviews and our hypotheses, we think that morning cortisol samples are especially valuable in the present study. Although we also collected one sample at 20:00 h in the evening, there are two main reasons for not including this sample in the present study. The first is a theoretical one. Since the results with evening cortisol samples (i.e. stress related with increased levels) (Miller et al., 2007) does not fit with the reviews and hypotheses in our study (i.e. stress related with decreased levels), inclusion of the Cort\textsubscript{00h} sample separately requires additional hypotheses. This is beyond the scope of this paper. The second reason is a methodological one. We believe that it is highly problematic to include the Cort\textsubscript{00h} sample in the AUC\textsubscript{C} measure, because there is too much time between the second sample in the morning (07:30 h) and the evening sample (20:00 h), given the documented systematic interindividual differences in the circadian rhythm after awakening. For example, girls have steeper slopes and more curvature to their rhythm than boys (Shirtcliff et al., 2011). In addition, in the same sample of early adolescents between 9 and 15 years old, it was found that age was related to circadian rhythm. That is, the slope becomes flatter as children age (Shirtcliff et al., 2011). On balance, we believe that including the evening sample would lead to a greater systematic error in our data than excluding the evening sample would do.

A future direction we would like to point out is investigating the developmental mechanisms behind the (inverse) U-shaped associations between stress axes functioning and family environmental factors. It is very likely that different mechanisms underlie development of similar basal and reactivity profiles in children from low-stress compared to children from high-stress environments. From animal studies evidence is available that a lack of stress inoculation results in high reactivity profiles, for example in unhandled animals compared to animals who experienced the mild stress of regular handling, while stress sensitization seems to underlie the high reactivity profiles following severe stress (Macri et al., 2011). Whether similar mechanisms underlie the inverse U-shape with basal HPA-axis activity reported in the present study should be investigated, as well as the generalizability of findings in animal models to humans.

In the present study, findings with and without adjusting for behavioral problems were the same. One could argue that individuals with less behavioral problems report a more positive family environment, resulting in a bias in the relationship between family environment and HPA-axis activity. Adjusting for behavioral problems reveals the ‘pure association’ between parenting and HPA-axis activity, since behavioral problems may act as a confounder. In our
previous study, we already found associations between behavioral problems and HPA-axis activity (Marsman et al., 2008). In addition, the fact that we found significant correlations between perceived parental Rejection on the one hand, and severity and directionality of behavioral problems on the other hand, underlines the potential value of adjusting for behavioral problems.

The interpretation of the results of this study is limited by its cross-sectional design. We were unable to verify whether parenting and SES represent long-lasting environments. Another limitation concerns the cortisol sampling. Firstly, home collection of saliva is much more susceptible to situational influences than collection of saliva in the more controlled conditions at the laboratory. In addition, home collection relies heavily upon participant adherence (Clow et al., 2004). However, home collection is more ecologically valid than assessment under laboratory conditions and provides the same results (Wilhelm et al., 2007). The major strengths of the present study are the large sample size and the child–report of parenting, since the child’s perception of parenting is likely to be more relevant for the child’s stress system than parent reports.

In conclusion, this study suggests that there may exist an inverse U-shaped relationship between socio-economic status on the one hand and basal cortisol levels and possibly the CAR on the other hand. In addition, the present study underlines the importance of taking into account positive aspects of the environment. Though the effect sizes of the findings were relatively small, our findings with regard to SES confirmed our hypothesis that was derived from the evolutionary–developmental theory of BSC. Whereas this theory suggests a curvilinear relationship between family environment and stress reactivity, we found evidence of an inverse curvilinear relationship between family environment and other measures of HPA-axis functioning.

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