

*Original Research Article***Are Cortisol Profiles a Stable Trait During Child Development?**

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**ABSTRACT** Exposure to stressful experiences can increase vulnerability to adverse health outcomes. A potential neuroendocrine mechanism mediating the link between stress and health is the hypothalamic-pituitary-adrenal (HPA) system, with a key role attributed to the glucocorticoid hormone cortisol. Retrospective and cross sectional clinical studies of humans and experimental studies with nonhuman primates and rodents suggest that traumatic experiences during critical periods in development may have permanent effects on HPA regulation, which in turn can have deleterious effects on health. Here I report results from a continuous 20-year study (1988–2009) of children in a rural community on Dominica. Sequential data on cortisol levels, social stressors, and health in naturalistic, everyday conditions are examined to assess developmental trajectories of HPA functioning. Saliva aliquots were assayed for cortisol in concert with monitoring of growth, morbidity, and social environment. Analyses here include data from 1989 to 1999 for 147 children aged 3–16 years with >100 saliva samples each. Cortisol values were standardized by elapsed time since wake-up. Results do not support the hypothesis that traumatic stress during childhood causes permanent general elevation of cortisol levels. *Am. J. Hum. Biol.* 21:769–771, 2009. © 2009 Wiley-Liss, Inc.

Humans, like most animals, have complex physiological systems that are responsive to stimuli from the social environment. The sensitivity of the neuroendocrine stress system to social challenges presents an evolutionary puzzle. We do not have good explanations for why natural selection favored links between the neuropsychological mechanisms involved with assessment of the social environment and the neuroendocrine mechanisms that regulate stress hormones such as cortisol. Furthermore, we do not understand why these links are modifiable during ontogeny, such that early traumatic experiences may have long-term effects on neuroendocrine stress response (Anisman et al., 1998; Mirescu et al., 2004). This puzzle is accentuated by the apparent negative consequences of social stress and concomitant abnormal cortisol levels for health and psychological development (Sapolsky, 2005).

The dominant model in stress research has targeted the homeostatic mechanisms of the hypothalamic-anterior pituitary-adrenal cortex (HPA) system, which are posited to be permanently affected by exposure to high levels of glucocorticoids during ontogeny. Glucocorticoid receptors (GRs) in the hippocampus that are part of the negative feedback loop regulating release of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) can be damaged by the neurotoxic levels of cortisol associated with traumatic or chronic stressors. Hence early trauma is hypothesized to result in permanent HPA dysregulation and hypercortisolemia, with consequent deleterious effects on the hippocampus, thymus, and other neural, metabolic, and immune system components (McEwen, 2004; Sapolsky, 2005). These effects may have additional consequences resulting from the high density of GRs in the prefrontal cortex in primates (de Kloet et al., 2005). Other potential mechanisms include DNA methylation (Cameron et al., 2008; McGowan et al., 2009; Weaver et al., 2004, 2006). The specific mechanisms affecting relations between exposure to trauma during development and subsequent HPA system function in humans are not as well documented as in animal studies. Nonetheless, a similar causal linkage appears plausible (e.g., Heim et al., 2000; Lupien et al., 2000).

The HPA pathology hypothesis is supported by a number of clinical and laboratory studies establishing that exposure to traumatic or chronic stress during development is associated with subsequent high levels of cortisol during adulthood (Essex et al., 2002; Gunnar and Quevedo, 2007; Heim et al., 2000). Other studies, however, indicate that children exposed to early life stress may have normal or subnormal HPA reactivity to experimental stressors such as the Trier Social Stress Test (e.g., Gunnar et al., 2009; Tarullo and Gunnar, 2006). Studies of post-traumatic stress disorder (PTSD) also suggest subnormal cortisol levels (Yehuda et al., 2007). Attenuation of initial hypercortisolemia is often followed by reduction of cortisol levels associated with comorbid social withdrawal and depressive symptoms. Studies of children in school and naturalistic environments indicate a variable relation between exposure to stress during development and subsequent cortisol levels, suggestive of individual differences (Flinn, 2006; Lupien et al., 2000).

Several key issues in regard to relations between stress during development and the HPA system remain unresolved: (1) do permanent changes in HPA regulation occur? (2) If there are changes in HPA regulation and cortisol levels (as per no. 1), are there functional consequences? (3) What specific mechanisms are affected by early stress (e.g., GRs, DNA methylation, neural circuits in amygdala, or something else)? (4) Are there “sensitive periods” during development in regard to HPA modification by exposure to stress? Here I present analyses of longitudinal data that primarily address the first question above, but the results also have indirect relevance for the other issues.

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## RESEARCH DESIGN, METHODS, AND SAMPLE

For the past 20 years (1988–2009) I have conducted research on child health in a rural community on the island of Dominica. In this study, sequential longitudinal monitoring was used to assess physiological stress response to everyday events, including social challenges. Saliva was collected from children by members of the research team at least twice a day, wherever the children happen to be in the context of their everyday activities—usually at their household, but sometimes at other locations such as family gardens, en route to school, playing at the ocean, and so forth. This direct collection and observation procedure avoided errors that can occur with at-home self- or parent-collection and report protocols. The large sample size of cortisol measures for each child (>100 samples for most children) in a variety of naturalistic contexts provided a more extensive picture of HPA stress response than small sample designs. The prospective, long term research design allowed for examination of temporal changes over many years of child development (Flinn, 2006).

In this report yearly averages of cortisol from 1989 to 1999 are analyzed to assess longitudinal patterns. The sample includes 147 children aged 3–16 years that each had a total of more than 100 saliva samples from at least eight collection years. All saliva samples were assayed with the same RIA procedure at the University of Michigan Hospitals ligand assay laboratory under the supervision of Barry England. Because the samples were collected at varied times of the day (5:00 AM to 9:00 PM), raw cortisol values were standardized to Z-scores by 5-min intervals since wake-up time. Cortisol z-scores were averaged over a yearly collection period for each child. Year-to-year averages were then examined for changes greater than 0.5 z-score for multiple-year periods. Children with two or more consecutive years of elevated cortisol that cumulatively averaged more than 1 z-score higher than the preelevation years, with no subsequent years of reduction, were coded as major changes. Seven children were out of the village or had small sample sizes for one or two interim years. These missing years were coded to place children into categories least favorable to the hypothesis tested.

Traumatic events were defined based on previous analyses that identified loss of a primary care provider from death or marital discord in the child's household, serious abuse, and sexual harassment as primary stressors (Flinn, 2006). Traumatic events that were brief in duration and apparently resolved within a year—such as a marital separation without continued discord or distress—were coded as “brief trauma.” Traumatic experiences that continued for several years or more were coded as “persistent trauma.”

This study has received continuous approval from the IRB at the University of Missouri.

## RESULTS

Case examples of the three categories of patterns of yearly averages of cortisol are presented in Figure 1a–c. Case no. 17 (Fig. 1a) is a child with no major changes. This is a common pattern; almost half of the cases exhibit this stable level of cortisol. Case no. 32 (Fig. 1b) is a child

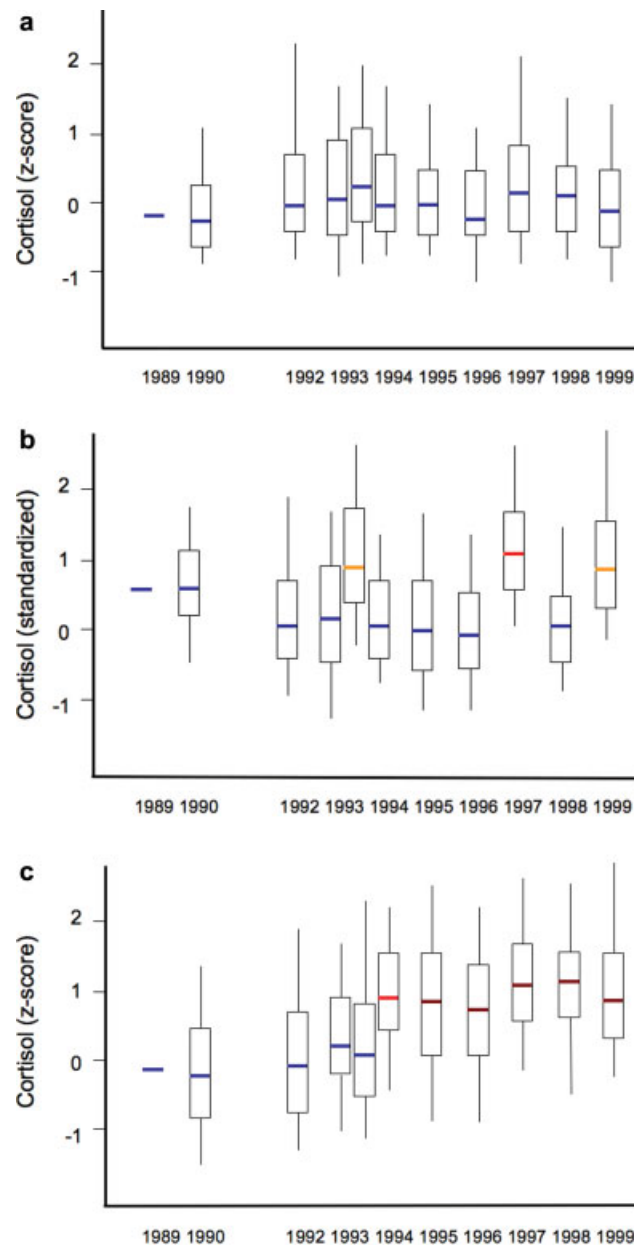


Fig. 1. Box (25–75%) and whisker (range) plots of salivary cortisol z-scores (standardized for time elapsed since wake-up). Median values indicated by thick horizontal lines. (a) Case no. 17: No major yearly changes (44% of cases). (b) Case no. 32: No consistent major yearly changes (46% of cases). (c) Case no. 55: Major multi-year change (9% of cases). [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

that endured some stressful conditions in her household, but did not evidence a permanent elevation of cortisol. Case no. 55 (Fig. 1c) exhibits a shift to a continuous elevation of cortisol, coincident (summer 1994) with sexual harassment in her household that eventually caused her to leave as a teenager and reside with other relatives.

All 13 cases of children with continuous multiple years of elevated cortisol had stressful conditions that persisted throughout the period (the two cases of potential major

TABLE 1. Childhood trauma and stability of yearly cortisol levels

	No trauma	Brief trauma	Persistent trauma
Stable	55 (44.3)	12 (16.89)	1 (6.85)
Variable	40 (42.97)	25 (16.39)	1 (6.64)
Major change	2 (9.76)	0 (3.725)	13 (1.51)

df = 4, Pearson  $\chi^2 = 115.8$ ,  $P < 0.01$ . Two cells have low expected frequency.

change from children without trauma had missing years that were coded as elevated). There is a strong relation between major changes in cortisol and traumatic experiences (Table 1). It is not clear in these cases of long term major changes of cortisol, however, if permanent HPA dysregulation had occurred, or if the continued high yearly averages reflect responses to the continued stressful circumstances. Examination of daily cortisol levels suggests that the latter is more likely; high cortisol spikes are usually associated with stressors experienced that day that are sometimes followed by an apparent recovery period with subnormal cortisol (see Flinn, 2006).

There were no apparent "critical periods" during which traumatic experiences at certain ages were more likely to result in long-term elevation of cortisol levels. The sample size of children with trauma, however, was small and hence it was difficult to evaluate age differences. Eight of the 13 cases of major cortisol change were adolescents (ages 11–15), with stressful conditions characteristic of that life history stage (e.g., school failure, sexual harassment). Previous analysis of relations between the age of exposure to trauma (pre-natal, infancy, early childhood) and subsequent cortisol levels also did not find significant differences, and suggested that changes were stressor-specific, with some apparent elevation to social events (Flinn, 2006; Nepomnaschy and Flinn, 2009).

## DISCUSSION

Returning to the paradox of why natural selection favored sensitivity of stress response to social stimuli in the human child, several points emerge. Previous results from the Dominica study suggest that family environment is a primary source and mediator of stressful events in a child's world (Flinn, 2006). The sensitivity of stress physiology to the social environment may facilitate adaptive responses to this most salient and dynamic puzzle (Huether, 1998). Childhood appears necessary and useful for acquiring the information and practice to build and refine the mental algorithms critical for negotiating the webs of ever-changing social relationships that are key to success in our species.

Context-dependent sensitivities to the social environment may explain some aspects of the apparent contradictory results among studies of cortisol response (e.g., Bartolomucci et al., 2005). Children that have endured difficult situations such as abusive environments or other types of trauma often have reduced cortisol levels in some types of mildly stressful environments. Hence studies that collect samples under clinical or school conditions may find different patterns of cortisol than studies that collect samples under the naturalistic conditions that include the stimuli that an individual has become sensitized to. For example, children from difficult family environments in

this study tend to have higher than average cortisol levels at home, but lower than average levels at school.

## Concluding remarks

Results here indicate that long-term changes in yearly average cortisol levels were uncommon in this study community. The rare cases of multi-year elevation were associated with persistent changes in social conditions. There were no clear cases of significant changes to HPA regulation as a result of a brief limited traumatic event. Children do, however, appear to become sensitized or habituated to specific stressors. At this stage of analysis the most parsimonious explanations of long-term changes in cortisol levels among children in this community are concomitant changes in their social environment and their psychology.

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