Development and Psychopathology **26** (2014), 1185–1188

doi:10.1017/S0954579414000819

ERRATUM

Diurnal cortisol rhythms in youth from risky families: Effects of cumulative risk exposure and variation in the serotonin transporter linked polymorphic region gene—ERRATUM

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doi:10.1017/S0954579414000558, Published by Cambridge University Press, 23 June 2014

The title and two places in the article require important corrections to the name of the genetic polymorphism under study to remedy errors that were introduced in typesetting. The first three pages that contain these errors are reprinted here to replace and correct those of the article. The correct title is "Diurnal cortisol rhythms in youth from risky families: Effects of cumulative risk exposure and variation in the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*)."

These same changes are at the first citation of the term in the abstract on the first page on the third line: ". . . effect of environmental risk is moderated by allelic variation in the promoter region of the serotonin transporter gene-linked polymorphic region (5-*HTTLPR*). Results show that youth . . ." and on the third page in the third line of the second column paragraph beginning "One genetic marker . . .:" ". . . stressors is a variable length polymorphism in the promoter region of the serotonin transporter (*5-HTT*) gene, *SLC6A4*. This polymorphic region, termed *5-HTTLPR*, displays short and long allelic variants, with the short allele . . ."

We sincerely regret these errors and any problems or misunderstandings they may have caused.

Reference

Willner, C. J., Morris, P. A., McCoy, D. C., & Adam, E. K. (2014). Diurnal cortisol rhythms in youth from risky families: Effects of cumulative risk exposure and variation in the serotonin transporter linked polymorphic region gene. *Development and Psychopathology*. Advance online publication. doi:10.1017/S0954579414000558

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Development and Psychopathology **26** (2014), 1186–1188

doi:10.1017/S0954579414000558

Diurnal cortisol rhythms in youth from risky families: Effects of cumulative risk exposure and variation in the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*)

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Abstract

Building on research on cumulative risk and psychopathology, this study examines how cumulative risk exposure is associated with altered diurnal cortisol rhythms in an ethnically diverse, low-income sample of youth. In addition, consistent with a diathesis-stress perspective, this study explores whether the effect of environmental risk is moderated by allelic variation in the promoter region of the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*). Results show that youth with greater cumulative risk exposure had flatter diurnal cortisol slopes, regardless of *5-HTTLPR* genotype. However, the association of cumulative risk with average cortisol output (area under the curve [AUC]) was moderated by the *5-HTTLPR* genotype. Among youth homozygous for the long allele, greater cumulative risk exposure was associated with lower cortisol AUC, driven by significant reductions in cortisol levels at waking. In contrast, there was a trend-level association between greater cumulative risk and higher cortisol AUC among youth carrying the short allele, driven by a trend-level increase in bedtime cortisol levels. Findings are discussed with regard to the relevance of dysregulated diurnal cortisol rhythms for the development of psychopathology and the implications of genetically mediated differences in psychophysiological adaptations to stress.

A large body of research has documented the association between the accumulation of risk factors and the psychosocial adjustment of young children (Barocas, Seifer, & Sameroff, 1985; Sameroff, Seifer, Zax, & Barocas, 1987). The central notion behind this work is that the experience of any single risk factor may not result in an increased risk of problems with psychosocial adjustment per se; instead, risk factors "accumulate" such that exposure to a higher number of risks increases the likelihood of poor adjustment, overwhelming coping resources and tipping the scale from healthy to unhealthy trajectories. Such models reflect the fact that risks tend to covary (Evans & Kantrowitz, 2002; Rutter, 1993).

An exciting new line of research is beginning to examine the associations between cumulative risk exposure and physiological markers of stress (Evans, 2003; Evans & English, 2002; Evans & Kim, 2007; Evans, Kim, Ting, Tesher, & Shannis, 2007; Gustafsson, Anckarsäter, Lichtenstein, Nelson, & Gustafsson, 2010). Research on the neurobiology underlying the stress response (and in particular, the concept of allostasis; McEwen, 1998; Sterling & Eyer, 1988) makes a compelling case for the consideration of physiological as well as psychosocial outcomes of cumulative risk. The concept of allostasis implies that when an organism experiences or anticipates a stressor, it accommodates physiologically by adjusting parameters across multiple systems to be better adapted to the stressful circumstances. Following a single, acute stressor, the system may revert to its initial setpoints, but repeated or chronic exposure to stress requires the organism to make lasting adaptations to its physiology. These changes come at a physiological cost: *allostatic load* (McEwen & Stellar, 1993), or the accumulating *wear-and-tear* that results from making repeated or sustained adaptive shifts across a broad range of physiological systems in order to match internal functioning to environmental demand (McEwen, 1998; McEwen & Seeman, 2003). Failure to make adaptive shifts in stress biology, and as a result being unprepared for environmental disruptions, also comes at a cost; and this is another contributor to allostatic load (McEwen, 1998).

Stress research in both the social and biological sciences implies costs to the individual of repeated exposures to stress. In this paper, we examine the influence of such stressors, in the form of cumulative risk, on levels of the hormone cortisol, a key product of the stress-sensitive hypothalamic–pituitary–

Funding for this project was provided by the Annie E. Casey Foundation, a William T. Grant Foundation Scholars Award (to P.A.M.), Grant R305B090007 from the Institute of Education Sciences (to C.J.W.), and Grant R305B080019 from the Institute of Education Sciences (to D.C.M.). The authors thank the participating families for their generous provision of information, time, and effort to the research process. We also thank MDRC for collecting the data used in the present study and permitting its use for the present analyses. In particular, we thank Electra Small, Ximena Portilla, and Matthew Kim for their work on processing the data used in this study.

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adrenal (HPA) axis. The HPA axis is an important physiological marker of neurobiological accommodations to stress that may underlie the link between experiences of adversity and psychopathology. Consistent with diathesis-stress theory (Eaton, 2000), we examine individual differences in the response to stress through the study of gene–environment interactions (Moffitt, Caspi, & Rutter, 2006). Prior work has suggested that individual differences, including genetically influenced predispositions, might modify the individual's first and subsequent allostatic accommodations to stressors (Ganzel, Morris, & Wethington, 2010). Thus, we examine how an individual's genetic profile may alter the association between cumulative risk exposure and physiological markers of stress. Although many studies have examined gene–environment interactions predicting mental health outcomes (especially with regard to the serotonin transporter gene [*5-HTT*]; Caspi et al., 2003), fewer studies have examined the moderating role of genetic markers in predicting physiological outcomes of life stressors (but for some exceptions, see Alexander et al., 2009; Cicchetti, Rogosch, & Oshri, 2011; Mueller et al., 2011).

In sum, this study bridges three bodies of research: social science research on the consequences of cumulative risk; neurobiological research on the physiological response to stress; and research on measured gene–environment interactions, with genetic polymorphisms as moderators of the stress/risk process. In particular, we address these associations for a sample of low-income children in preadolescence and early adolescence. As others have cogently argued (Evans & Kim, 2007), this is a key age group in which to examine such risk–physiology associations, given the hormonal, social, emotional, and physical changes that occur during this period alongside the important shifts that occur in children's ecological contexts (e.g., the changing school context of middle school).

The HPA Axis: Diurnal Rhythms, Stress, and Psychopathology

The HPA axis, one of the body's key stress-sensitive physiologic systems, has been of much interest in research on psychopathology as a mechanism by which subjective stress may be translated into biological changes relevant to the development of psychopathology (Adam, Sutton, Doane, & Mineka, 2008). Activation of the HPA axis results in increased adrenal secretion of the hormone cortisol. Basal cortisol levels follow a strong circadian pattern across the day, with momentary stress-related HPA axis activation producing increases in cortisol levels that are superimposed on this underlying diurnal pattern. The diurnal cortisol rhythm is typically characterized by high levels upon waking, a substantial (50%–60%) increase in cortisol concentration in the 30–40 min after waking (the cortisol awakening response [CAR]), and a subsequent decline over the remainder of the day, reaching a low point or nadir around midnight (Kirschbaum & Hellhammer, 1989; Pruessner et al., 1997; Weitzman et al., 1971). This diurnal rhythm is driven by a light-activated central "clock" in the suprachiasmatic nucleus of the hypothalamus (Nader, Chrousos, & Kino, 2010) and occurs as part of the basic circadian machinery for regulating alertness, appetite, and metabolic function (Dallman et al., 1994).

Prior research has revealed that children's cumulative exposure to psychosocial and physical environment risk factors is associated with elevated total cortisol production along with other physiological indicators of allostatic load (Evans, 2003; Evans & English, 2002). However, fewer studies have examined the associations between cumulative risk exposure and aspects of the diurnal cortisol rhythm. One study of early adolescents revealed an inverse U-shaped pattern of association between cumulative risk exposure (low socioeconomic status and number of negative and traumatic life events) and the CAR, such that moderate but not high levels of cumulative risk were associated with an elevated CAR (Gustafsson et al., 2010). Another recent study with preschool children found that cumulative family risk was associated with lower morning cortisol levels and a flatter diurnal cortisol slope (Zalewski, Lengua, Kiff, & Fisher, 2012). These studies provide evidence that cumulative risk exposure may be associated with alterations in the diurnal cortisol rhythm, but further research is needed to replicate and extend these findings.

More generally, exposure to a range of specific, adverse psychosocial experiences has been found to modify the shape of the diurnal cortisol rhythm (Adam, Klimes-Dougan, & Gunnar, 2007). For example, perceived loneliness, perceived stress and anger, living in a home with lower parent relationship satisfaction and low maternal warmth, and exposure to low socioeconomic status in childhood and adolescence have all been associated with flatter diurnal cortisol slopes (Adam, Hawkley, Kudielka, & Cacioppo, 2006; DeSantis, Kuzawa, & Adam, 2011; Doane & Adam, 2010; Hauner et al., 2008; Pendry & Adam, 2007). Antenatal exposure to maternal anxiety has also been associated with a flattened diurnal cortisol slope in early adolescence (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). Exposure to maternal postnatal depression has been associated with higher morning cortisol levels (Halligan, Herbert, Goodyer, & Murray, 2004), and experiencing inconsistent and disorganized parenting in childhood has been associated with a higher CAR in adolescence (Ellenbogen & Hodgins, 2009). In a meta-analysis of studies investigating the CAR in relation to specific life stressors and mood states, Chida and Steptoe (2009) found that feelings of fatigue, burnout, and exhaustion were associated with a lower CAR, although current job stress and general life stress were both associated with a higher CAR. Finally, a meta-analysis revealed a significant association of chronic stress exposure with flattened diurnal slope, lower morning cortisol levels, higher evening cortisol levels, and greater daily cortisol volume (Miller, Chen, & Zhou, 2007). The association between morning cortisol and chronic stressor exposure, however, was moderated by the controllability of the stressor and the time since stressor onset; morning cortisol levels were elevated during stressors that were still ongoing or potentially controllable, but depressed for

https://doi.org/10.1017/S0954579414000819 Published online by Cambridge University Press

stressors that were uncontrollable or were no longer ongoing. Thus, the direction of effects of psychosocial adversity may depend on what portion of the diurnal rhythm is being measured, and may also vary according to stressor timing and the ability of the individual to actively cope with the stressor.

Alterations in diurnal cortisol rhythms have in turn been associated with a host of negative physical and mental health outcomes (Adam & Kumari, 2009). Regarding mental health outcomes specifically, flattened diurnal cortisol rhythms have been shown to predict greater mental health symptom severity among early adolescents both concurrently and longitudinally (Shirtcliff & Essex, 2008). Similarly, cortisol levels have been found to be elevated across the day in children and adolescents with concurrent depression, with elevated evening cortisol in particular being associated with greater severity of depressive symptoms (Dahl et al., 1991; Lopez-Duran, Kovacs, & George, 2009; Van den Bergh & Van Calster, 2009). In prospective studies, high peaks in morning cortisol and a higher CAR have been found to predict the onset of major depressive disorder in youth (Adam et al., 2010; Goodyer, Herbert, Tamplin, & Altham, 2000; Halligan, Herbert, Goodyer, & Murray, 2007). Conversely, prior episodes of major depressive disorder have been found to predict flattened diurnal cortisol slopes in late adolescence (Doane et al., 2013).

Brain-Based Allostatic Load and the HPA Axis: Reciprocal Interactions

Although the precise neurobiological mechanisms linking diurnal cortisol rhythms and psychopathology are still unclear, altered HPA axis function may be both a product and a cause of central nervous system adaptations to stress that increase risk for psychopathology. Activity of the HPA axis is modulated by various brain regions that are involved in the processing of threat-related information, including the amygdala, hippocampus, and medial prefrontal cortex (mPFC; Franklin, Saab, & Mansuy, 2012; Herman, Ostrander, Mueller, & Figueiredo, 2005). Structural and functional abnormalities in these regions are observed following chronic stress in humans and animals (Frodl & O'Keane, 2013; McEwen, 2007; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006) and are associated with stress-related psychopathology, including depression and posttraumatic stress disorder (Disner, Beevers, Haigh, & Beck, 2011; Koenigs & Grafman, 2009; Sheline, 2003). Such central allostatic accommodations to stress may disrupt the normal pattern of cortisol secretion throughout the day through top-down regulation of HPA axis activity, thereby resulting in disrupted diurnal cortisol rhythms as a peripheral marker of central allostatic load.

Cortisol also exerts bottom-up actions on brain structure and function via glucocorticoid receptors and mineralocorticoid receptors expressed in numerous brain regions, including the hippocampus, amygdala, and mPFC (Herman et al., 2005). Over time, chronically elevated cortisol concentrations, such as are associated with chronic stress exposure, can induce potentially deleterious structural and functional changes in these regions (de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998; McEwen, 2007; Wellman, 2001), which may mediate some of the cognitive and emotional symptoms observed in affective disorder (Liston et al., 2006; McEwen, 2005). It is intriguing that recent research suggests that atypically elevated cortisol concentrations during the low point of the diurnal rhythm (evening in humans) may exert amplified effects on target tissues because of enhanced glucocorticoid receptor activity at this time (Kino & Chrousos, 2011). Thus, elevated cortisol concentrations in the evening may be particularly likely to contribute to brain-based allostatic load.

The *5-HTTLPR* Genotype: A Potential Moderator of the Association Between Life Adversity and HPA Axis Functioning

The degree to which diurnal cortisol rhythms are sensitive to life stressors can vary greatly between individuals. For example, some but not all children who experience maltreatment exhibit abnormal diurnal cortisol rhythms (Cicchetti & Rogosch, 2001; Cicchetti, Rogosch, Gunnar, & Toth, 2010; Cicchetti et al., 2011). Consistent with the diathesis-stress perspective, these findings suggest that some individuals are more psychophysiologically susceptible to adverse experiences than are others. A growing research base has documented that genetic variations, among many other personal and environmental risk and protective factors, influence individual differences in susceptibility to disorder following life adversity (Moffitt et al., 2006).

One genetic marker that has been shown to moderate individuals' psychological and physiological responses to life stressors is a variable length polymorphism in the promoter region of the serotonin transporter (*5-HTT*) gene, *SLC6A4*. This polymorphic region, termed *5-HTTLPR*, displays short and long allelic variants, with the short allele exhibiting lower transcriptional efficiency and reduced serotonin transporter function in vitro (Heils et al., 1996; Lesch et al., 1996). The accumulated evidence suggests that the short allele is associated with a phenotype of negative affectivity (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) or hypervigilance to environmental stimuli (Homberg & Lesch, 2011). Numerous studies have revealed that individuals carrying the *5-HTTLPR* short allele show increased vulnerability to a variety of psychopathological conditions in the context of environmental adversity. The strongest evidence has emerged for the *5-HTTLPR* short allele as a marker of vulnerability to depression following life stressors (reviewed in Caspi et al., 2010; Karg, Burmeister, Shedden, & Sen, 2011; Uher & McGuffin, 2008, 2010). The short allele has also been found to increase the risk of antisocial behavior in maltreated children (Cicchetti, Rogosch, & Thibodeau, 2012) and aggression in chronically stressed young adults (Conway et al., 2012).

Research in both humans and animal models reveals that variations in the *5-HTTLPR* can influence HPA axis functioning. The serotonergic system is involved in early developmental programming of the HPA axis, particularly through

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