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Research Paper

Individual differences in early adolescents' latent trait cortisol: Interaction of early adversity and 5-HTTLPR

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ABSTRACT

The present study aimed to examine the interaction of 5-HTTLPR and early adversity on trait-like levels of cortisol. A community sample of 117 early adolescent girls (*M* age = 12.39 years) provided DNA samples for 5-HTTLPR genotyping, and saliva samples for assessing cortisol 3 times a day (waking, 30 min post-waking, and bedtime) over a three-day period. Latent trait cortisol (LTC) was modeled using the first 2 samples of each day. Early adversity was assessed with objective contextual stress interviews with adolescents and their mothers. A significant 5-HTTLPR × early adversity interaction indicated that greater early adversity was associated with *lower* LTC levels, but only among individuals with either L/L or S/L genotype. Findings suggest that serotonergic genetic variation may influence the impact of early adversity on individual differences in HPA-axis regulation. Future research should explore whether this interaction contributes to the development of psychopathology through HPA axis functioning.

1. Introduction

At the core of the allostatic load framework is an attempt to explain biological mechanisms in the effects of cumulative stress on health and human development (McEwen, 1998). Within this framework, environmentally induced alterations in the activity of the hypothalamic-pituitary-adrenal (HPA) axis are considered key mediators in the pathway linking adversity to differential outcomes (Danese & McEwen, 2012; Gunnar & Quevedo, 2007; McEwen, 2000). More recently, researchers have begun to explore the role of gene-by-environment (G x E) interactions in the allostatic load model. One of the candidate genes under investigation is a functional polymorphism located in the promoter region of the serotonin transporter gene (SLC6A4; also known as 5-HTT). Research suggests that serotonin transporter-linked polymorphic region (5-HTTLPR) conveys sensitivity to stress (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). This is supported by the largest and most recent meta-analysis (Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014), although earlier, smaller meta-analyses drew negative conclusions (e.g., Risch et al., 2009).

Several studies have revealed the moderating effect of this serotonin transporter genotype in the relationship between early adversity and indicators of allostatic load (e.g., Alexander et al., 2009; Mueller et al., 2011; Willner, Morris, McCoy, & Adam, 2014). Findings such as these raise intriguing questions about genetic susceptibility to allostatic load in altering HPA-axis functioning. Recent research has primarily focused on the association between cumulative adversity or stressful life events, 5-HTTLPR, and stress-related HPA reactivity (Alexander et al., 2009; Mueller et al., 2011). However, allostatic load manifests not only in dynamic responses to acute stress but also in changes in the overall typical diurnal patterns of the HPA-axis. Latent trait cortisol (LTC) provides an index of variation in HPA-axis functioning that is independent of state-specific change (Doane, Chen, Sladek, Van Lenten, & Granger, 2015). LTC has been associated with early adversity (Stroud, Chen, Doane, & Granger, 2016a), recent stress (Stroud, Chen, Doane, & Granger, 2016b), problem behavior (Shirtcliff, Granger, Booth, & Johnson, 2005), and cardiovascular risk factors (Yeung et al., 2016). In the current study, we begin to address an important knowledge gap by exploring whether early adversity interacts with allelic variation in 5-HTTLPR to influence LTC level.

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1.1. Early adversity and the HPA-axis

Child abuse and neglect (i.e., childhood maltreatment) have received considerable attention in research examining the impact of early adversity on HPA-axis activity (Alink, Cicchetti, Kim, & Rogosch, 2012; Cicchetti & Rogosch, 2001; Rogosch, Dackis, & Cicchetti, 2011; Tarullo & Gunnar, 2006). Not surprisingly, childhood maltreatment is associated with a broad range of adverse outcomes later in life, including posttraumatic stress disorder (e.g., Widom, 1999), major depression (e.g., Vrshek-Schallhorn et al., 2014; Widom, DuMont, & Czaja, 2007), and substance use (e.g., Scott, Smith, & Ellis, 2010). Furthermore, childhood maltreatment is associated with alterations in HPA-axis functioning, as indexed by diurnal cortisol profiles (i.e., the daily pattern of cortisol secretion), and cortisol reactivity (i.e., changes in cortisol level in response to a stressor; Alink et al., 2012; Cicchetti, Rogosch, Gunnar, & Toth, 2010; Neigh, Gillespie, & Nemeroff, 2009). Under the allostatic load framework, childhood maltreatment leads to "wear and tear" in the HPA-axis and alters its function, which in turn contributes to a variety of adverse health outcomes (McEwen, 2000)

Less severe, but more common, types of early adversity have also been linked to variation in HPA-axis functioning (e.g., Miller, Chen, & Zhou, 2007; Repetti, Taylor, & Seeman, 2002). Such early adversity often captures adverse experiences within the family environment, including, for example, exposure to marital conflict, financial hardship, and death or illness of family members (e.g., Miller et al., 2007; Repetti et al., 2002). Importantly, the allostatic load model emphasizes the cumulative effects of early adversity on regulatory systems (Lupien et al., 2006). Thus, even though some of these early adverse experiences may be relatively less severe when considered in isolation, it is posited that their cumulative effect over time can generate allostatic load. In support of this, studies have found that the cumulative effect of multiple early adversities was associated with alterations in HPA axis activity (Repetti et al., 2002; Stroud et al., 2016a; Zalewski, Lengua, Kiff, & Fisher, 2012). For instance, a recent study showed that the *cumulative* effect of multiple adverse family environment factors (e.g., parental divorce, residential instability)—but not most of the individual effects of each adverse family environment factor—was associated with lower morning cortisol levels (Zalewski et al., 2012).

In studies examining the effects of early adversity on HPA axis functioning, investigators have operationalized HPA-axis functioning using several indicators of the diurnal cortisol rhythm, including the cortisol awakening response (CAR), the diurnal slope, and the area under the curve (AUC) (Almeida, Piazza, & Stawski, 2009; Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Stalder et al., 2016). As expected of an environmentally sensitive system, close evaluation of the psychometrics properties of these indicators suggests that they exhibit considerable day-to-day variation. For example, Ross, Murphy, Adam, Chen, and Miller (2014) reported that over 70% of the variability in the CAR, and between 50% and 75% of the variability in the diurnal slope, could be attributed to day-to-day variation. Similarly, Doane et al. (2015) collected salivary cortisol data multiple times within a day, over a three-day period, at three measurement occasions, and reported that 82.30% and 81.25% of the variance in the CAR and diurnal slope (respectively) were attributable to day-to-day variation. In an effort to index stable intrinsic individual differences in HPA axis functioning, rather than day-to-day variation, researchers have employed a latent variable approach to isolate a latent trait factor that represents stable individual differences in cortisol (e.g., Doane et al., 2015; Stroud et al., 2016a). Consistent with the allostatic load framework, the handful of studies to date have demonstrated associations between LTC level and early adversity and recent acute stress (Doane et al., 2015; Stroud et al., 2016a, 2016b).

1.2. 5-HTTLPR as a moderator of the relationship between early adversity and LTC level

Cumulative early adversity is thought to get "under the skin" by altering individuals' biological stress systems, including HPA-axis activity. Factors that affect sensitivity to stress at the individual level are also likely to affect the influence of cumulative early adversity on HPA axis activity. Although no prior research has examined the heritability of LTC levels, twin studies support substantial genetic contributions to other cortisol indices, including cortisol reactivity and the diurnal rhythm, across multiple developmental stages (Bartels, Berg, Sluyter, Boomsma, & Geus, 2003; Federenko, Nagamine, Hellhammer, Wadhwa, & Wüst, 2004; Steptoe, Jaarsveld, Semmler, Plomin, & Wardle, 2009). This suggests that genetic factors may also contribute to LTC level. Furthermore, research suggests that variation in one such factor—a functional polymorphism, 5-HTTLPR—modulated individuals' sensitivity to stress (Caspi et al., 2010). More specifically, individuals who expressed the short (S) as opposed to the long allele (L) exhibited lower transcriptional efficiency, and reduced serotonin transporter function (Heils et al., 1996; Lesch et al., 1996), which has been linked with hypervigilance to environmental stimuli (Homberg & Lesch, 2011).

The serotonin transporter genotype may moderate the association between cumulative early adversity and HPA-axis functioning for at least three reasons. First, the 5-HTTLPR genotype has been linked to individual differences in the functioning of brain regions involved in emotion processing and regulation. For example, 5-HTTLPR S-carriers show heightened amygdala neuronal activity in response to fearful stimuli (Hariri et al., 2002; Heinz et al., 2005), and greater coupling between the amygdala and the ventromedial prefrontal cortex, which integrates input from amygdala to guide behavioral responses in decision making (Heinz et al., 2005; Pezawas et al., 2005). Additionally, research suggests that the amygdala may enhance cortisol secretion, and there is increasing evidence supporting limbic-HPA interaction (Herman, Ostrander, Mueller, & Figueiredo, 2005).

Second, accumulating evidence indicates that the serotonergic system is involved in the development of HPA-axis. For example, findings from animal studies suggest that the serotonergic system affects early programming of the HPA-axis (for review see Andrews & Matthews, 2004). Furthermore, a meta-analysis of 11 studies with human participants revealed a significant association between the 5-HTTLPR genotype and cortisol stress reactivity, with individuals with S/S genotype displaying heightened levels of cortisol reactivity to acute stressors, as compared to individuals with S/L or L/L genotypes (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2013). Fewer studies have examined associations between the 5-HTTLPR and diurnal cortisol indicators. Chen, Joormann, Hallmayer, and Gotlib (2009) found that adolescent girls with S/S genotype had higher waking cortisol levels, as compared to L-carriers, a finding consistent with a prior study which demonstrated that the S carriers had higher morning cortisol levels (Goodyer, Bacon, Ban, Croudace, & Herbert, 2009).

Third, a few studies have explicitly examined the interplay between 5-HTTLPR, stress (early adversity or recent acute stress), and HPA axis functioning (e.g., Alexander et al., 2009; Willner et al., 2014). Two studies have focused on laboratory-based cortisol reactivity. First, Alexander et al. (2009) revealed that S/S young adults who self-reported higher degree of stressful life events based on the Life Events Checklist (e.g., motor vehicle accident, combat, the sudden unexpected death of a loved one) showed the greatest stress-related cortisol reactivity. Second, Mueller et al. (2011) also found a significant interaction between self-reported early adversity (i.e., the number of stressful life events during the first five years assessed with life history calendar) and 5-HTTLPR among young adults. Specifically, among