



Genetic and environmental influences on individual differences in cortisol level and circadian rhythm in middle childhood

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ABSTRACT

Individuals differ widely in cortisol output over the day, but the etiology of these individual differences remains poorly understood. Twin studies are useful for quantifying genetic and environmental influences on the variation in cortisol output, lending insight into underlying influences on the components of Hypothalamic–Pituitary–Adrenal (HPA) axis functioning.

Salivary cortisol was assayed on 446 twin pairs (157 monozygotic, 289 dizygotic; ages 7–8). Parents helped youth collect saliva 30 min after waking, mid-afternoon, and 30 min prior to bedtime across 3 consecutive days. We used hierarchical linear modeling to extract predicted cortisol levels and to distinguish cortisol's diurnal rhythm using a slopes-as-outcome piecewise growth curve model; two slopes captured the morning-to-afternoon and afternoon-to-evening rhythm, respectively. Separate genetic models were then fit to cortisol level at waking, mid-afternoon, and evening as well as the diurnal rhythm across morning-to-afternoon and afternoon-to-evening hours.

Three results from these analyses are striking. First, morning-to-afternoon cortisol level showed the highest additive genetic variance (heritability), consistent with prior research. Second, cortisol's diurnal rhythm had an additive genetic component, particularly across the morning-to-afternoon hours. In contrast, additive genetic variation did not significantly contribute to variation in afternoon-to-evening slope. Third, the majority of variance in cortisol concentration was associated with shared family environments. In summary, both genetic and environmental factors influence cortisol's circadian rhythm, and they do so differentially across the day.

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Introduction

The Hypothalamic–Pituitary–Adrenal (HPA) axis is both highly sensitive to context and highly responsive to stress; it helps individuals to recalibrate or adapt their physiological activity to meet the demands of a constantly changing environment. Cortisol is the principal end-product steroid hormone produced by the HPA axis. A single measure of cortisol differentially reflects the confluence of momentary, day-to-day, rhythmic and individual difference factors (Adam et al., 2006, 2007). Cortisol reactivity to acute challenges has often been investigated (Dickerson and Kemeny, 2004), yet cortisol is also responsive to chronic environmental forces; moreover, cortisol has a stable, trait-like component (Essex et al., 2002; Shirtcliff and Essex, 2008). Individual differences in cortisol have been linked to a broad range of physiological outcomes such as cardiovascular function, metabolism, and neural functions (Lupien et al., 2006; Sapolsky

et al., 2000), as well as to mental and physical health outcomes (Boyce et al., 1995; Pajer et al., 2001; Smider et al., 2002; Taylor et al., 2004), rendering HPA functioning clearly important but difficult to attribute to any single process.

Arguably, the strongest influence on cortisol is the time of day when a sample is collected (Vreeburg et al., 2009). An individual's physiological activity is recalibrated daily to allow intrinsic biological rhythms to adjust to extrinsic environmental signals (Carskadon et al., 1997). Basal HPA activity thus follows a circadian rhythm with the highest activity occurring within the first hour after awakening, after which activity decreases throughout the day (Kirschbaum and Hellhammer, 1989). This rhythm is also an outcome of interest as (a) disruptions in rhythmicity are key components of allostasis and allostatic load (Lupien et al., 2006; Skinner et al., 2011); (b) rhythmicity is a reliable indicator of a broad range of (dys)regulatory processes (Siever and Davis, 1985); (c) large individual differences in cortisol levels exist at all points of the circadian cortisol curve (Smyth et al., 1997); and (d) there are multiple illustrations that high (or low) cortisol levels are associated with negative outcomes differentially depending on the time of day (Ruttle et al., 2011; Shirtcliff and Essex, 2008). Thus, understanding

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influences on HPA functioning is important because the underlying components may be partly controlled by unique genetic mechanisms (Veen et al., 2011), and these underlying mechanisms may be differentially related to behavioral, emotional and physiological characteristics and persistent risk factors (Shirtcliff and Essex, 2008).

Summary of twin study findings

Twin methodology constitutes a powerful approach for identifying the genetic and environmental (shared and unique) influences on HPA functioning. Nevertheless, few studies have explored the genetic architecture of cortisol in humans. Bartels et al. (2003a, 2003b) reviewed nine published twin studies. Results varied widely, with some studies reporting no twin similarity in cortisol levels and others finding that genetic factors accounted for 45–72% of individual variation. Bartels and colleagues noted that many of these earlier studies suffered from small sample sizes, with samples ranging from as low as 7 twin pairs to a high of only 150 twin pairs. Several studies failed to account for the diurnal rhythm at either the sample collection or analysis phase. In addition, most of the studies reviewed focused on adults. Simultaneously analyzing all available data from twin studies using similar methodologies, without regard to timing of sample collection, Bartels et al. reported that 62% of cortisol variation was associated with genetic variation.

Since the Bartels et al. (2003a) review, some larger twin studies have been published that avoided many of the problems highlighted in the review. Riese et al. (2009) measured salivary cortisol in adult female twins at four time points – waking, 30, 45, and 60 min after waking. Genetic factors contributed to the variance in all measures of early morning cortisol (heritability ranged from 46% to 69%) with the remaining variation was accounted for by non-shared environmental factors. Kupper et al. (2005) also found evidence for genetic influences on early morning cortisol (waking and 30 min after waking) in adult twins. Mid-day to late evening samples, however, did not appear to be affected by familial factors. Turning to studies of children and adolescents, Bartels et al. (2003a, 2003b) measured salivary cortisol in 12 year-old twins at multiple time points from waking to evening across two days. Familial factors, genes or shared environment, influenced cortisol at all times, except for the evening sample. However, only the mid-morning sample was influenced unambiguously by genetic factors (heritability = 56%). Genetic and shared environmental factors could not be disambiguated at other collection times (waking and mid-day). Steptoe et al. (2009) measured afternoon salivary cortisol in 11 year old twins. Genetic factors accounted for 56% of cortisol's variance. In contrast, Schreiber et al. (2006) found that shared family environment accounted for the majority of variation in afternoon cortisol measured in 7–8 year old twins (69%), with the remaining variation accounted for by non-shared environmental factors, and no significant additive genetic influences.

In summary, previous studies consistently find that variation in morning cortisol level appears to be at least partially heritable. This is true regardless of the age of the participants. Evidence for genetic or shared environmental influences on cortisol in mid-afternoon, however, remains mixed. Interestingly, previous studies suggest that variation on cortisol sampled in the late evening is largely influenced by individual specific factors in both adults and children, despite the vastly increased time twins spend together in childhood compared to adulthood.

Even within these newer, more rigorous investigations, few studies attempted to obtain *stable* measures of basal cortisol. Most investigators relied on cortisol measured at a single time point or, at best, within a single day. Studies that did collect multiple cortisol measures typically analyzed the cortisol serially, rather than employing analytic strategies that would help uncover the underlying unique components of cortisol measures (Shirtcliff et al., *in press*). Importantly, the possibility of an independent genetic contribution to

cortisol's diurnal rhythm has never been assessed although the heritability patterns across the day hint that the diurnal rhythm itself may be partially heritable.

Goals of the study

We aimed to clarify outstanding issues concerning the quantitative genetic of variation in basal cortisol. We used hierarchical linear modeling (HLM) to extract predicted cortisol levels and to distinguish cortisol's diurnal rhythm using a slopes-as-outcome piecewise growth curve model (Shirtcliff et al., *in press*). Using these improved measures of cortisol level and slope, we sought to powerfully test the emerging hypothesis suggested by trends in the literature: a) individual differences in stable measures of morning cortisol will be primarily influenced by the heritable factors, but late day stable measures of cortisol will be influenced to a greater degree by shared environment; and b) likewise, morning-to-afternoon *slope* will exhibit significant heritable influences whereas afternoon-to-evening *slope* will be influenced primarily by environmental factors.

Materials and methods

Participants

Participants included a subset of twin pairs (N=452 pairs) recruited from the birth record-based Wisconsin Twin Project; all twins were born between the years 1997 and 2002. Salivary samples were collected during a follow-up study, when most twins were between the ages of 7–8 years (M = 90.4 months, SD = 8.5). The sample was 50% female and included approximately equal numbers of monozygotic (MZ; 35%), same-sex dizygotic (DZ; 33%) and opposite-sex DZ (31%) twin pairs. Mothers had an average education of 15.2 years and fathers had an average education of 14.7 years, median family income was \$60,000–\$70,000, and the majority of twin pairs were Caucasian (98%). Compliance was very high and missing data were minimal, with 873 twins (97% of the total sample) providing at least one saliva sample (N's per collection time/day ranged from 762 to 820) and 59% providing all nine saliva samples. Out of the 7857 saliva samples requested, the N = 7142 samples obtained were sufficient enough to measure cortisol (90.9%).

Zygosity

Zygosity was classified during the age two assessment using the Zygosity Questionnaire for Young Twins (Goldsmith, 1991), which has demonstrated over 95% agreement with genotypic zygosity determination (Forget-Dubois et al., 2003). Cases of ambiguous zygosity were resolved via hospital placenta(e) reports (an unambiguous monozygotic placenta indicating monozygosity) and follow-up zygosity questionnaires. If this information was not definitive, photographs, video images, and genotyping were utilized. Five pairs of twins (1.1%) with unknown or ambiguous zygosity who were not genotyped were excluded from genetic analyses.

Procedure

We contacted families for a telephone interview to screen for symptoms of psychopathology when twins were aged 7–8 years. Twins were selected for a follow-up study if they were deemed broadly "at-risk" or "control" (see Lemery-Chalfant et al., 2006 for selection details). We also included all unselected co-twins in the follow-up study. This resulted in 37% children designated at-risk, 34% designated control, and 29% unselected co-twins. Shortly after the screening process (6–10 months), parents completed a series of telephone interviews and mailed questionnaires; there was also a home visit. Families provided saliva samples for assaying as described

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