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Etiologic specificity of waking Cortisol: Links with maternal history of depression and anxiety in adolescent girls

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ABSTRACT

Background: Many previous studies have indicated that individuals who are depressed or at risk for depression are characterized by increased levels of morning cortisol and a greater cortisol awakening response (CAR). However, despite the high comorbidity between depressive and anxiety disorders, fewer studies have examined whether these diurnal cortisol abnormalities are also characteristic of anxiety or risk for anxiety.
Methods: In the present study we examined cortisol in a community sample of 476 female adolescents and related it to maternal history of depression and/or anxiety disorders. Salivary cortisol was collected at waking, 30 min post waking, and in the evening on three weekdays.
Results: Contrary to prior results, offspring at risk for depression did not have increased morning cortisol or CAR. However, offspring at risk for anxiety disorders had elevated 30 min cortisol and total cortisol produced throughout the day; this effect was primarily driven by offspring of mothers with panic disorder or agoraphobia. Additionally, levels of cortisol were highest among offspring of mothers with multiple anxiety diagnoses.
Limitations: The study is limited to female adolescents and maternal diagnostic history. Additionally, some diagnoses could not be examined as a result of too few cases (e.g. GAD).
Conclusions: Overall, these results underscore the importance of considering anxiety when examining the association of diurnal cortisol abnormalities with risk for psychopathology, as it may have influenced prior observations of elevated morning cortisol in depression.

1. Introduction

Response to stress is thought to play a major role in the etiology of depression (Brown et al., 1987), which has led to a large literature examining associations of depression with salivary cortisol, an easily accessible index of the limbic-hypothalamic-pituitary-adrenal axis (LHPA), the primary biological stress system. Salivary cortisol has a diurnal pattern that is characterized by a sharp increase shortly after waking referred to as the cortisol awakening response (CAR; e.g. Fries et al., 2009; Wüst et al., 2000), followed by a decrease throughout the rest of the day. Several studies have found that depressed individuals exhibit increased morning salivary cortisol and an elevated CAR compared to healthy controls (e.g. Bhagwagar et al., 2005; Pruessner et al., 2003; Vreeburg et al., 2009). Although there have been some conflicting reports (Huber et al., 2006; Stetler and Miller, 2005), a meta-analysis indicates that morning cortisol is elevated in depression (Stetler and Miller, 2011).

Morning cortisol and CAR have also been posited to serve as vulnerability markers for the subsequent development of depression. For example, studies of child, adolescent, and adult offspring of depressed mothers have exhibited increased morning cortisol and/or CAR relative to offspring of never depressed mothers (e.g. Dougherty et al., 2009, 2013; Foland-Ross et al., 2014; Halligan et al., 2004; LeMoult et al., 2015; Vreeburg et al., 2010a). In addition, several studies have reported that increased morning cortisol and CAR predict the onset of depression (Adam et al., 2010; Goodyer et al., 2000; Harris et al., 2000; but see Carnegie et al. (2014) for negative findings).

Despite the well-established comorbidity between depression and anxiety, (e.g. Cummings et al., 2014), less is known about the association of cortisol and CAR with common anxiety disorders such as specific phobia, social phobia, and panic/agoraphobia (posttraumatic stress disorder, no longer classified as an anxiety disorder, has

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been much better studied). A small, but growing body of research suggests that morning cortisol and CAR are also elevated in anxious individuals (e.g. Mantella, et al., 2008; Vreeburg et al., 2010b). However, others find decreased morning cortisol in individuals with anxiety disorders (Hek et al., 2013). Unfortunately, most studies have either collapsed across all anxiety disorders or examined only a single anxiety disorder; hence, it is unclear whether particular forms of anxiety have differential associations with cortisol.

There are also fewer studies examining morning cortisol/CAR as a vulnerability marker of anxiety in offspring. However, similar to the literature on cortisol and risk for depression, a few studies have reported increased morning cortisol in offspring of mothers with anxiety disorders. Studies of 6-year old (Dougherty et al., 2013) and adult (Vreeburg et al., 2010a) offspring of mothers with anxiety disorders found increased morning cortisol and CAR compared to controls, although one study found decreased CAR in adolescents as a function of maternal prenatal anxiety (O'Donnell et al., 2013). In addition, there is recent evidence that increased CAR predicts the first onset of social anxiety disorder in young adults (Adam et al., 2014).

Thus, offspring and prospective studies suggest that increased morning cortisol/CAR may be a vulnerability marker for depression. A similar pattern of increased morning cortisol/CAR may also be a vulnerability factor for anxiety disorders, but the literature is limited. Additionally, most studies of salivary cortisol in individuals at risk for depression and anxiety compare offspring of parents with and without only one of these disorders rather than look among anxiety disorders, and do not consider comorbidity. The only two studies to consider this question were in conflict, with one reporting that increased morning cortisol in offspring at risk for anxiety is largely explained by risk for depression (Vreeburg et al., 2010a), whereas the other found increased morning cortisol in offspring at risk for anxiety even after adjusting for maternal depression (Dougherty et al., 2013).

In the present study, a cohort of female adolescents provided salivary cortisol at waking, 30 min post waking, and in the evening. We examined whether offspring cortisol was differentially associated with maternal histories of anxiety and depression taking comorbidity into account as well as diagnoses in the offspring themselves.

2. Methods

2.1. Participants

A sample of 550 adolescent females with at least one available biological parent were recruited from Long Island, New York, to participate in the Adolescent Development of Emotions and Personality Traits (ADEPT) study. Details of the recruitment and inclusion criteria can be found elsewhere (Nelson et al., 2015). Briefly, girls in the sample were included if they were between ages 13.5–15.5, fluent in English such that they could independently read/understand questionnaire materials, and had at least one biological parent available for participation. While not the focus of the current study, this project was designed to identify predictors of the first onset of depression. Therefore, families were excluded if the adolescent was suspected of having met criteria for either depressive disorder or dysthymia based on a phone screen using the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) or in person diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS; Kaufman et al., 1997). Families were also excluded if the adolescent was suspected of having an intellectual disability.

We excluded participants if they did not complete at least one full day of saliva sampling that met quality standards described below (N=21), if the diagnostic interview was not conducted with the mother (N=39), or if the participant did not report information on puberty status (N=10). We also excluded offspring of mothers who were diagnosed with PTSD, GAD, and OCD, but no other diagnosis (N=4) because there were too few cases to analyze as separate groups. Thus, the final analysis sample includes 476 adolescent offspring. Adolescents had an average age of 14.4 years of age (SD=0.62) and were predominately white and non-Hispanic (N=387, 81.3%). Most families had at least one parent who completed a 4-year college degree (N=315, 66.2%). Pubertal development using the total Tanner pictures score (Morris and Udry, 1980) for this sample was an average of 7.76 (SD=1.27) on a scale of 1–10 and suggesting that most girls were nearing completion of the development of secondary sex characteristics. Self-reported pubertal development on the Pubertal Development Scale (Petersen et al., 1988) averaged 12.93 (SD=1.95) out of a possible 16 with the vast majority of girls (83.4%) having reached menarche (pubertal measures described in greater detail below). Most participants were not taking medication at the time of assessment; 12 reported taking medication for depression or anxiety, 13 reported taking medication for ADHD, and 37 reported taking allergy medication.

2.2. Maternal psychopathology

The Structured Clinical Interview for the DSM-IV (SCID; First et al., 1996) was used to assess parental psychopathology. Where applicable, dates of disorder onset and offset were calculated for the mother's first episode and current episode. All interviews were conducted by trained research staff and supervised by experienced clinical psychologists (R.K., G.P., and D.K.). Inter-rater reliability was established using 25 SCID recordings and ranged from fair to excellent (kappa=0.69–1.00 with the lowest for specific phobia and the highest for panic). While the SCID was completed with the participating parent regardless of gender, only 39 fathers completed the SCID (7% of the overall sample). We excluded these cases from the analysis sample as we would not have had sufficient power to examine effects of psychopathology differences by parent gender on offspring cortisol. Therefore, the present study only uses data concerning maternal diagnoses (final N=476).

Maternal lifetime diagnoses included major depressive or dysthymic disorders (N=101), panic disorder (N=44), agoraphobia (N=6), specific phobia (N=92), social phobia (N=84), GAD (N=16), PTSD (N=18), and OCD (N=6). Of 225 mothers with at least one diagnosis, 91 mothers (41.2%) had comorbid depression and anxiety. Of mothers with only a single depression or anxiety diagnosis, 46 had a depressive disorder, 10 had panic or agoraphobia, 39 specific phobia, 36 social phobia, and none had only GAD, PTSD, or OCD. Therefore, offspring with of mothers with a history of only GAD, PTSD, or OCD were excluded from analyses because of low caseness (defined as <20 cases). However, to ensure that our results were not altered by excluding offspring of mothers with pure diagnoses of GAD, PTSD, and OCD, we repeated our analyses including these participants and found that the results did not change. In analyses, panic disorder and agoraphobia were collapsed (N=50); however, results did not differ when using panic alone.

Based on evidence that timing of parental psychopathology can influence association with offspring cortisol (e.g., Halligan et al., 2004), we examined two aspects of the timing of maternal diagnoses in relation to the offspring's cortisol assessment: (1) current diagnosis at time of saliva collection vs. remitted and (2) prenatal onset vs. postnatal onset. For the maternal diagnoses included in analyses diagnostic status was: 16 current and 85 remitted for depressive or dysthymic disorder, 44 and 48 for specific phobia, 27 and 57 for social phobia, and 9 and 41 for panic/agoraphobia. Timing of onset was: 70 after birth of the participant and 31 prior for depressive disorders, 17 and 71 for specific phobia (onset is unknown for four mothers), 5 and 76 for social phobia (unknown for three), and 17 and 32 for panic/agoraphobia (unknown for one).