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Prospective associations between the cortisol awakening response and first onsets of anxiety disorders over a six-year follow-up — 2013 Curt Richter Award Winner

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Summary Cross-sectional associations have been found between anxiety disorders (ADs) and hypothalamic-pituitary-adrenal (HPA) axis functioning, as measured by levels of salivary cortisol, but prospective data are lacking, as are studies examining specific ADs. We have previously shown that one aspect of the diurnal rhythm of cortisol, the cortisol awakening response (CAR), prospectively predicts both new onsets and recurrences of major depressive disorder (MDD). Here we sought to examine whether it also predicts ADs. Participants ($N = 232$) were drawn from the larger Northwestern-UCLA Youth Emotion Project, a two-site, longitudinal study of older adolescents, which aims to identify common and specific risk factors for mood and anxiety disorders. After baseline interviews for mental health diagnoses, a subset of adolescents completed a three-day cortisol sampling protocol measuring the CAR and other diurnal rhythm indices. Participants with past or current anxiety disorders at the time of cortisol measurement were excluded and Cox regression (survival analysis) was used to predict first onsets of ADs over the subsequent six years. AD onsets ($N = 25$), the largest subset of which were social anxiety disorder (SAD) onsets ($N = 11$), were observed over six annual follow up diagnostic interviews. Even when statistically adjusting for past and prospective MDD onsets and other covariates, a

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higher CAR significantly predicted increased first onsets of ADs ($HR = 2.20$, $p < .05$). A higher CAR was also a strong and significant predictor of the subset of SAD onsets ($HR = 5.37$, $p < .005$). Implications for the etiology of ADs, with a focus on SAD, are discussed.

1. Introduction

Alterations in hypothalamic pituitary adrenal (HPA) axis functioning are frequently observed in individuals with major depressive disorder (MDD) (Ehlert et al., 2001; Thase et al., 2002; Doane et al., 2013; Herbert, 2013). Recent meta-analytic evidence suggests that depressed individuals show higher basal cortisol, on average, than individuals without depression (Lopez-Duran et al., 2009; Knorr et al., 2010). Not all studies and not all depressed individuals show elevated cortisol, and differences are not sufficiently large for basal cortisol to be used to discriminate depressed individuals from controls (Adam et al., 2008; Knorr et al., 2010). Evidence is sufficient, however, for altered HPA axis activity to be proposed as a risk marker that potentially plays an etiological role in the development of major depressive disorder (Ehlert et al., 2001; Thase et al., 2002; Herbert, 2013). Although prospective studies are rare, our own prior research has shown that one element of the cortisol diurnal rhythm, the cortisol awakening response (i.e., increase in cortisol levels from waking to 30 or 40 min after waking), is a significant prospective predictor of MDD, with individuals with a higher CAR showing increased risk for MDD over the subsequent 2.5 years (Adam et al., 2010; Vrshek-Schallhorn et al., 2013). Other studies have found high morning levels (measured at 8 AM) to be a significant prospective predictor of MDD (Goodyer et al., 2000; Harris et al., 2000; Halligan et al., 2007).

Despite the fact that MDD and anxiety disorders (ADs) are highly comorbid and share many features and risk factors (e.g., Clark and Watson, 1991; Mineka et al., 1998; Watson, 2005), far less research has examined HPA-axis activity in ADs. Cross-sectional research has suggested associations between current ADs and HPA-axis activity, as indexed by salivary cortisol (see below). Prospective longitudinal studies, however, predicting first onsets of ADs from premorbid basal cortisol levels, are to our knowledge entirely absent from the literature. In the current study, we examined whether measures of basal cortisol, including the CAR, collected in late adolescence, predicted first onsets of anxiety disorders over the subsequent six years.

Cortisol, the primary hormonal product of the HPA axis, is the most frequently measured HPA-axis marker in research on emotional disorders, including ADs, in part because the non-invasive nature of salivary cortisol collection allows repeated measurement of cortisol in the context of daily life (Kirschbaum and Helhammer, 2000; Adam et al., 2008). Cortisol levels increase in response to stress, and also follow a strong circadian rhythm. The typical basal/diurnal cortisol rhythm involves high levels upon waking, a substantial (50—60%) increase in the 30—40 min after waking (the cortisol awakening response or CAR), and a subsequent decline over the remainder of the day, reaching a low point or nadir around midnight (Weitzman et al., 1971; Kirschbaum and Hellhammer, 1989; Pruessner et al., 1997).

Anxiety disorders (such as panic disorder with or without agoraphobia, specific phobia, social anxiety disorder, and generalized anxiety disorder) and related disorders (obsessive-compulsive disorder, post-traumatic stress disorder, and acute stress disorder)[1] are very prevalent. They also tend to be chronic in nature (e.g., Ferdinand and Verhuist, 1995; Pollack et al., 1996), and contribute high disease burden and cost to society (Greenberg et al., 1999; Kessler and Greenberg, 2002). In addition, individuals with anxiety disorders often go on to develop later MDD (Fava et al., 2000; Stein et al., 2001). Among the anxiety disorders, social anxiety disorder (SAD; also known as social phobia) is one of the most common mental disorders in the U.S. (Kessler et al., 2005), and is often associated with a high degree of impairment, including increased rates of unemployment, absenteeism from work, financial dependence on the state, use of prescription medications, and drug dependency (Lecrubier et al., 2000; Patel et al., 2002).

SAD is of particular theoretical interest in relation to HPA-axis activity (Schiefelbein and Susman, 2006), and the CAR in particular. The hallmark of social anxiety disorder is fear of negative social evaluation (American Psychiatric Association, 2000), and compared to other types of stressors, social evaluative threat has been found to be the most powerful activator of the HPA axis in studies of experimentally-induced stress (Dickerson and Kemeny, 2004). Social anxiety symptoms in adolescents are associated with perceived loneliness, perceived peer rejection and peer conflict (Storch and Masia-Warner, 2004; La Greca and Harrison, 2005). Perceived peer rejection and peer conflict have in turn been associated with cortisol activation (Flinn and England, 1995; Stroud et al., 2009) and perceived loneliness has been associated with a higher cortisol awakening response, in particular (Steptoe et al., 2004; Adam et al., 2006; Doane and Adam, 2010).

Establishment of effective peer and romantic relationships are some of the core developmental challenges of adolescence and the transition to adulthood (Roisman et al., 2004). Recent theory and research proposes the cortisol awakening response as an allostatic response, helping to mobilize the body's physiological resources to cope with anticipated daily challenges, including social engagement (Adam et al., 2006). Following these proposals, one would expect to see an elevated CAR in response to either anticipated or perceived acute social challenges. Elevations in the CAR have, however, been proposed to be costly in the long-term. The high and rapidly increasing levels of cortisol found in the morning hours and associated with the CAR in particular, are likely to occupy low-affinity glucocorticoid

[1] These three disorders were previously classified as anxiety disorders in DSM-IV (American Psychiatric Association, 2000); DSM-V (American Psychiatric Association, 2013) classifies them as a distinct but related category of disorder.