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Diurnal coupling between testosterone and cortisol from adolescence to older adulthood

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ABSTRACT

The hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes are typically conceptualized as mutually inhibitory systems; however, previous studies have found evidence for positive within-person associations (*i.e., coupling*) between cortisol and testosterone. One developmental hypothesis is that positive testosterone-cortisol coupling is unique to the adolescent period and that coupling becomes attenuated, or even switches direction, in adulthood. This study used a lifespan sample ($N = 292$, ages 11–88) to test for age-related differences in coupling between cortisol and testosterone in daily life. Participants provided salivary hormone samples at waking, 30 min after waking, and during the evening for two days. Hierarchical linear modeling was used to test the within-person and between-person associations between testosterone and cortisol. Within-person associations were further decomposed into associations due to coupled diurnal change *versus* coupled variability around diurnal change. Results indicated positive associations between cortisol and testosterone at all levels of analysis. Additionally, positive coupling was evident across the lifespan, even in older adults who are no longer expected to reproduce, but further investigation of developmental differences with a larger sample is necessary. Potential mechanisms and functions for positive coupling are discussed.

1. Introduction

1.1. The HPA and HPG axes across the lifespan

Cortisol and testosterone are the most commonly studied end-products of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, respectively. Testosterone, which is produced by the testes and ovaries, and, to a lesser extent, by the adrenal cortex, is necessary for the development of reproductive maturity and secondary sex characteristics in males, and is an anabolic steroid that promotes protein synthesis in both sexes (Rubinow and Schmidt, 1996). Cortisol is the primary hormone released as part of the biological stress response (Dickerson and Kemeny, 2004; Miller et al., 2007). Cortisol and testosterone have been extensively studied as biomarkers in relation to social behavior, psychiatric illness, and physical health (*e.g.*, Ford et al., 2016; Vreeburg et al., 2009). Increasingly, a dual axis approach that considers the interaction between HPA and HPG output is recognized as critical for understanding the predictive value of either hormone.

The functioning of the HPA and HPG axes changes dynamically across the lifespan. The HPG axis is active during fetal development, but then is quiescent during childhood, when sex hormones function in a negative feedback loop to inhibit HPG axis activity. The HPG axis is then re-activated at puberty as the inhibitory effect of sex hormones diminishes (Sisk and Turek, 1983). Similarly, human and animal research suggests that the HPA axis is significantly less reactive in early childhood (Sapolsky and Meaney, 1986; Gunnar

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and Cheatham, 2003) than in adolescence, when average cortisol levels increase with puberty in both sexes (Apter et al., 1979). Sex hormone levels decline in older adulthood, and older non-human animals exhibit a hyper-reactive cortisol response in comparison to young adult animals (Sapolsky and Meaney, 1986). Overall, there are lifespan changes in HPA and HPG functioning, and the two axes show parallel developmental trends, at least in early life.

1.2. Evidence for positive testosterone-cortisol coupling in adolescence

The HPA and HPG axes are typically conceptualized as mutually inhibitory systems: Stress impedes reproductive function, and gonadal hormones dampen the stress response (Rivier and Rivest, 1991; Toufexis et al., 2014; Viau, 2002). This conceptualization is supported by experimental animal research in which one hormonal system is directly manipulated. Research using rats has shown, for example, that gonadectomy increases the HPA response to acute stress (Viau and Meaney, 1996) and that injecting an antagonist to corticotropin-releasing factor directly into an animal's brain can reverse the dampening effects of electric shocks on HPG axis function (Rivier et al., 1986). Moreover, correlational research in humans has suggested that testosterone and cortisol may each inhibit the behavioral effects of the other hormone. For example, at low levels of cortisol, testosterone exhibits the strongest associations with social dominance (Edwards and Casto, 2013; Mehta and Josephs, 2010; Mehta et al., 2008), aggression (Popma et al., 2007), psychopathy (Glenn et al., 2011; Tackett et al., 2014), and callous-unemotional traits (Johnson et al., 2014).

Given experimental evidence for mutual inhibition of the HPA and HPG axes, one might expect that concentrations of cortisol and testosterone would be inversely associated. Indeed, one study of adult humans found that baseline levels of testosterone were negatively correlated with cortisol response to an acute in-lab stressor in men (but not in women; Stephens et al., 2016), and another found that baseline levels of cortisol were negatively correlated with testosterone response to acute stress (Bedgood et al., 2014). A recent series of papers, however, presented evidence that cortisol and testosterone showed positive within-person associations, *i.e.*, were positively coupled, in several independent samples of adolescents (ranging in age from 11 to 18). Interestingly, positive coupling between cortisol and testosterone was observed across different time frames and different research paradigms, including endogenous (*i.e.*, naturally-occurring) change across the course of a normal day (Marceau et al., 2015a), change across the course of a stressful laboratory day (Dismukes et al., 2015b), and longitudinal change from early- to mid-adolescence (Ruttle et al., 2015).

Overall, these papers presented results that appear discrepant from what is known about the antagonistic actions of the HPA and HPG axes on each other. To explain this apparent discrepancy, Marceau et al. (2015a) presented a developmental hypothesis – that positive coupling may be unique to the adolescent period, when activity in both axes is resurging following a period of childhood quiescence. Similarly, Ruttle et al. (2015) surmised (p. 697–698): "... initially both the HPA and HPG axes are developing and maturing, resulting in positive coupling but, as the axes mature over time, their cross-talk develops into a more mutually inhibitory pattern." These studies, however, did not include any adult participants and did not directly test developmental differences.

1.3. Competing hypotheses regarding developmental specificity

Other studies have questioned the idea that positive testosterone-cortisol coupling is unique to the adolescent period. In two independent samples of pre-/early-pubertal boys and girls (M age = 9.4) and young adult men (M age = 21.1), testosterone and cortisol responses to acute social stress were positively coupled, leading Turan et al. (2015) to conclude that "the positive coupling of cortisol and testosterone found in previous research is not limited to adolescence" (p. 85). This study, however, did not present any data on adult women or on adults in middle or older adulthood. Additionally, they focused on testosterone and cortisol responses to an experimentally-induced social stressor, and this design does not resolve whether coupling between endogenous, naturally occurring changes in testosterone and cortisol would be evident in developmental periods other than adolescence.

More generally, the expectation that testosterone and cortisol will be negatively associated in adults may be based on an overly simplistic conceptualization of the relationship between the HPA and HPG axes as purely antagonistic. Both testosterone and cortisol follow a predictable diurnal rhythm, with concentrations peaking in the morning and declining through the afternoon and evening (Matchock et al., 2007; Smyth et al., 1997), and "these parallel circadian changes suggest that the two hormones may routinely serve complementary rather than antagonistic functions under day-to-day conditions" (Gettler et al., 2011). Coincident increases in both testosterone and cortisol have been observed in female collegiate (*i.e.*, young adult) athletes following athletic competition (Edwards and Casto, 2013), in middle-aged men and women following a laboratory social stress test (Lennartsson et al., 2012), and in adult male subsistence hunters following a successful kill (Trumble et al., 2014). Yet another study found that young men (ages 21–23) who were "mating-oriented" (*i.e.*, neither fathers nor in a pair bonded relationship) were more likely than men who were fathers to have high levels of both cortisol *and* testosterone (Gettler et al., 2011). Additionally, in a wide variety of non-human species, biologists have observed situations in which activity in the HPG axis is maintained or even increased during periods of intense stress (Sapolsky, 1982; Wingfield and Sapolsky, 2003). These studies support the perspective that coupled activation of both axes facilitates the ability of an organism – even in adulthood – to respond to adaptive challenges, such as threats to social status (Turan et al., 2015) or mating opportunities (Gettler et al., 2011).

Finally, how the relationship between the HPA and HPG axes changes as adults lose reproductive capacity is unknown, as previous research on testosterone-cortisol coupling has focused primarily on adolescents or adults under 50. For organisms nearing the end of their reproductive lifespan, it would be adaptive to maintain reproductive functions even in the face of acute stress, as an opportunity deferred is potentially an opportunity lost forever (Wingfield and Sapolsky, 2003). However, for older adults who are unable or very unlikely to have any further offspring, co-elevated cortisol and testosterone may no longer be functional. In addition, unlike in the early lifespan when the HPA and HPG axes follow parallel trends (*i.e.*, fetal activity, childhood quiescence, adolescent re-activation), developmental trends seem to diverge in older adulthood, when levels of gonadal hormones decrease but cortisol reactivity increases. These lines of evidence suggest that perhaps the biggest developmental shifts in testosterone-coupling occur after mid-life, rather than after adolescence.

1.4. Goals of the current study

The current study presents results of the first investigation to use a lifespan sample to examine potential age-related differences in the sign and strength of within-person testosterone-cortisol coupling. Over the course of two days, adolescents and adults, ages 11–88 years, provided six salivary hormone samples (each day at waking, 30 min after waking, and in the evening). Samples were taken at home to assess awakening responses and naturally fluctuating hormone concentrations in daily life. Data were analyzed using hierarchical linear modeling to account for the nested