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Interactive effects of testosterone and cortisol on hippocampal volume and episodic memory in middle-aged men

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ABSTRACT

Animal and human research suggests that testosterone is associated with hippocampal structure and function. Studies examining the association between testosterone and either hippocampal structure or hippocampal-mediated cognitive processes have overwhelmingly focused on the effects of testosterone alone, without considering the interaction of other neuroendocrine factors. The aim of the present study was to examine the interactive effects of testosterone and cortisol in relation to hippocampal volume and episodic memory in a sample of late-middle aged men from the Vietnam Era Twin Study of Aging. The average age of participants was 56.3 years (range 51–60). Salivary hormone samples were collected at multiple time-points on two non-consecutive at-home days, and an in-lab assessment. Area under the curve with respect to ground measures for cortisol and testosterone were utilized. Significant testosterone-by-cortisol interactions were observed for hippocampal volume, and episodic memory. When cortisol levels were elevated (1 SD above the mean), testosterone levels were positively associated with hippocampal volume and memory performance. However, when cortisol levels were low (1 SD below the mean), testosterone levels were inversely related to hippocampal volume and memory performance. These findings suggest that in context of high cortisol levels, testosterone may be neuroprotective. In contrast, low testosterone may also be neuroprotective in the context of low cortisol levels. To our knowledge this is the first demonstration of such an interaction in a structural brain measure and an associated cognitive ability. These results argue in favor of broadening neuroendocrine research to consider the simultaneous and interactive effects of multiple hormones on brain structure and function.

1. Introduction

Increasing evidence suggests that the primary male androgen testosterone is associated with hippocampal structure and function. Although androgen receptors, the primary cytosolic binding sites for testosterone, are distributed widely throughout the central nervous system (Choate et al., 1998), mRNA concentrations in the human hippocampus have been shown to be of the same order of magnitude as concentrations in the prostate, a major site of testosterone action (Beyenburg et al., 2000). Animal studies have found that testosterone promotes hippocampal neurogenesis (Galea et al., 2006), regulates synaptic plasticity in the hippocampus (Harley et al., 2000), and maintains hippocampal volume (Galea et al., 1999). In rats, cognitive abilities regulated by the hippocampus, such as spatial learning, become impaired following gonadectomy, with performance improving following hormone replacement (Kritzer et al., 2001). Testosterone also appears to be neuroprotective with respect to Alzheimer's disease-related pathology, helping to regulate the accumulation of β-amyloid in cultured hippocampal neurons (Pike, 2001), as well as prevent the formation of tau-related pathology (Papasozomenos and Shanavas, 2002).

Human studies have shown that testosterone levels are positively

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correlated with hippocampal volume in male and female adolescents (Neufang et al., 2009), as well as with cerebral blood flow within the hippocampus in elderly men (Moffat and Resnick, 2007). Testosterone has been found to have positive associations with hippocampal-mediated cognitive processes in healthy adults, though findings in this area remain mixed (Boss et al., 2014). In middle-aged men, individuals with both low testosterone and at least one copy of the apolipoprotein-E (*APOE*) ε4 allele were found to have smaller hippocampal volumes relative to individuals with none or only one of these risk factors (Panizzon et al., 2010). Within the same cohort, the correlation between testosterone and verbal memory was found to significantly differ as a function of ε4 status, such that lower testosterone was associated with poorer memory performance in ε4-positive, but not ε4-negative, individuals (Panizzon et al., 2014).

In nearly all areas of neuroendocrine research, studies examining the association among a particular hormone with brain structure and function have been restricted to individual hormone effects, and have not considered the potential roles that other hormones might play in regulating the relationships of interest. The literature on testosterone is no exception to this trend. A hormone that is likely critical to understanding how and the degree to which testosterone is associated with brain structure and function is the glucocorticoid cortisol. Elevated cortisol has been negatively associated with structural aspects of the hippocampus and its related cognitive abilities; however, as with testosterone, findings have at times been inconsistent across both neuroimaging and cognitive studies (Franz et al., 2011; Frodl and O'Keane, 2013; Geoffroy et al., 2012; Lupien and Lepage, 2001; Lupien et al., 2009; Schwabe et al., 2012). Like androgen receptors, the receptors that mediate the effects of cortisol, specifically the glucocorticoid and mineralcorticoid receptors, are prominent in the hippocampus (McEwen et al., 1968), and for all three receptor types the binding to the respective hormone results in alterations of receptor-regulated gene expression (Beato, 1989). The glucocorticoid receptor is particularly relevant to the action of testosterone, as it has been shown to directly interact with the androgen receptor, such that the two receptors have inhibitory effects on the transcriptional activity on one another (Chen et al., 1997). Moreover, in certain tissues glucocorticoid receptors can be upregulated by either knockout of the androgen receptor or castration-induced androgen depletion, as well as downregulated by high testosterone levels (Miyamoto et al., 2007; Silva et al., 2010). These receptor-level interactions provide a mechanism whereby the association of testosterone with hippocampal structure and function might be moderated by cortisol, or vice versa.

We are aware of no studies that have examined the simultaneous or potentially interactive effects of testosterone and cortisol on hippocampal structure and related cognitive function. The interplay of these two hormones, however, has been examined in research on traits such as social aggression, dominance, and leadership. For example, Popma et al. found that testosterone was positively associated with overt aggression in adolescent boys, but only in those who had lower cortisol levels, defined as 1 standard deviation or more below the mean (Popma et al., 2007). No relationship was observed in participants with higher cortisol levels (1 standard deviation or more above the mean). Similar findings, in samples consisting of both men and women, have been reported for observer-based ratings of dominance in a leadership task, self-reported empathy, anger response, and risk taking (Mehta et al., 2015). In men with lower cortisol, testosterone was positively associated with activation in the dorsolateral prefrontal cortex in response to an insult, whereas no association was observed in the high cortisol participants.

The aim of the present study was to examine the interactive effects of testosterone and cortisol on hippocampal volume and episodic memory performance. That is, we sought to determine whether associations with testosterone would differ as a function of cortisol level. We predicted that cortisol would moderate the associations of testosterone with hippocampal volume and memory performance, such that these associations would be prominent when cortisol is in a lower (i.e., healthy) range and be abated when cortisol is elevated.

2. Materials and methods

2.1. Participants

Data were obtained as part of the Vietnam Era Twin Study of Aging (VETSA), a longitudinal study of cognitive and brain aging with baseline in midlife (Kremen et al., 2006). VETSA participants are drawn from the larger Vietnam Era Twin Registry, a nationally distributed sample of male-male twin pairs, both of whom served in the United States military at some point between 1965 and 1975 (Goldberg et al., 2002). To be eligible for the VETSA both members of a twin pair had to agree to participate, and be between the ages of 51 and 59 years at the time of recruitment. In total, 1237 men participated in wave 1 of the VETSA. The average age was 55.4 years (SD = 2.5, range = 51–60), average education was 13.8 years (SD = 2.1), and participants were predominantly white non-Hispanic (89.7%). Although all VETSA participants served in the military, the majority (~80%) did not experience combat situations during their military careers. Compared to U.S. census data, participants in the VETSA are similar in demographic and health characteristics to American men in their age range (Schoenborn and Heyman, 2009).

VETSA participants traveled to either the University of California, San Diego or Boston University for a daylong series of physical, psychological, and neurocognitive assessments. On rare occasions (2.7% of subjects) project staff traveled to the participants in order to conduct the assessments. Prior to data collection, approval from local institutional review boards was obtained at all participating sites, and all participants provided signed informed consent upon their arrival at the testing site. Beginning in the second and third years of the project, funding was obtained to collect structural neuroimaging (N = 526) and endocrine data (N = 795) on the remaining eligible participants. Due to incomplete overlap between these two sub-studies, all participants with endocrine data underwent cognitive testing whereas both endocrine and neuroimaging data were available on 445 participants.

2.2. Hormone collection and assay

Hormone collection and assay methods have been described in detail elsewhere (Franz et al., 2010; Panizzon et al., 2013). Briefly, saliva samples were collected on two non-consecutive days at home during a participant's typical week, as well as on the in-lab assessment day. At-home samples were collected approximately two weeks prior to the assessment day. Samples were collected at waking, 30 min after waking, 10:00 a.m., 3:00 p.m., and bedtime on all days in order to capture diurnal changes in cortisol levels. Times of sample collections were recorded by the participant, and were later confirmed against data from electronic track caps.

Saliva samples were centrifuged prior to assay at 3000 rpm for 20 min to separate the aqueous component from mucins and other suspended particles. Concentrations of cortisol and free testosterone were determined in duplicate using commercial radioimmunoassay kits (Beckman Coulter Inc., formerly Diagnostics Systems Laboratories, Webster, TX; Siemens Medical Solutions Diagnostics, Los Angeles, CA). The least detectable concentrations for the assays were 1.3697 pg/ml for testosterone (intra-assay coefficient of variation = 3.141, inter-assay coefficients of variation = 4.878) and 1.3854 nmol/l for cortisol (intra-assay coefficient of variation = 3.962, inter-assay coefficients of variation = 5.662). Data from one to three individuals were included in each assay batch, and assays were always performed without knowledge of the zygosity of the twin pairs.

Procedures for handling outliers and missing data are described in detail elsewhere (Franz et al., 2010; Panizzon et al., 2013). In brief, individual testosterone and cortisol measurements greater than three

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