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Examining the developmental interface of cortisol and depression symptoms in young adolescent girls

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Summary Despite the substantial amount of data supporting a link between HPA-axis functioning and depression, the ontogeny of this association is not known. The aim of the present study was to contribute data on the developmental interface of HPA-axis functioning and depression in girls by testing associations between repeated measures of depression symptoms and cortisol levels in childhood and early adolescence. Girls ($N = 232$) and their mothers, who were participating in a longitudinal study, were interviewed about depression symptoms annually from ages 9 to 12 years. Cortisol was assayed from saliva at ages 10 and 12 years upon arrival to the lab and following administration of the cold pressor task (CPT). Time of day of collection of saliva and level of pubertal development were included as covariates in model testing. Although most girls did not show an increase in cortisol in response to the CPT, lower levels of output during the CPT were associated with higher levels of depression symptoms. These findings were observed only for cortisol levels assessed at age 12 years. Girls with low levels of cortisol output at age 12, and decreases in output from ages 10 to 12, had stable or slightly increasing depression symptoms from ages 9 to 12 years. We conclude that associations between HPA-axis functioning and depression emerge as early as age 12. However, individual differences in cortisol levels at age 12 also were associated with depression symptoms at earlier ages. The data suggest two possibilities: (1) that childhood depression is associated with HPA-axis dysregulation, but that age related changes in the sensitivity or plasticity of the HPA-axis may result in a delay in the emergence of such an association, or (2) that dysregulation of the functioning of the HPA-axis develops following repeated experience of depression symptoms.

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1. Introduction

A substantial amount of data exists linking the functioning of the HPA-axis to depression in adults (see Plotsky et al., 1998, for a review), leading to the hypothesis that glucocorticoids play a role in the pathophysiology of depression. Moreover, developmental and sex differences in functioning of the HPA-axis mirrors those observed for depression. Sex differences in depression symptoms or disorders are generally not evident until adolescence, at which point increases in depression are evident for girls but not for boys (Keenan and Hipwell, 2005). Similar sex by age effects are observed in HPA-axis functioning. In terms of diurnal levels and awakening response, Shirtcliff et al. (2012) collected three saliva samples across the day (after awakening, in the late afternoon and before bed) from approximately 300 children every two years from ages 9 to 15 years. Girls had higher cortisol levels at awakening and steeper slopes across the day. Significant age by sex effects were observed for awakening cortisol level, which declined within individual across age, but significantly less so for girls than for boys. Platje et al. (2013) reported sex differences in the cortisol awakening response at ages 15, 16, and 17 years; girls had higher cortisol levels than boys at 30 and 60 min post-awakening, and by age 17 the CAR for girls was in a positive direction (i.e., increase in cortisol following awakening) whereas boys continued to show a decrease in cortisol following awakening.

Sex and age or pubertal effects are also found for cortisol reactivity to a stressor. Stroud et al. (2011) used a corticotropin releasing hormone (CRH) challenge in children and adolescents and reported that stage of pubertal development was associated with the pattern of response in girls, characterized primarily as a slowing of the recovery to baseline response with more advanced maturation: stage of pubertal development was not associated with cortisol response among boys.

The effects of age and puberty and sex on stress response also are evident in animal models. Pubertal female rats have prolonged corticosterone release in response to restraint stress compared to adult females (Romeo et al., 2004). Compared to controls, females rats exposed to chronic social stress during adolescence did not habituate to the stressor, showed a prolonged corticosterone response to a subsequent heterotypic stressor, and were more likely to engage in depression-like behavior during a forced swim test (e.g., less time climbing and more time immobile). Males habituated to the repeated social stressor, had an increase in corticosterone level but no difference in shape of response, and demonstrated no difference in behavior during the forced swim test as a function of social stress (Mathews et al., 2008).

The possibility that the HPA axis is maximally sensitive to experiences during adolescence has implications for psychopathology, especially for females, who demonstrate increased risk for distress disorders during adolescence (Keenan and Hipwell, 2005). Specifying the developmental interface between HPA-axis functioning and depression in humans, however, has been challenging. The use of cross sectional designs is not highly informative regarding the timing and direction of effect. Moreover, because base rates of depression symptoms and disorders are low in childhood (Son and Kirchner, 2000; Kessler et al., 2001), tests of association between cortisol levels and depression are often conducted later in adolescence. Among the few studies in which child participants were included no association between cortisol levels assessed in response to a challenge, such as CRH, and depression symptoms was observed (e.g., Birmaher et al., 1996; Puig-Antich et al., 1989).

In contrast, studies in which the association between cortisol levels and depression participants were assessed during mid- to late adolescence typically yield significant associations. Cortisol levels among depressed adolescents in response to a social stressor were elevated and slower to return to baseline compared to non-depressed adolescents (Rao et al., 2008). Higher and flatter diurnal rhythms were observed among adolescents with high depression scores ($n = 9$) compared to adolescents with moderate ($n = 12$) or low ($n = 45$) scores (Van den Bergh and Van Calster, 2009). Adam et al. (2010) reported that a higher baseline CAR was associated with the incidence of major depressive disorder one year later in a sample of 230 17-year olds, many of whom had a history of mood and anxiety disorders based on retrospective report.

In others studies the pattern of association between cortisol output and depression is a negative one. Results from a study on diurnal cortisol in a sample of youth whose mental health had been assessed longitudinally since childhood revealed that childhood internalizing behaviors, but not externalizing behaviors, were prospectively associated with *lower* morning cortisol levels in early adolescence (Ruttle et al., 2011). Measures of cortisol functioning in childhood, however, were not available for the sample. Badanes et al. (2011) also reported significant associations between *low* cortisol output and depression scores. In that study, cortisol levels for children in grades 3, 6, and 9 were operationalized as the average of five samples taken before and after a social stress test. Effects of age were not tested.

In summary, the pattern of association between depression symptoms, scores or disorders and cortisol reactivity, awakening response, or diurnal rhythm during adolescence is typically positive. The pattern of association involving assessment of depression in children, in contrast is inconsistent: typically no effects have been observed between depression and cortisol reactivity, and a negative association has been observed between childhood internalizing problems and cortisol levels in adolescence.

Further probing of age-related changes in the association between cortisol and depression are important for understanding the pathophysiology of depression, especially with regard to potential phenotypic differences between depression that is manifest prior to the completion of pubertal development and depression that occurs post-pubertal development. Kaufman et al. (2001) concluded from reviewing the available literature that depressed children differ from depressed adults on measures of basal cortisol secretion, and in response to a corticotropin releasing hormone (CRH) challenge. These differences along with others in neurobiology and treatment response suggested to the authors that depression in adults may be phenotypically different from childhood depression. For example, replicated findings of differences in changes in electroencephalographic (EEG) sleep associated with depression in adults and adolescents are generally not present in studies of depressed and non-depressed children (Kaufman et al., 2001). Most of the research reviewed by Kaufman and colleagues, however,