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Editorial

Susceptibility or Vulnerability? The Role of Basal Cortisol in Psychopathology

In this issue of the *Journal of Adolescent Health*, Zandstra et al. [1] use an impressive sample of 1,664 participants from the TRacking Adolescents' Individual Lives Survey in the Netherlands to test whether basal cortisol levels, measured at awakening, predicted changes in mental health symptoms over the transition to middle school. Importantly, rather than assuming the transition to middle school is stressful as was the case in the past research that motivated this article [2], the authors examined whether the transition was perceived by adolescents to be a positive or negative experience and whether basal cortisol interacted with negative and positive experiences of the transition to predict changes in mental health.

Why might positive experiences interact with cortisol levels to predict changes in mental health? Is not cortisol considered a "stress" hormone, and should not an elevated level therefore confer vulnerability, either on its own or in response to the impact of stressors? That is one way to view elevated basal cortisol: as a vulnerability factor, under a traditional diathesis-stress viewpoint [3]. If elevated basal cortisol is a vulnerability factor, it should be associated with worsening mental health after the occurrence of negative life experiences. Another view is to consider elevated basal cortisol as a susceptibility factor, making the individual more "tuned in" to all types of environmental experience and thus more sensitive to both positive and negative events. According to this latter perspective, the presence of elevated basal cortisol would predict a worsening of mental health symptoms after negative experiences but an improvement in mental health symptoms after positive experiences. This latter hypothesis derives from recent influential theories of "biological sensitivity to context" and "differential susceptibility" [4,5].

A strong contribution of this article is that it tests both possible models, by examining not only whether adolescents with high waking cortisol responded to a stressful transition experience with a greater increase in symptoms, but also whether adolescents with high waking cortisol responded to a positive transition experience with a reduction in symptoms. That is, they ask whether elevated waking cortisol makes the individual more vulnerable to negative events or more susceptible or sensitive to both negative and positive events. The authors offer evidence in support of the first hypothesis (greater vulnerability to negative experience with high but not low basal cortisol) but not the second hypothesis (also greater sensitivity to positive experience with high basal cortisol). In follow-up analyses, they also find that the greater vulnerability appears to be particularly driven by greater vulnerability among the females in the sample.

There are numerous strengths of this study, including the large sample size, its strong theoretical framing, and its prospective longitudinal design—examining basal cortisol as a predictor of subsequent changes in symptoms, rather simply assessing cross-sectional correlations between cortisol and symptomatology. Taking a prospective approach has been recommended as an essential next step in research on the role of cortisol in the development of emotional disorders [6]. Although prior studies have prospectively tested basal cortisol as a vulnerability factor for mental health problems over the transition to middle school, Zandstra et al. [1,2] are the first to include measures of the transition experience, rather than assuming the experience is stressful for all youth. By obtaining ratings of how stressful the transition is, they are more precisely defining the "stress" component of the diathesis-stress model. In addition, measuring the instances in which the transition is experienced as positive frees them up to test the additional differential susceptibility hypothesis. The authors account for the potential role of pubertal status and seasonal variability and also for various types of medication use among the study youth; these are important covariates that are sometimes neglected in cortisol research.

The authors choose to combine both internalizing and externalizing disorders into a single mental health problems index. This choice is justified by the past research in which basal cortisol predicted changes in symptom severity (including both internalizing and externalizing symptoms) but not symptom type or directionality (externalizing vs. externalizing) [2]. Their choice is also supported by their follow-up analyses suggesting that the vulnerability findings are similar when changes in internalizing and externalizing problems are considered separately. By what mechanism high waking cortisol simultaneously confers risk for internalizing and externalizing problems remains somewhat of a mystery—additional discussion and research is warranted on how a similar biological vulnerability translates into outcomes with different symptom profiles. In the future, more attention should be given to why or how cortisol may matter for mental health—what are the proposed mechanisms by which high waking cortisol translates into increased

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symptoms in the presence of risk? For example, the impact of glucocorticoids on the brain and the potential role of glucocorticoid receptor systems merit more attention and discussion [7].

Although the prospective analyses, and their focus on changes in mental health symptoms over time, are a strength of the article by Zandstra et al., it would have been helpful to also know the cross-sectional associations between basal cortisol and mental health symptoms, particularly at the time of baseline (pre-transition) measurement. Were the individuals with high basal cortisol at baseline already showing signs of elevated symptoms at baseline, which were then exacerbated by negative transition experiences? Or were those with high basal cortisol low on symptoms before the transition, showing symptom increases that are precipitated for the first time by the transition experience? A combination of cross-sectional and longitudinal analyses would have provided an even more comprehensive picture of the associations between basal cortisol and mental health functioning.

The biggest limitation of the article by Zandstra et al. is their limited measurement of basal cortisol levels. They focus only on awakening cortisol; it is not clear whether cortisol was also gathered at other points in the day and not examined, or whether it was available, examined, and found not to be significant. Sorely needed in research on the role of cortisol in psychopathology, and the literature on salivary cortisol more generally, is standardization across studies in both measurement and reporting of basal cortisol. It is now becoming conventional in basal/diurnal cortisol research to measure, at a minimum, waking and bedtime cortisol, and the size of the cortisol awakening response (the surge in cortisol in the 30 minutes after waking). These measures allow at least a rough estimate of key diurnal cortisol measures—waking cortisol, bedtime cortisol, average cortisol and the slope of diurnal cortisol decline across the waking day, and the size of the cortisol awakening response [8]. Prior literature on cortisol as a potential risk factor for major depressive disorder has found that the size of the cortisol awakening response predicts risk for both major depression and anxiety disorders [9,10]; other literature has found flattened diurnal cortisol profiles or elevated evening cortisol to be associated with mental health symptom increases [2,11]. In future research, it would be helpful to examine and report these aspects of cortisol also, rather than focusing solely on waking cortisol, to get a more complete picture of what type of baseline diurnal cortisol profile confers risk.

On a related note, the choice to replace missing waking cortisol values using information from samples obtained 30 minutes after waking is problematic and should be avoided in future research. Cortisol values increase 50%–75% on average in the first 30 minutes after waking [12]; as a result, despite their proximity in time, waking and 30-minute postawakening cortisol values are by no means equivalent or substitutable. Also, as noted by the authors, adding more than 1 day of cortisol measurement would have provided a stronger measure of waking cortisol.

Overall, this study makes some important and provocative contributions to understanding the role of basal cortisol in the emergence of mental health problems, highlighting the importance of considering interactions between biology and experience, and of characterizing the nature and personal interpretation of those experiences. If future studies take the lead from Zandstra et al. [1] and use prospective designs to test theory-driven hypotheses about the interactions between cortisol and both stressful and positive life experiences, we will soon have a much better understanding of the role of basal cortisol in the emergence of mental health problems.

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