Cortisol and Brain: Beyond the Hippocampus

To the Editor:

Carroll et al. (1) reported a negative association between bedtime cortisol level and left ventral prefrontal cortex volume in a group of 33 children and adolescents. Correlations did not differ between their posttraumatic stress symptom subgroup and their healthy comparison subgroup. They concluded that cortisol secretion may have an impact on prefrontal cortex development and that its impact does not appear to be a function of posttraumatic stress symptoms. In addition, they noted that larger samples are needed to address this issue.

We were pleased to see that their results essentially replicate the results of our whole-brain analysis of 404 late middle-aged twin men (2). In that study, we showed that mean daily cortisol output (based on five samples from awakening to bedtime) was negatively correlated with the thickness of several prefrontal regions, including left and right dorsolateral, left ventrolateral, and right medial orbital frontal cortex. Although significant, these associations were much smaller in magnitude than that found by Carroll et al. (1). Our whole-brain analysis also indicated relative specificity for the frontal-cortisol associations compared with other brain regions.

We do not know all the factors underlying these associations, but common genetic influences do appear to be one of them. This notion is supported by our data showing that there were significant correlations between the genetic influences on cortisol levels and the genetic influences on cortical thickness in some prefrontal regions (2). Given the apparent importance of genetic factors, it will be important to separately examine cortical thickness and cortical surface area (rather than volume, which is the product of the two) because it has been shown by our group (3) and others (4, 5) that thickness and surface area are influenced by discrete, independent genetic factors.

It is tempting to conclude from these associations, as did Carroll et al. (1), that cortisol secretion impacts prefrontal cortical development. However, caution is warranted in making that directional inference because both studies were cross-sectional. Indeed, there is evidence from animal and human studies that prefrontal lesions can result in alteration of cortisol secretion (6, 7). It is also worth noting that the associations in our study were with mean daily cortisol levels compared with bedtime levels in the Carroll et al. (1) study. Therefore, the specificity of the associations for any individual time point in the diurnal pattern of cortisol secretion is another issue that remains to be fully resolved.

With regard to brain structure or function, the cortisol literature has focused overwhelmingly on the hippocampus. Given the high concentration of glucocorticoid receptors in the prefrontal cortex, it is encouraging to see the growing body of research on cortisol and prefrontal cortex.

Funded by National Institute on Aging AG022982, AG018386, AG018384, and AG022381. The US Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin Registry.

Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University.

All authors report no biomedical financial interests or potential conflicts of interest.

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doi:10.1016/j.biopsych.2010.08.035