Physiological and Behavioral Responses to Increases in Circulating Cortisol:
Assessing the Fragility of the Adolescent Brain

By

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The adolescent brain is the product of the many changes and alterations in neural plasticity that occur during infancy and childhood. However, the adolescent brain is not a static entity as it, itself, is a substrate upon which further plasticity related processes eventually operate to yield the functional adult brain. Specifically, continuous communication between elements of the endocrine system and neural structures and circuits mediates proper adaptive function of the brain in response to the ongoing socio-emotional flux that characterizes adolescence. It is important to note that such adaptive function relies heavily upon reasonably precise endocrine activity. As such, a distinct physiological range for all circulating hormones is maintained within the brain. When these ranges are ignored, abnormal hormonal activity ensues giving rise to severe structural and behavioral neurological dysfunction.

Cortisol, a glucocorticoid, is one example of a tightly regulated hormone that, when in excess of optimal circulatory concentrations, gives rise to maladaptive psychological development. At moderate basal levels, cortisol triggers an arsenal of adaptive behaviors and physiological processes in response to stress. However, chronic overexposure to this stress-related hormone is significantly correlated with Schizophrenia, Post-traumatic Stress Disorder, Cushing's disease, and a multitude of other psychological pathologies. Further, excessive cortisol secretion by the pituitary has been recently associated with particular cognitive impairments e.g. in episodic memory retrieval. On a neurobiological scale, secretion of cortisol has been observed to be inversely related to the volume of the hippocampus, a neural structure that is sensitive to cortisol flux and is responsible for providing the pituitary with feedback pertaining to the hormone's release. Unfortunately, prior studies have been unable to assess which of the two is the causal factor.

For our study, we chose to focus on the hippocampus' sensitivity to cortisol fluctuation as a model of the fragility of the adolescent brain. Specifically, our study attempts to assess the effects of prolonged overexposure to cortisol on both cognitive/behavioral and neurobiological performance. First, rats of the same age would be randomly assigned to either the control group or the experimental group for their particular sex so as to control for gender differential responses to cortisol (which have been

documented in prior studies). Participants in the experimental group would be subjected to infusion of a specified dose of hydrocortisone (a compound that is metabolized within the body to yield functional cortisol) twice each day at specified times to control for cyclic fluctuation in an individual's physiological response to the hormone. This treatment would be carried out for a 6-month period, documenting both physiological and behavioral function at one-week intervals for each of the groups. Neurophysiological alteration (or lack thereof) could be accurately monitored using PET scan or MRI technology while behavioral capacity could be measured using various indices of both cognitive performance (i.e. tests of procedural memory) and emotional stability (i.e. anxiety response assessment tasks). Finally, immunochemical assays could be used to quantitatively assess the abundance of cell-surface cortisol receptors on hippocampal cells.

The fact that our study allows us to monitor the progression of both neurophysiological degeneration and behavioral malfunction enables us to test several predictions regarding the effects of prolonged overexposure to cortisol. If, in fact, hyper-secretion of cortisol has an atrophic effect on neurons in the hippocampus, then we should expect to see significant cell loss within this neural region of the experimental rats. In addition, we might expect to observe a genetic down-regulation of cortisol receptor expression within the hippocampus of those rats subjected to hydrocortisone infusion. Behaviorally, we predict a significant decline in the cognitive abilities of experimental rats, especially in those cognitive abilities which rely heavily on hippocampal function. We would also predict that individuals in the experimental group would display high levels of anxiety as manifest in particular symptoms of psychological distress.

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