

Online Supplement 8.2

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Functional Somatic Symptoms in Children and Adolescents: The Stress-System Approach to Assessment and Treatment

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Brain Plasticity and Epigenetic Research in Rat Pups Subjected to Stress

Michael Meaney and colleagues began to study the stress response in rat pups in the 1980s (Meaney et al. 1985). Rat pups that are separated from their mothers and handled by researchers find this experience stressful. This stress is reflected in activation of the HPA axis and secretion of corticosteroid, the primary glucocorticoid in rats. When the pups are returned to the mother rat, she typically responds by licking and grooming them. Licking and grooming lowers HPA activation and glucocorticoid levels.

Because glucocorticoids play a central role in the stress response and coordinate adaptive plasticity changes throughout the body, the focus of research with rat pups quickly changed to the epigenetic modifications to the glucocorticoid receptor gene in specific regions of the brain. Some researchers focused on the hippocampus, a region of the brain that modulates HPA-axis activity by inhibiting the paraventricular nucleus in the hypothalamus, which switches on the HPA axis in response to stress (see Hyman [2009] for a more detailed summary of findings).

In rat pups separated from their mothers, handled by researchers, and then returned to mothers who did a lot of licking and grooming, researchers found high levels of glucocorticoid receptor expression in the

hippocampus—enabling inhibition of the HPA axis and keeping the responsiveness of the HPA axis in check. By contrast, in rat pups separated from their mothers, handled by researchers, and then returned to mothers who did *little* licking and grooming, researchers found low levels of glucocorticoid expression in the hippocampus—hindering inhibition of the HPA axis and resulting in high stress responsiveness and an overly robust HPA response.

The underlying mechanism for these findings involves epigenetic changes. The researchers found that the stress of being handled resulted in increased methylation of the glucocorticoid receptor gene, and that this increased methylation, in turn, decreased expression of the gene itself. They also found, however, that the level of methylation was influenced by the quality of maternal care that the pups received after their separation and handling. Rat pups whose mothers engaged in low levels of licking and grooming continued to demonstrate high levels of methylation, decreased glucocorticoid receptor expression (a less efficient negative feedback system for shutting down the HPA axis) in the hippocampus, and increased the HPA-axis response (HPA reactivity) to stress. By contrast, high levels of licking and grooming were protective; these behaviours lowered pups' methylation, increased glucocorticoid receptor expression (a more efficient negative feedback system for shutting down the HPA axis) in the hippocampus, and reduced the HPA-axis response to stress. Importantly, this process of methylation modification and the expression of the glucocorticoid receptor gene in the hippocampus in rat pups stabilizes as the pups mature and can affect rats' HPA-axis stress reactivity, for better or worse, across the lifespan—and also across generations (Jawaid et al. 2018).

References

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