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Stress system genetic variation, cortisol, hippocampal volume, and amygdala reactivity in preschool-onset major depression. Presented at 2012 meeting of the Society for Neuroscience.

Abstract:

Recent work has established the validity of major depression in school-age children, and further research has shown that children as young as 3-5 years old can experience a form of early onset depression termed preschool-onset major depressive disorder (PO-MDD). As in adult depression, a family history of mood disorders and a personal history of stressful life events are significant risk factors for the development of PO-MDD. This suggests that genetic influences and environmental factors, like exposure to stress, contribute a portion of the risk for developing PO-MDD. Yet, it is presently unclear what neural mechanisms underlie the influence of these risk factors. Variations in genes related to the function of the stress system have been implicated in the development of adult depression. This mirrors findings that dysregulation of the stress system is observed in a large majority of patients with childhood and adult depression. Given this, our work examines the relationship between a panel of four stress-system genes -- CRHR1, NR3C1, NR3C2, and FKBP5 -- and changes in cortisol reactivity, hippocampal volume, and amygdala reactivity that are characteristic of depression. These genes code for proteins that are critically involved in the activation and regulation of the hypothalamic- pituitary-adrenal axis. Variation in these genes has been previously associated with depression and/or cortisol reactivity. In a unique sample of children with a history of PO- MDD and healthy children, we computed multi-locus genetic profile scores, which represent the additive genetic effects of single nucleotide polymorphisms across the four genes of interest. Consistent with the functional role of these genes, these profile scores predicted salivary cortisol levels after lab stressor paradigms, when controlling for time of day, ethnicity, PO-MDD severity,

and gender. Hippocampal volumes will be assessed using high-dimensional brain mapping methods. Amygdala reactivity to emotional stimuli will be assessed using an emotional face-processing fMRI task. Additional analyses will test the hypothesis that these multi-locus genetic profile scores predict reductions in hippocampal volume and increases in amygdala reactivity to emotional stimuli, either as a main effect or in interaction with a history of PO-MDD. Such alterations in hippocampal volume and amygdala reactivity are though to serve as neural markers of depression. These potential intermediate phenotypes allow us to test whether these neural changes serve as a causal link between genetic/environmental risk factors and the phenotypic expression of depression via changes in the stress system.