

5-HTTLPR Polymorphism impacts cingulate-amygdala interactions: A genetic susceptibility mechanism for depression

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In this talk, Dr. Pezawas presents the results from a multimodality imaging study of the neural correlates of 5-HT transporter gene polymorphisms in healthy volunteers, completed in conjunction with Dr. Meyer-Lindenberg and under the advisory of the Genes, Cognition and Psychosis Program Director at NIH, Dr. Daniel Weinberger. Since the most widely prescribed class of antidepressants –the Selective Serotonin Reuptake Inhibitors (SSRIs) - act by blocking the 5-HT transporter (SERT), researchers have focused on the phenotypic consequences of a functional 5' promoter polymorphism present across individuals that results in the inheritance of two variants of the SERT gene, the short allele and the long allele. Previous NIMH-supported studies have shown that inheriting the short allele more than doubles the risk of depression following stressful life events, increase amygdala activation to fear-inducing visual stimuli and has been linked to anxious temperament. In this study, the research team first scanned 114 healthy subjects using MRI. By means of optimized voxel-based morphometry (VBM) methods, they found reduced gray matter volume in short-allele carriers in limbic regions critical for processing negative emotion, particularly perigenual cingulate and amygdala. Next, they investigated BOLD signal changes in 97 healthy volunteers at the same brain regions during perceptual processing of fearful stimuli, and demonstrated a tight coupled feedback circuit implicated in the extinction of negative affect. Short-allele carriers showed relative uncoupling of this circuit. Furthermore, the magnitude of coupling inversely predicted almost 30% of variation in temperamental anxiety. These genotype-related alterations in anatomy and function of an amygdala-cingulate feedback circuit critical for emotion regulation implicate a developmental, systems-level mechanism underlying normal emotional reactivity and genetic susceptibility for depression.