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The impact of COMT, environmental adversity and their interaction on brain activity related to the dopaminergic reward system: a simultaneous EEG-fMRI investigation in the framework of a longitudinal study

Autor: Regina Boecker
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. D. Brandeis

Over the past decade, researchers have shown that the processing of rewards plays a fundamental role in ensuring an individual's mental health. Moreover, substantial research has implicated alterations of reward processing in the development of mental disorders. In this line, the neurotransmitter dopamine has been attributed a pivotal role, suggesting genetically driven causes of altered neural processing. Additionally, environmental factors might contribute to the detrimental effects on the reward circuit. However, so far, the investigation of environmental and genetic risk factors and their interaction in terms of their impact on neural reward processing, as a potential mediator for the development of psychopathology, remains inconclusive.

In order to address this issue, the present thesis investigated the impact of early and childhood life stress, the catechol-O-methyltransferase gene (*COMT*) Val^{158}Met polymorphism and the interaction thereof on reward processing in healthy young adults and its relevance for related psychopathology such as attention-deficit/hyperactivity disorder (ADHD). Based on previous research implicating childhood maltreatment as a factor influencing fMRI activation during reward anticipation, the first study of this thesis aimed to extend these findings by using a prospective and continuous measure of mild to moderate early life stress in the framework of an epidemiological cohort study. 162 healthy young adults participated in a simultaneous electroencephalography (EEG) - functional magnetic resonance imaging (fMRI) study using a monetary incentive delay task to examine both reward anticipation and reward delivery. Early life stress was assessed according to an early family adversity index at the offspring's age of 3 months and lifetime ADHD symptoms using standardized parent interviews conducted between 2 and 15 years. fMRI results revealed a differential long-term impact of early life adversity on reward processing, implicating hyporesponsiveness of the ventral striatum, putamen and thalamus during reward anticipation and hyperresponsiveness of the insula, pallidum and putamen when receiving a reward. These results were partly corroborated by EEG data which indicated decreasing contingent negative variation activity with the level of early adversity. Further analysis revealed a significant association of lifetime ADHD symptoms with decreased activation in the left ventral striatum during reward anticipation and increased activation in the right insula during reward delivery. In conclusion, the study highlights the long-term impact of early life stress on neuronal reward functioning in adulthood as a potential mediator in the development of ADHD.

Given the inconsistent findings of genetic association studies of ADHD, the second study, conducted in the same longitudinal study context as the first, focused on the influence of the *COMT* Val^{158}Met polymorphism in interaction with childhood adversity on reward processing. Results proved a direct effect of both *COMT* and childhood adversity on reward anticipation, with decreased activation in Met homozygotes and in individuals exposed to high childhood adversity, respectively. At reward delivery, an interaction effect of *COMT* with childhood adversity emerged, indicating that activity increased with the level of childhood adversity in Met homozygotes, but not in Val allele carriers. These results suggest a potential reward processing deficit in adults exposed to stress during childhood and implicate *COMT* in interaction with childhood adversity as a potential risk factor for the development of reward-related mental disorders such as ADHD. To conclude, both studies of this thesis extend previous findings and provide first evidence of a neuronal mechanism compromising reward processing and underlying the emergence and persistence of dopamine-related psychopathology as a possible target for prevention and intervention.