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# Urban upbringing – Impact of an established environmental risk factor for schizophrenia on neural social stress processing and brain anatomy in healthy individuals

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Even though schizophrenia is a highly genetic disorder, several environmental risk factors have been reported with convincing consistencies and effect sizes. One of these risk factors is urban upbringing, referring to the finding that individuals who were born and raised in cities are at least twice as often affected by the disorder when compared to individuals who were brought up in rural areas. Despite strong hints for causative effects, the underlying mechanisms of this risk factor are widely unknown. Given the worldwide tendency towards urbanization and the high population attributable risk of urban upbringing on schizophrenia incidence, it seems valuable to reveal these mechanisms. Several lines of evidence emphasize the role of social stress in the etiology of schizophrenia and suggest social stress to mediate the increased risk conferred by urban upbringing. However, effects of urban upbringing on neural social stress processing and brain morphology have been entirely unexplored.

In order to address this, magnetic resonance imaging (MRI) was applied in several samples of healthy adults, who were stratified by early-life urbanicity. The effects of urban upbringing on social stress processing were investigated in a sample of 32 individuals using a social-evaluative stress paradigm suitable for the scanner environment. Thereby, a positive correlation between early-life urbanicity and perigenual anterior cingulate cortex (pACC) activation under social stress induction was detected. This result was replicated in an independent sample of 23 students with a modified social-evaluative stress paradigm. The specificity of this result to social stress processing was furthermore demonstrated by showing the absence of an according correlation in 80 subjects who performed two cognitive tasks without social stress induction. Post-hoc analyses in the sample of 32 individuals revealed that the modulation of pACC activation by early-life urbanicity persisted, even when controlled for the potentially confounding effects of various sociodemographic and mental health-related variables. A functional connectivity analysis, which was conducted in the same sample, identified an inverse correlation between early-life urbanicity and the connectivity of pACC and right amygdala. In an additional study, the effects of urban upbringing on brain morphology were investigated applying voxel-based morphometry (VBM) in a sample of 115 healthy individuals. Early-life urbanicity was negatively correlated to the gray matter volume of a posterior section within the right dorsolateral prefrontal cortex (DLPFC). This result was regionally specific and not explained by confounding effects of common sociodemographic variables.

In sum, these results might indicate underlying neural mechanisms of the increased risk by urban upbringing. The pACC is crucially implicated in the regulation of stress, particularly via its dense projections to the amygdala. An overactivation of the pACC under social stress and a decreased functional connectivity between pACC and amygdala can therefore be regarded as markers of an exaggerated sensitivity to stress in individuals who were raised in cities. The DLPFC is considerably susceptible to the effects of stress and early adversity, and alterations of this region are highly involved in schizophrenia pathology. The volumetric reduction in the DLPFC might therefore represent a biological embedding of an elevated exposure to stress in individuals who were raised in cities, and might contribute to their increased vulnerability for schizophrenia. Both an overactivation of limbic structures and a DLPFC dysfunction have been related to an exaggerated striatal release of dopamine, which can initiate the manifestation of schizophrenia, particularly under acute exposure to stress. Overall, it can be hypothesized that urban upbringing is associated to an elevated exposure to social stress during childhood and adolescence, which sensitizes affected individuals to social stress in a way that facilitates the development of schizophrenia later in life.