Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis

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Alterations in hippocampal volume are a known marker for first-episode psychosis (FEP) as well as for the clinical high-risk state. The Polygenic Schizophrenia-related Risk Score (PSRS), derived from a large case-control study, indicates the polygenic predisposition for schizophrenia in our clinical sample. A total of 65 at-risk mental state (ARMS) and FEP patients underwent structural magnetic resonance imaging. We used automatic segmentation of hippocampal volumes using the FSL-FIRST software and an odds-ratio-weighted PSRS based on the publicly available top single-nucleotide polymorphisms from the Psychiatric Genomics Consortium genome-wide association study (GWAS). We observed a negative association between the PSRS and hippocampal volumes (β=-0.42, P=0.01, 95% confidence interval (CI)=(-0.72 to -0.12)) across FEP and ARMS patients. Moreover, a higher PSRS was significantly associated with a higher probability of an individual being assigned to the FEP group relative to the ARMS group (β=0.64, P=0.03, 95% CI=(0.08-1.29)). These findings provide evidence that a subset of schizophrenia risk variants is negatively associated with hippocampal volumes, and higher values of this PSRS are significantly associated with FEP compared with the ARMS. This implies that FEP patients have a higher genetic risk for schizophrenia than the total cohort of ARMS patients. The identification of associations between genetic risk variants and structural brain alterations will increase our understanding of the neurobiology underlying the transition to psychosis.
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