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Effects of BDNF Val^{66}Met genotype and schizophrenia familial risk on a neural functional network for cognitive control using functional magnetic resonance imaging in humans

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Cognitive control mechanisms ensure the allocation of cognitive resources in a constantly changing environment. Although cognitive control abilities implicate flexible adjustment to novel conditions, they further comprise resilience to distracting stimuli and inhibition of prepotent impulses. Aberrant cognitive control abilities are frequent across the spectrum of heritable mental disorders like schizophrenia or depression and account for a significant share of the neurocognitive symptoms experienced by those affected. Previous neuroimaging research has highlighted the contribution of the anterior cingulate (ACC) and prefrontal cortex (PFC) to successfully implementing cognitive control mechanisms.
This study tested the effect of a genetic variation in the BDNF gene, the BDNF Val66Met polymorphism, on cognitive control mechanisms. The functional polymorphism is known to impact synaptic transmission and plasticity profoundly; thus, an effect on cognitive control mechanisms was hypothesized. First, the effect of BDNF Val66Met on brain activation was investigated in a sample of 85 healthy individuals, which yielded a negative finding. Concurrently, a whole brain significant effect on interregional connectivity between ACC and mPFC was detected. In a second step, the effect BDNF Val66Met on ACC connectivity was tested in a larger independent sample of 253 individuals and the increase in ACC-PFC connectivity was replicated. The ACC-mPFC connectivity result during cognitive control in healthy 66Met -carriers was specific to the active challenge of the cognitive network and independent of structural differences. In a third step, connectivity between ACC and mPFC during cognitive control was investigated in a sample of 58 healthy first-grade relatives of schizophrenic patients. Paralleling the primary results, a similar pattern of increased connectivity between ACC and mPFC was observed. These results show that a key neural circuit for cognitive control is influenced by a plasticity-related genetic variant, which may render this circuit particular susceptible to genetic and environmental risk factors. These outcomes further suggest a possible mechanism through which a common genetic variation might modify the course and clinical outcome of schizophrenia.