Genetic characterization of prefrontal-subcortical interactions in humans

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Genetic variation can cause subtle molecular abnormalities, which leads to abnormal information processing in the brain and changes in behavior. The complex path from genes to behavior of patients with schizophrenia or depression can benefit from analyzing brain systems associated with memory, emotional regulation, and reward. Brain systems of interest include prefrontal-subcortical interactions, which link to basal ganglia and associated structures such as substantia nigra and ventral-tegmental area. Prefrontal/premotor and parietal/temporal cortex converge on caudate/putamen, which receive input from the substantia nigra. From the caudate and putamen the outputs flows via globus pallitius into thalamus and gets redistributed into prefrontal cortex, creating functional loops. Putamen and caudate are important input structures of the dorsal-lateral prefrontal cortex. Prefrontal function and subcortical dopaminergic activity are related; according to an attractive hypothesis, this enables prefrontal cortex to regulate its own dopaminergic stimulation. Genetic variation of COMT affects dopaminergic stimulation and tonic levels of dopamine in the prefrontal cortex but not in the striatum. Studies have shown that the COMT genotype has an effect on frontal lobe activity associated with executive cognitive functioning. More specifically, functional Val158Met polymorphism interacts with a 2P promoter region SNP and a SNP in the 3’ region in predicting prefrontal working memory response. The neural mechanism underlying this nonadditive genetic effect is the result of a nonlinear response of prefrontal neurons to dopaminergic stimulation. Recent findings indicate that the regulation of midbrain dopamine by prefrontal cortex also depends on COMT genotype. Imaging observations are compatible with a dopaminergic tuning mechanism. The COMT genotype has also been shown to affect amygdala-orbitofrontal coupling in tasks tapping into emotional processing. DARPP32 in the striatum is a molecular switch, which has activating/inhibiting effects on phosphoprotein. Variations in this gene have been associated with effects of antidepressants, neuroleptics, drugs of abuse, and neural plasticity. DARPP32 mRNA expression has been associated with many cognitive and working memory functions and abnormalities in schizophrenia. Genetic variation of DARPP32 predicts striatal structure, function, and frontostriatal interactions. A very frequent haplotype associated with DARPP32 predicts risk for schizophrenia, efficient striatal activation, and increased frontostriatal activity.