

Multilocus Genetic Profile for Glutamatergic Pathway and Frontostriatal Connectivity in Obsessive-compulsive Disorder

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Introduction: Research integrating neuroimaging and molecular genetics has yielded important insights into how variability in brain chemistry predicts brain function and structure, behaviour and risk for psychopathology. Disrupted neurotransmission of glutamate within cortical-striatal-thalamocortical circuitry has been hypothesized to play a role in the pathogenesis of Obsessive-Compulsive Disorder (OCD). Candidate gene studies have identified associations between variants in glutamate system genes and OCD, particularly for SLC1A1, although these results remain controversial after GWAS and meta-analytical approaches.

Objectives: To examine the effects of multiple polymorphisms of the glutamatergic pathway on frontostriatal connectivity, measured by resting state functional magnetic resonance imaging (fMRI), in OCD.

Methods: Individual multilocus genetic profile scores (MGPS) reflecting the additive effects of multiple alleles of the glutamatergic pathway, analysed by the Affymetrix GeneticChip® SNP array, were compiled for 134 OCD patients and 63 healthy controls. Association between these genetic scores and brain functional connectivity patterns between the dorsal and ventral striatal regions and limbic cortical areas including the orbitofrontal cortex and surrounding areas, such as the anterior prefrontal and perigenual anterior cingulate cortex, were investigated.

Results: In the entire group, glutamatergic MGPS were significantly associated with connectivity patterns involving the ventral striatum and orbitofrontal cortex. Distinct relationships between MGPS and functional connectivity between the ventral striatum, amygdala, ventromedial frontal cortex and insula between OCD and healthy subjects emerged.

Conclusions: Glutamatergic genetic risk variants are related to normal frontostriatal connectivity; a fact that might explain the role of glutamatergic pathway disruptions in the susceptibility to develop OCD.