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EFFECTS OF THE DAT 3'UTR VNTR GENOTYPE ON BRAIN FUNCTION IN HEALTHY SUBJECTS AND PATIENTS WITH SCHIZOPHRENIA

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Aims: To examine the effect of a polymorphism in the Dopamine Transporter (DAT) gene on brain activation during executive function and, for the first time:

1. determine the extent to which this is altered in schizophrenia and
2. use a verbal fluency paradigm.

This is relevant since:

1. DAT plays a key role in the regulation of dopamine, which modulates cortical activation during cognitive tasks and
2. a disruption of dopamine function is a fundamental pathophysiological feature of schizophrenia.

Method: Functional magnetic resonance imaging was used to measure whole-brain responses during overt verbal fluency in 85 subjects: 44 healthy volunteers and 41 DSM-IV schizophrenia patients. Main effects of genotype and diagnostic group on activation and their interaction were estimated using an ANOVA in SPM5.

Results: The 10-repeat allele of the 3'UTR VNTR was associated with greater activation than the 9-repeat allele in the left (Z=4.8; FWEp=0.005) and right (Z=4.2; FWEp=0.057) anterior insula and with decreased activation in the rostral anterior cingulate (Z=4.3 FWEp=0.04) during word generation (versus baseline). These effects were irrespective of diagnostic group but generally more marked in patients. There were also strong trends for groupxgenotype interactions in the left middle frontal gyrus and the left nucleus accumbens. Analysis was controlled for task performance, IQ, antipsychotic medication, psychopathology and demographics.

Conclusion: Cortical function during executive tasks is normally modulated by variation in the DAT gene, effect which is dependent on the brain region. DAT's effect may be altered in schizophrenia patients, which may reflect altered central dopamine function.

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