Mechanisms underlying a gene*environment interaction between COMT and cannabis use

DPhil Supervisor: Dr Liz Tunbridge

Understanding how genes and environmental factors interact to regulate brain function and dysfunction is a major research challenge. Catechol-O-methyltransferase (COMT) modulates cortical dopamine (DA) and regulates cognitive function (Tunbridge et al 2006). Recent studies have demonstrated an interaction between a functional polymorphism in COMT and cannabis use in precipitating psychotic symptoms and impaired cognition (Caspi et al 2005; Henquet et al 2006; 2008). The aim of the proposed research is to investigate the mechanisms underlying the COMT-cannabis gene*environment interaction. We hypothesise that this it arises from shared effects of COMT and cannabis on dopaminergic function, although other potential mechanisms will also be studied.

This project will use a multidisciplinary approach to model the gene*environment interaction in transgenic mice. We have access to mice carrying the human-specific functional polymorphism ($Val^{158}Met$) shown to interact with cannabis use in these studies. These transgenic mice will be administered D-9-tetrahydrocannabinol (D9THC; the primary psychoactive constituent of cannabis) and a range of techniques will be used to investigate the separate and interactive effects of COMT and D9THC on brain function. These will include (1) behavioural testing, (2) neurochemical analysis, to assess dopamine and its metabolites (microdialysis, tissue neurotransmitter quantification), and (3) molecular characterisation (microarrays, real-time PCR, Western blotting) of the brains of treated mice.

Given the range of techniques involved in this project, an undergraduate degree in neurosciences or a related subject would be an advantage. The work will be based in the Department of Psychiatry, but research will also be conducted in the Departments of Pharmacology and Experimental Psychology.

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