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Perspective

Does *COMT* val^{158}met Affect Behavioral Phenotypes: Yes, No, Maybe?

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The *COMT* gene functional polymorphism val^{158}met is one of the most intensively studied variants in psychiatric genetics. Due to small effect size and various methodological issues, its role in various psychiatric disorders and behavioral traits has still not been unequivocally established. In this issue of *Neuropsychopharmacology*, several studies are presented supporting a role for *COMT* as a factor in cocaine addiction, brain reward activation, response to tolcapone, distractibility in ADHD, and fMRI bold response. The studies make important contributions to the growing literature that aim to establish an effect of this functional variant on behavioral phenotypes and treatment response.

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Catechol-*O*-methylransferase (COMT) had an illustrious beginning. The enzyme, which metabolizes catecholamines and catechol-estrogens in the CNS and periphery, was discovered by Julius Axelrod in the late 1950s, contributing to his share of the 1970 Nobel Prize for Physiology or Medicine (Axelrod and Tomchick, 1958). COMT soon captured the attention of pioneering biological psychiatrists, largely as a consequence of the catecholamine hypothesis, the prevailing early biological model for affective disorders (Schildkraut, 1965). Analysis of red blood cell COMT activity and norepinephrine metabolites in the CNS in psychiatric disorders developed into a cottage industry. These studies, in retrospect, seem quaint (even naive) in terms of the miniscule number of subjects analyzed, the lack of attention to confounders, such as population stratification, and the analytical tools used (compare measuring red cell COMT enzyme activity in a few dozen subjects with the current craze of genotyping one million SNPs in thousands of carefully matched cases and controls). Foretelling the experience of more 'sophisticated' future generations of psychiatric geneticists, the early COMT studies were characterized by a grab bag of findings; increased, decreased or no change in activity in depression, bipolar disorder, and schizophrenia were all described.

Interest in COMT surged in the 1990s following the discovery of a common functional genetic variant at codon 158 (val^{158}met), which leads to substantial differences in enzyme activity (Lachman *et al*, 1996; Lotta *et al*, 1995). Genetic analysis of this functional SNP provided a simple, and biologically meaningful way by which psychiatric geneticists could reexamine *COMT* as a candidate gene for psychiatric disorders in large numbers of subjects. Since then, hundreds of studies have been published in which *COMT* val^{158}met has been examined for essentially every neuropsychiatric disorder. Given the recalcitrant nature of complex traits, however, the modern generation of researchers has fared only a little better than its predecessors, and the role of *COMT* in psychiatric disorders remains largely an open question (Craddock *et al*, 2006). However, as reported in the perspective by Harrison and Tunbridge (2008), evidence for sexual dimorphism with respect to *COMT* val^{158}met in OCD is arguably one of the more robust associations. In addition, based on the original work by Egan *et al* and a number of follow-up studies *COMT* val^{158}met has become a leading contender to explain part of the genetic variance underlying interindividual differences in prefrontal executive function, with val^{158} being associated with worse performance, albeit with a small effect size (Egan *et al*, 2001). However, a recent meta-analysis questions the validity of those findings (Barnett *et al*, 2008).

This issue of Neuropsychopharmacology with five original papers and the Harrison and Tunbridge perspective features the analysis of val^{158}met in a variety of behavioral and pharmacological paradigms adding to the everincreasing *COMT* literature, with some interesting new twists and experimental designs. One of the most intriguing is the study by Giakoumaki *et al* (2008). The investigators carried out a double blind crossover assessment of executive function and prepulse inhibition using the centrally acting COMT inhibitor tolcapone in 24 healthy subjects homozygous for one or the other codon 158 variant. They found

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that tolcapone improved executive function and prepulse inhibition, but only in val/val homozygotes, a finding consistent with the lower levels of cortical dopamine expected of individuals with this genotype. The small sample size and preliminary nature of the observations prevents one from extrapolating too quickly to treating patients with cognitive dysfunction with tolcapone or similarly acting drugs, as suggested previously by Apud and Weinberger (2007), perhaps in a *COMT* genotype dependent manner. However, the results are sufficiently interesting and potentially of such clinical importance that further investigation must be carried out.

Sengupta *et al* (2008) report another 'pharmacogenomic' type of analysis related to *COMT* genotype in which task-oriented behaviors and response to methylphenidate in ADHD were assessed. Children with ADHD ($n = 188$) were subjected to a double blind, placebo controlled cross over study and evaluated by RASS (Restricted Academic Situation Scale), which records fidgety and distracting behavior in a simulated academic setting (lower scores mean greater attention). Although no significant association between *COMT* genotype and ADHD susceptibility had been described previously, Sengupta *et al* found that children with met/met and met/val had lower RASS scores compared with val/val. However, although methyphenidate significantly improved RASS scores, the response was independent of genotype. If the findings are confirmed, it would support the idea that an ADHD endophenotype is associated with val^{158}met. Although this understanding may not be clinically relevant with respect to predicting methyphenidate responsiveness, the findings suggest that a COMT inhibitor might benefit children with ADHD who carry the val/val genotype.

Two of the studies in this issue are related in their assessment of val^{158}met as a candidate for addiction or addiction-related phenotypes. Lohoff *et al* (2008) provide evidence for an association between met^{158} and cocaine dependent African Americans. This is in contrast to positive associations made in methamphetamine abusers, nicotine addiction, and polysubstance abusers to the val^{158} allele in previously published studies (Beuten *et al*, 2006; Li *et al*, 2004; Vandenberg *et al*, 1997). If the findings are replicated, it could suggest that *COMT* may play a role in addiction vulnerability in a genotype/drug-dependent manner. However, this is unlikely considering that many cocaine addicts are polysubstance abusers. Whether the Lohoff *et al* study and the contrary findings in other addiction studies stand the test of time (and replication) remains to be seen; most studies examining the role of *COMT* in addiction have been negative.

Consistent with the Beuten *et al*, Li *et al*, and Vandenberg *et al* findings, the paper reported here by Wichers *et al* (2008) also supports the idea that val^{158} could be an addiction susceptibility allele. Test subjects (all women to reduce COMT-related sex effects as a confounder) were asked to assess their daily living environments using ESM (experience sampling method), a structured diary technique. Events were rated as very unpleasant, neutral, and very pleasant. 'Positive affect' was also assessed using four mood adjectives (cheerful, content, energetic, enthusiastic) rated on a seven-point Likert scale, as was 'negative affect' (by six adjectives; feeling insecure, lonely, anxious, low, guilty, suspicious). Ability to experience everyday reward was associated with met^{158}, whereas subjects with the val/val genotype experienced significantly less reward. This finding is compatible with the 'reward deficiency' hypothesis, which posits that individuals who do not experience sufficient reward from everyday pleasures (food, sex, social interaction, work, and school, for example) are prone to habitually seek the intensity of brain reward region activation induced by addicting substances. Wichers *et al* suggest that individuals with val/val genotypes who have suboptimal reward experiences are more at risk for depression and addiction. Longitudinal studies to follow the progression from lack of reward sensation to addiction, in the context of *COMT* genotype, would be especially interesting.

Finally, the paper by Ettinger *et al* (2008) contributes to the growing literature involving the analysis of brain functional responses as plausible endophenotypes that can be used to identify genes involved in complex psychiatric disorders more effectively, as suggested by Meyer-Lindenberg and Weinberger (2006). Ettinger *et al* evaluated the effect of val^{158}met on fMRI BOLD response during prosaccade and antisaccade task performance and found differential effects of val^{158} and met^{158}. Although val^{158} carriers (homozygotes and heterozygotes) showed lower BOLD response in the prefrontal cortex during antisaccades, met^{158} homozygotes showed lower BOLD response in postsaccades in the posterior cingulate and precuneus. This differential response is compatible with the hypothesis proposed by Bilder *et al* (2004) who suggested that val^{158} and met^{158} have opposite effects on phasic and tonic dopamine transmission in cortex and subcortical regions, influencing cognitive function and behavior. Although intriguing, the Ettinger study is limited by small sample size ($n = 36$).

Fortunately we are beyond the stage where we must measure levels of enzymes and substrates in every conceivable bodily fluid to piece together the role played by COMT in a biological system of interest. The *COMT* gene provides a relatively rare example where there is a common functional polymorphism that can be used to track differences between individuals in enzyme activity important for neurotransmission. Although our ability to study this variant has opened a proverbial window into the brain through which we can begin to observe individual differences in catecholaminergic metabolism, there are few 'eureka' moments in complex traits genetics, and none of the original studies reported here fulfill this lofty ambition. However, if one is content presenting novel and interesting first-stage findings, then the investigators contributing to the *COMT* papers in this volume have successfully accomplished this goal.

DISCLOSURE/CONFLICT OF INTEREST

The author declares that he has not received financial support or compensation from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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