Warriors Versus Worriers: *The Role of COMT Gene Variants*

By Dan J. Stein, MD, PhD, Timothy K. Newman, PhD, Jonathan Savitz, PhD, and Rajkumar Ramesar, PhD

ABSTRACT

Behavioral phenotypes are generally complex, reflecting the action of multiple different genes. Nevertheless, there is growing evidence that key gene variants can alter activity within specific neuronal circuits and, therefore, influence particular cognitive-affective phenomena. One example is the catechol-O-methyltransferase (COMT) gene, which has a common variant at codon 158. Those with valine (Val^{158}) alleles have increased greater COMT activity and lower prefrontal extracellular dopamine compared with those with the methionine (Met^{158}) substitution. Val^{158} alleles may be associated with an advantage in the processing of aversive stimuli (warrior strategy), while Met^{158} alleles may be associated with an advantage in memory and attention tasks (worrier strategy). Under conditions of increased dopamine release (eg, stress), individuals with Val^{158} alleles may have improved dopaminergic transmission and better performance, while individuals with Met^{158} alleles may have less efficient neurotransmission and worse performance. Some evidence suggests that Val^{158} alleles are associated with schizophrenia, while Met^{158} alleles are associated with anxiety.

CASE REPORT

Jolene was discussing her fraternal twin sons with her primary care physician. It was amazing how different they were. Jason loved to be outside, excelled at downhill skating, and looked forward to anything that involved thrills and spills (martial arts, roller coasters, etc.). John, on the other hand, loved reading, was superb at chess, and tried to avoid anything that involved possible injury (martial arts, roller coasters, etc.). She was quite sure that her sons had differed from birth; although she had provided them with the same home, they had developed different likes and different skills. She found it necessary to respond to them in entirely different ways in order to prevent the various excesses that each was prone to and to bring out the best in them.

COGNITIVE-AFFECTIVE NEUROSCIENCE

Neuroanatomy/Neurochemistry

Frontolimbic circuits play a key role in the regulation of human cognitions, affects, and behaviors. A growing database of studies suggests that poorly regulated impulses may reflect decreased frontal control and increased limbic drive.[1,2] There is preliminary evidence that overly regulated impulse control may be characterized by contrasting regional abnormalities.[3,4] Frontolimbic circuits are controlled by multiple genes, and several neurotransmitters, including catecholamines (eg, dopamine) and indoleam-

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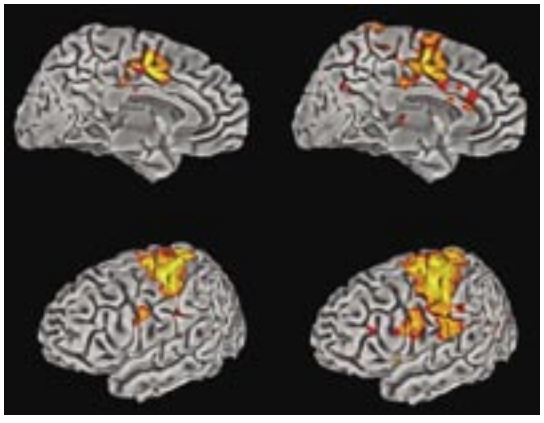
ines (eg, serotonin), may contribute to the mechanisms that underpin the regulation of cognition, affect, and behavior.

The catechol-O-methyltransferase (COMT) enzyme plays a particularly crucial role in regulation of prefrontal dopamine; there is a relative scarcity of dopamine transporters in this region. A common functional variant in the COMT gene involves substitution of valine (Val^{158}) by methionine (Met^{158}) at codon 158. Those with Val^{158} alleles have greater enzyme activity, reduced extracellular dopamine, and weaker prefrontal neuronal activation (Figure 1).[5] Val^{158} carriers have compensatory prefrontal hyperactivation and worse performance on memory[6,7] and attention[8,9] tasks, but Met^{158} carriers have increased limbic activation and more pain in response to unpleasant stimuli (Figure 2).[10,11]

Research continues to be done on the relationship between COMT genotype and brain function and structure in healthy subjects and in psychopathology.[12-16] These initial findings suggest that Val^{158} alleles are associated with an advantage in processing aversive stimuli (where rapid disengagement of cortical circuits is optimal), while Met^{158} substitutions are associated with an advantage in memory and attention tasks (where information is held in working memory).[17-19] Consistent with these findings, Val^{158} alleles may confer protection against anxiety and pain susceptibility,[20,21] while Met^{158} alleles may confer protection against schizophrenia[6] (although the data remain controversial).[22,23]

Under conditions of increased dopamine release (eg, stress), individuals with Val^{158} alleles presumably have a beneficial increase in extracellular dopamine, and so improved performance on working memory.[24] In contrast, individuals

FIGURE 1.
A weaker and less extended BOLD response is seen during a visual oddball task in Val^{158} carriers (left) than in homozygous Met^{158} carriers (right) in the area of the supplementary motor cortex extending into the anterior cingulate cortex, dorsolateral PFC, and parietal cortex[5]



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BOLD=blood-oxygen level dependent; Val^{158}=valine; Met^{158}=methionine; PFC=prefrontal cortex.

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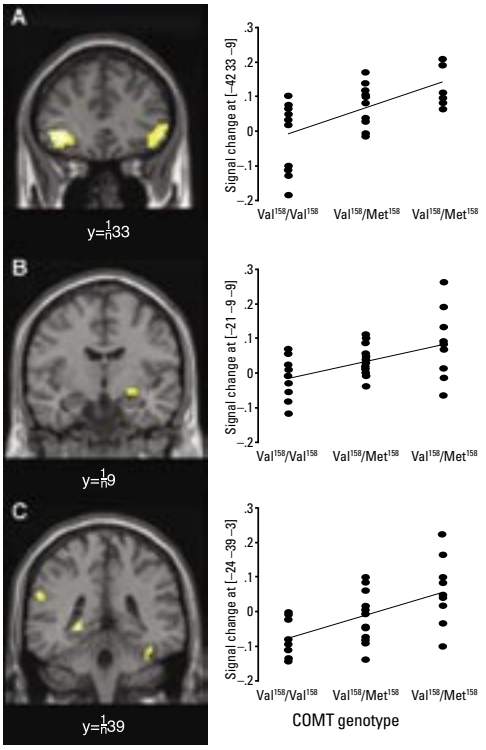
FIGURE 2.
On exposure to unpleasant visual stimuli, there is a positive correlation between the number of Met^{158} alleles and the BOLD fMRI response (A) in ventrolateral PFC, (B) right amygdala, and (C) left dorsal hippocampus[11]



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Met^{158}=methionine; BOLD=blood-oxygen level dependent; fMRI=functional magnetic resonance imaging PFC=prefrontal cortex; Val^{158}=valine; COMT=catechol-O-methyltransferase.

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with Met[158] alleles may not be able to improve the efficiency of dopaminergic neurotransmission, and indeed may have decreased performance on working memory.[24] These data have been modeled using an inverted-U graph, which helps explain why a rightward shift in dopamine signaling is useful in Val1[158] carriers but not in Met[158] carriers (Figure 3).[24]

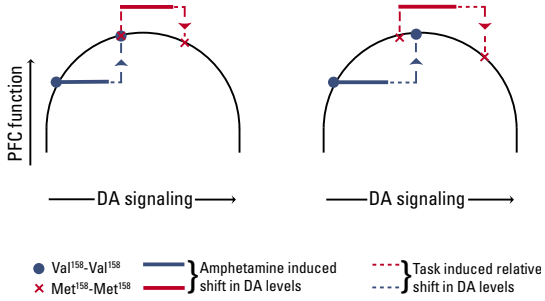
Gene/Environment

There is growing data on other polymorphisms in COMT which affect its activity. In addition, gene X environment interactions may act to affect function. For example, Val[158] carriers show increased risk for developing schizophreniform disorder and psychotic symptoms if they have used cannabis during adolescence.[25] A recent study of monozygotic twins[26] found that there was considerable variation in the concordance of methylation of sites in the COMT gene. This epigenetic variation may reflect differences in environment, and may help explain differences in susceptibility to psychopathology in monozygotic twins.

Evolutionary Approaches

Speculatively, COMT gene variants have particular evolutionary advantages. Val[158] alleles may be particularly useful in threatening environments where maximal performance is required despite threat and pain (a warrior strategy). Met[158] alleles appear to have evolved more recently and may be particularly useful in complex environments where maximal performance is required on tasks of memory and attention (a worrier strategy). The persistence of both variants may reflect the possibility that both warrior and worrier strategies can potentially be advantageous, depending on the circumstances.

FIGURE 3.
Theoretical model to describe the effects of COMT genotype, working memory load, and amphetamine on PFC dopamine signaling and function*[24]



* At baseline, Val[158] carriers (with greater COMT activity, less dopamine, and worse prefrontal function) are found on the up slope of the normal range, whereas Met[158] carriers are found at the peak. In Val[158] carriers, amphetamine improves DA signaling and prefrontal function, but in Met[158] carriers DA shifts onto the down slope of the inverted-U curve[26]

Reprinted from Mattay VS, Goldberg TE, Fera F, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A.* 2003;100:6186-6191, Copyright (2003) National Academy of Sciences, U.S.A.

COMT=catechol-O-methyltransferase; PFC=prefrontal cortex; DA=dopamine; Val[158]=valine; Met[158]=methionine.

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CLINICAL IMPLICATIONS

DSM-IV-TR *Diagnosis*

A major criticism of current psychiatric nosological schemas is that they are not based on psychobiological mechanisms, so that such mechanisms are likely to cut across different diagnostic categories.[27] In this view, a more parsimonious approach would focus on different pathogenic mechanisms. At the same time, an approach that highlights variations in single genes will undoubtedly be unwieldy in the clinic. Hopefully, in the future, a balance between these extremes will be found, with the development of a psychobiologically based phenomenology that retains clinical utility.

Assessment/Evaluation

Impulsive and anxious symptoms and disorders can be assessed using a range of structured diagnostic instruments and symptom measures. The development of functional brain imaging has given rise to a range of cognitive-affective paradigms for use in research studies of control of impulses and regulation of emotions. In further research, we can expect increased use of genotyping of relevant candidate genes involved in impulse control and emotional regulation in the clinical setting. At present, however, genotyping of COMT variants is primarily a research tool.

Pharmacotherapy/Psychotherapy

There is evidence that COMT variants may play a role in predicting response to pharmacotherapy. COMT inhibitors may improve cognition in animals and in human Val[158] carriers, but worsen cognition in Met[158] carriers.[19] Preliminary research on such associations emerges from studies of a range of medications in a number of different indications.[28-33] Nevertheless, the prediction of treatment response to medication

is necessarily complex and needs to take into account a range of factors, including gene-gene interactions.[34,35] Thus, a good deal of additional work is needed before data on COMT genotyping in relationship to pharmacotherapy response has clear clinical utility.

CONCLUSION

Individual differences are not confined to superficial appearances; they more likely reflect crucial differences in underlying genes, circuits, and cognitive-affective function. Given the complexity of human behavior, one cannot expect that any gene variant is likely to explain a great deal of variance in phenotypes and the underlying mechanisms that contribute to explaining these phenotypes (endophenotypes). Nevertheless, when it comes to contrasting warriors with worriers, a growing set of studies suggests that specific variants in the COMT gene may play a crucial role in the embodiment of this distinction.

ADDENDUM

We are indebted to David Goldman, MD, for the phrase "warriors versus worriers" in relation to studies of COMT. This contrast has also been used by several authors in the scientific literature,[36,37] and can be found even earlier in the non-scientific literature. ***CNS***

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