Catechol-*o*-Methyltransferase, Cognition, and Psychosis: Val^{158}Met and Beyond

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This review summarizes our current understanding of catechol-o-methyltransferase (COMT) and how it relates to brain function and schizophrenia. We begin by considering the COMT gene, its transcripts and proteins, and its relevance for central catecholamine function. We then describe how variation in COMT activity affects the function of the prefrontal cortex (PFC) and associated areas, reviewing evidence that COMT modulates executive function and working memory and highlighting recent data that also implicate it in emotional processing. Finally, we discuss briefly the genetic association between COMT and schizophrenia, focusing in particular on the complex interaction of functional loci within the gene that may underlie the mixed results of studies to date. We conclude by outlining preliminary data indicating that COMT is a promising therapeutic target for ameliorating the cognitive deficits associated with schizophrenia.

Key Words: Catecholamine, dopamine, prefrontal cortex, schizophrenia

The COMT gene is located on chromosome 22, band q11.2 (Grossman et al 1992; Figure 1). It consists of six exons, the first two of which are noncoding, encoding two known transcripts, of 1.3 kb and 1.5 kb in humans, from two promoters (Tenhunen et al 1994). Unusually, the longer of the two transcripts encodes distinct COMT allozymes (membrane-bound [MB-] and soluble [S-] COMT) from two AUG start codons. Consequently, MB-COMT has an extension to the open reading frame that encodes 50 hydrophobic amino acids (43 in rat), containing the membrane-spanning region, that are not present in the 221 amino acid S-COMT (Bertocci et al 1991; Lundström et al 1991). Further complexity comes from a recent discovery of a putative novel and larger MB-COMT isoform, identified using immunoblotting, (Tunbridge et al, in press). The molecular identity of this variant, and its origin, is currently under investigation.

Most human tissues express both COMT mRNA transcripts, but in brain, only the longer transcript is readily detectable (Chen et al 2004a; Hong et al 1998; Tenhunen et al 1994). As a result, and in contrast to most peripheral tissues, MB-COMT is the dominant allozyme in brain, with only low amounts of S-COMT present (Chen et al 2004a; Tenhunen et al 1994; Tunbridge et al, in press).

A number of putative regulatory elements have been discovered in the COMT gene that may explain the differential expression of the long and short transcripts in various tissues (Tenhunen et al 1994). The COMT gene contains numerous estrogen response elements (Xie et al 1999) and estradiol has been shown to downregulate COMT expression in cell culture (Jiang et al 2003). The 5′ region of COMT also contains abundant methylation sites that have been shown to be actively regulated, at least in neoplastic tissue, suggesting that gene silencing through methylation may be a further regulatory mechanism (Sasaki et al 2003).

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COMT methylates a wide range of catechol substrates, including catecholamines and catecholestrogens. This reaction involves the transfer of the methyl group from S-adenosyl-L-methionine to the substrate in the presence of a magnesium ion (for review, see Männistö and Kaakkola 1999). Despite the fact that they share a large proportion of their sequences, MB-COMT and S-COMT differ in their substrate affinity and capacities. Significantly, despite having a lower capacity than S-COMT, MB-COMT has around a 10-fold greater affinity for dopamine and noradrenaline (Lotta et al 1995). Thus, MB-COMT is likely to be better suited to metabolizing catecholamines at the concentrations found in brain (Roth 1992).

There is a trimodal distribution of COMT activity in human populations (Floderus et al 1981) because of the presence of a functional polymorphism in the coding sequence (Lachman et al 1996). This polymorphism consists of a G → A substitution, resulting in a valine to methionine substitution at position 158 in MB-COMT (108 in S-COMT; Bertocci et al 1991; Lundström et al 1991). The Met^{158} form of COMT has a lower thermostability and therefore a lower activity at physiologic temperature (Chen et al 2004a; Lotta et al 1995). Thus, Val^{158} homozygotes have greater COMT activity in their blood compared with Met^{158} homozygotes (Lachman et al 1996). This decreased activity of the Met^{158} form is conserved in brain, with Met^{158} homozygotes showing approximately one third less activity than Val^{158} homozygotes (Chen et al 2004a). Because the alleles are codominant, heterozygotes have intermediate levels of COMT activity, explaining the observed trimodal distribution of COMT activity. No equivalent polymorphism has been found in any other species examined to date, including nonhuman primates (Palmitier et al 1999). Therefore, the Met^{158} variant may be specific to humans, and it appears that COMT activity has decreased during evolution (Chen et al 2004a; Palmitier et al 1999). This general decrease may reflect the beneficial effect of lowered COMT activity on prefrontal function (Egan et al 2001); however, the Met^{158} allele is also associated with some detrimental phenotypes, such as impaired emotional processing and obsessive–compulsive disorder, described later, and breast cancer (Lavigne et al 1997). These multiple and complex associations possibly underlie the persistence of both alleles and their variation in various human populations (Palmitier et al 1999) because selective forces are likely to depend largely on environmental context.

Localization of COMT in the Central Nervous System

Northern blots indicate that the 1.5-kb isoform of COMT mRNA is expressed in all regions of the human central nervous

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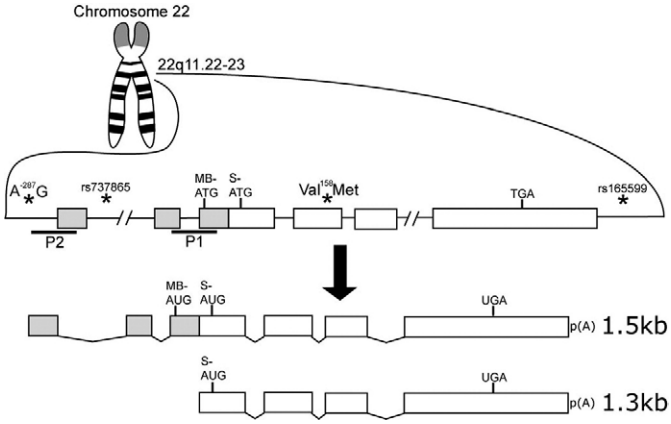

Figure 1. The catechol-*o*-methyltransferase (COMT) gene and transcripts. The COMT gene is located on chromosome 22q11.22–23. The gene consists of six exons (sequences in gray are unique to the 1.5-kb transcript) and has two promoters, P2 and P1, responsible, respectively, for controlling expression of the 1.5-kb and 1.3-kb transcripts. The COMT gene contains a number of polymorphisms of interest, including $A^{-287}G$, rs737865, $Val^{158}Met$, and rs165599. rs737865, $Val^{158}Met$, and rs165599 comprise the haplotype shown to be highly significantly associated with schizophrenia by Shifman and colleagues (2002). The positions of the MB-COMT and S-COMT start codons (ATG/AUG) and the termination codon (TGA/UGA), along with the poly-A tail (pA), are indicated. Note that MB-COMT can only be generated from the 1.5-kb transcript.

system (CNS) examined, including frontal, temporal, and parietal lobes of the cerebral cortex, cerebellum, amygdala, putamen, thalamus, and spinal cord (Hong et al 1998; Matsumoto 2003a). In situ hybridization data show COMT mRNA concentrated in the prefrontal cortex (PFC; especially layers II, III, and VI), with significantly lower levels in the striatum and very low levels in the ventral tegmental area and substantia nigra (Matsumoto et al 2003a). Data in rat brain are consistent with this distribution and also show abundant COMT mRNA in the hippocampus and choroid plexus. At the cellular level in both species, COMT mRNA appears primarily neuronal, not glial, with ependymal cells also showing strong expression (Matsumoto et al 2003a). In the PFC, COMT mRNA is particularly prominent in pyramidal neurons (Matsumoto et al 2003a, 2003b).

The localization of COMT protein remains much less clear, at both cellular and subcellular resolutions, largely because of the lack of suitable, allozyme-specific antibodies. For example, early studies suggested that COMT was predominantly a glial enzyme, although other data argued for a neuronal location as well (e.g., Karhunen et al 1994; Kastner et al 1994). To reconcile these data, it was proposed that the allozymes might be differently localized, with S-COMT localized to glia and MB-COMT residing in neurons (Roth 1992). Ultrastructurally, several studies have indicated that MB-COMT is present on the plasma membrane and therefore possibly protruding into the synapse (e.g., Raxworthy et al 1982). In support of this, Kastner et al (1994) demonstrated COMT associated with postsynaptic dendritic spines. If MB-COMT does protrude into the synaptic cleft, however, its activity would likely be inhibited by the high extracellular levels of Ca^{2+} (Roth 1992). Furthermore, sequence motifs indicate that MB-COMT is actually oriented so that it protrudes into the cytoplasm (Lundström et al 1995). To add to the controversy, Grossman and colleagues (1985) suggested that MB-COMT is present on the outer mitochondrial membrane. This proposal is supported by earlier cell fractionation studies (Broch and Fonnum 1972), whereas transfection studies have localized MB-COMT exclusively to intracellular membranes, particularly the rough endoplasmic reticulum (Ulmanen et al 1997). Thus, like its cellular location, the subcellular localization of COMT remains unresolved.

On balance, given the relative scarcity of COMT mRNA in dopamine neurons and in glia, available data suggest that, at least in human cerebral cortex, COMT is located primarily on intracellular membranes in postsynaptic neurons. The subcellular localization requires further investigation and it is not clear whether the primary membrane location of COMT is intracellular, on the cell surface, or both. Because COMT is clearly important for modulating activity-dependent PFC dopamine levels (discussed later), an intracellular location would appear to require a mechanism for importing dopamine into postsynaptic neurons, perhaps via the organic cation transporters (Busch et al 1998) for it to be accessible to the enzyme.

COMT and Catecholamine Regulation

Historically, the role of COMT in the catabolism of the catecholamines has been considered minor compared with that of monoamine oxidase, with COMT's primary role being the conversion of DOPAC to HVA (Figure 2; Kopin 1985). Mounting evidence suggests however, that COMT may be unexpectedly important for the breakdown of dopamine, particularly in PFC. First, 3-methoxytyramine (3-MT), formed by the *o*-methylation of dopamine by COMT (Figure 2), is the major metabolite of released dopamine in rat prefrontal cortex, suggesting that dopamine *o*-methylation is a prominent pathway in this region (Karoum et al 1994). Furthermore, in the COMT knockout mouse, males showed a two- to threefold increase in baseline frontal dopamine levels with no changes in other regions or in noradrenaline (Gogos et al 1998), with intermediate results in heterozygotes. In another study of COMT knockout mice, L-DOPA loading dramatically increased dopamine turnover specifically in PFC, a finding that was not gender specific (Huotari et al 2002). In support of these findings, we have shown that administration of tolcapone, a specific and brain-penetrant COMT inhibitor (Ceravolo et al 2002), doubles the increase in extracellular dopamine but not noradrenaline in the rat medial PFC when catecholamine efflux is induced (Tunbridge et al 2004a). Thus, it appears that COMT is important for regulating

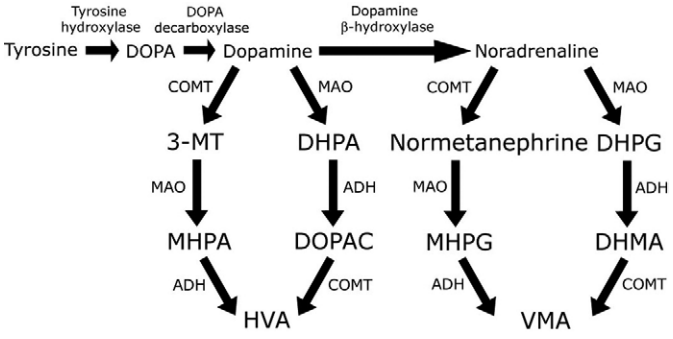

Figure 2. Synthesis and metabolism of dopamine and noradrenaline. Dopamine is degraded to homovanillic acid (HVA) and noradrenaline to vanillylmandelic acid (VMA) by the enzymes catechol-*o*-methyltransferase (COMT), monoamine oxidase (MAO), and aldehyde dehydrogenase (AD). The intermediate products are 3-methoxytyramine (3-MT); 3,4-dihydroxyphenylacetaldehyde (DHPA); 3-methoxy-4-hydroxyphenylacetaldehyde (MHPA); 3,4-dihydroxyphenylacetic acid (DOPAC), dihydroxyphenylglycol (DHPG); 3,4-dihydroxymandelic acid (DHMA); and 3-methoxy-4-hydroxyphenylglycol (MHPG).

dopamine but not noradrenaline levels in the PFC. The mechanism by which COMT modulates dopamine but not noradrenaline currently remains unclear (Figure 2); however, it is consistent with data showing a specific effect of depletion of the catecholamine precursor tyrosine on central dopaminergic but not noradrenergic function (McTavish et al 1999) and on abundant expression of noradrenaline transporters in cortex (Miner et al 2003), which may prevent COMT from accessing noradrenaline.

In addition, COMT activity influences the activity of dopaminergic neurons in the midbrain, but this seems to be an indirect effect mediated by prefrontal feedback. PFC dopamine function has been shown to regulate subcortical dopamine activity, a circuit thought to be dysfunctional in schizophrenia (Grace 2000; Weinberger 1987). It is hypothesized that activity of the PFC tonically inhibits striatal dopamine projections via inhibitory GABA neurons in the midbrain or striatum (Carr and Sesack 2001); thus, dopamine activity in the PFC and striatum may be inversely related. As might be anticipated, based on its importance in the PFC, COMT appears to affect the functioning of this circuit. Expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine biosynthesis (Figure 2), in the dopamine projection nuclei of the midbrain is associated with COMT Val^{158}Met genotype in postmortem human brain. Val^{158} homozygotes, which are expected to have relatively high COMT activity and therefore low PFC dopamine levels, show greater midbrain TH mRNA expression (and therefore presumably greater dopamine biosynthesis) than Val^{158}Met heterozygotes (Akil et al 2003). Furthermore, when individual dopaminergic nuclei were considered, this genotype effect was significant only in the ventral part of the substantia nigra, which projects to the striatum and amygdala (Haber and Fudge 1997), suggesting that the effect of COMT genotype on midbrain TH expression might be greatest in non-PFC projection regions. It seems likely that the altered midbrain TH expression is a downstream consequence of variation in PFC COMT activity, rather than a locally mediated effect, given the enzyme's relative scarcity in midbrain (Matsumoto et al 2003a). These findings are consistent with predictions based on the circuit anatomy and the evidence that prefrontal projections tonically inhibit the activity of midbrain dopamine neurons. Presumably, Val^{158} homozygotes exert less organized or coherent corticofugally regulated inhibition of dopamine cells. The effect of COMT genotype on TH mRNA expression was strikingly paralleled by a recent in vivo neuroimaging study in which Val^{158} carriers showed relatively greater radiolabeled F-DOPA uptake in the midbrain than Met^{158} homozygotes, presumably as a requirement for increased dopamine biosynthesis in this region (Figure 2; Meyer-Lindenberg et al 2005). Thus, higher COMT activity, as conferred by the Val^{158} allele, is associated with elevated midbrain dopamine synthesis, suggesting that the Val^{158}Met polymorphism may indirectly affect dopaminergic function in other brain regions, likely as downstream manifestations of changes in cortical processing.

It is unclear to what extent COMT modulates catecholamine function outside the dorsolateral PFC. The only other brain region in which the importance of COMT for modulating catecholamine function has been extensively studied is the striatum. It appears, however, that COMT activity plays an at most minor role in the removal of striatal extracellular dopamine, evidenced by the lack of effect of COMT inhibition on dopamine levels (Maj et al 1990; Napolitano et al 2003), the relative lack of 3-MT formation in this region (Karoum et al 1994), and the absence of changes in striatal catecholamines in the COMT knockout mouse

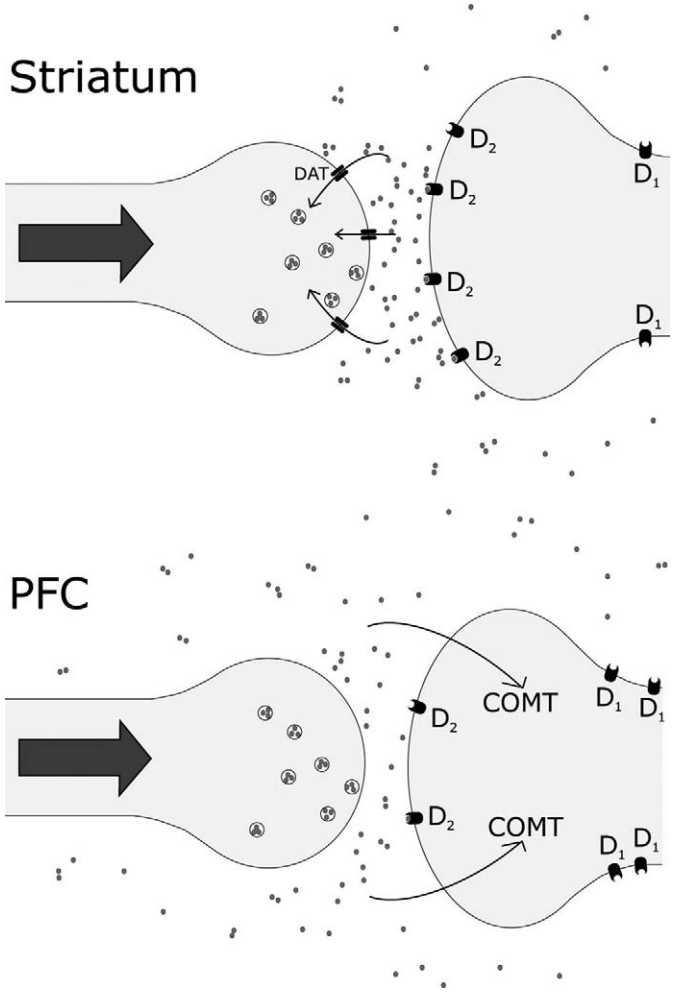

Figure 3. Dopaminergic transmission in prefrontal cortex (PFC) and striatum. In striatum, the dopamine transporter (DAT) is responsible for removing dopamine from the synaptic cleft, with catechol-*o*-methyltransferase (COMT) playing at most a minor role. In the PFC, lack of the dopamine transporter in the synapse (see text for discussion) means that COMT plays a more prominent role in inactivating dopamine. Thus, the lesser COMT activity found in Met^{158} carriers, compared with Val^{158} carriers, results in increased dopamine in PFC.

(Gogos et al 1998). Thus, COMT appears to be of particular importance in regulating dopamine in PFC. In rat, this may occur because of the relative scarcity of the dopamine transporter in this region, compared with the striatum (Sesack et al 1998; Figure 3). The dopamine transporter is found in greater abundance in the primate PFC; however, in contrast to the striatum, it does not appear to be associated with dopaminergic synapses (Lewis et al 2001). Therefore, it is likely that PFC dopamine is able to diffuse to extrasynaptic sites, increasing the likelihood that it is degraded by COMT during this process. The importance of COMT in other brain regions, including the hippocampus (where it is highly expressed) and the cingulate, the activity of which has been recently shown to be modulated by the Val^{158}Met polymorphism (Blasi et al 2005), remains to be as extensively studied.

COMT Function and Cognition

Dopamine levels in the PFC are critical for modulating cognitive function. A wealth of evidence suggests that there is an

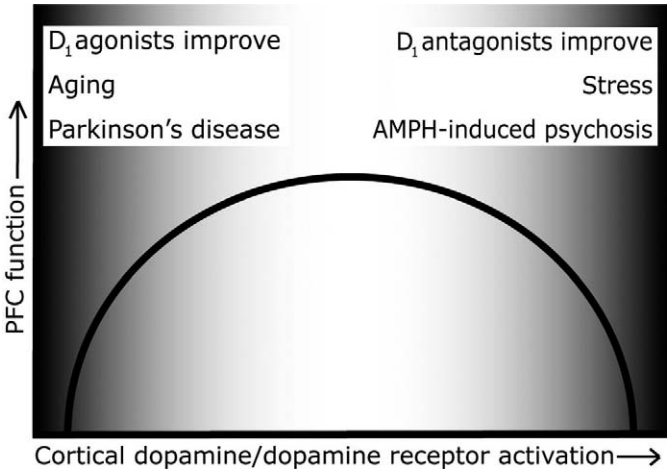

Figure 4. The inverted-U-shaped relation between dopamine and prefrontal cortex (PFC) function (Goldman-Rakic et al 2000). Prefrontal cortex function is optimal at intermediate levels of dopamine (light region), mediated by D_1 and D_2 receptors (Winterer and Weinberger, 2004); PFC function is impaired in states of dopaminergic hypofunction (e.g., in aged animals and patients with Parkinson's disease) and hyperfunction (e.g., in stressed animals or during amphetamine-induced psychosis).

inverted-U-shape relationship between dopamine activity in PFC and working memory performance (Figure 4; Goldman-Rakic et al 2000). This relationship appears to reflect complex effects of D_1 and D_2 receptor activation on local glutamate and GABA neurons (Seamans and Yang 2004). Consequently, working memory is impaired by local infusion of both D_1 antagonists and agonists into PFC (e.g., Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995; Zahrt et al 1997) and to a lesser degree by D_2 antagonists, with intermediate levels of dopamine appearing to be optimal for working memory performance.

As outlined earlier, COMT is important for modulating PFC dopamine levels, particularly under conditions that pertain during performance of PFC-dependent tasks (Tunbridge et al 2004a). Therefore, COMT represents an excellent candidate gene for modulation of PFC function. An expanding and surprisingly consistent body of recent research suggests that this is indeed the case. Egan and colleagues (2001) demonstrated that the Val^{158} allele of COMT is linked with relatively poorer performance on the PFC-dependent Wisconsin Card Sorting Test (WCST), with Met^{158} homozygotes performing better than Val^{158} homozygotes and heterozygotes showing intermediate performance. The COMT genotype was also associated with prefrontal activity, determined using functional magnetic resonance imaging (fMRI) during working memory. For a given level of performance, Val^{158} homozygotes show greater activation of the dorsolateral PFC and cingulate cortex than Met^{158} homozygotes, with heterozygotes again showing intermediate levels of activation (Egan et al 2001). Thus, Val^{158} homozygotes use their PFC relatively less "efficiently" than Met^{158} carriers, that is, they require greater prefrontal activation for a given level of performance. This pattern of inefficient cortical processing during working memory in normal individuals who have relatively diminished cortical dopamine flux is analogous to results in patients with Parkinson's disease who have been studied with fMRI during dopamine depleted and repleted states (Mattay et al 2002). Therefore, the high activity Val^{158} COMT is associated with both poorer performance and "inefficient" prefrontal function, presumably because these individuals have lower prefrontal dopamine levels (Figure 5).

A large number of studies have broadly replicated and extended these findings (e.g., Bilder et al 2002; Diamond et al 2004; Goldberg et al 2003; Joober et al 2002; Malholtra et al 2002; Mattay et al 2003; Meyer-Lindenberg et al, unpublished data), and it has been shown that this genotype effect is relatively specific to PFC cognitive tasks known to be dependent on dopamine (Diamond et al 2004). Further supportive data have been obtained in rats, which lack the Val^{158}Met polymorphism. Rat COMT has a leucine residue at position 158, and this variant has enzyme activity similar to (Lotta et al 1995), or possibly greater than (Chen et al 2004a), the human Val^{158} isoform. In this species, cognitive performance is improved following inhibition of COMT with tolcapone, somewhat comparable to the situation in human Met^{158} carriers (Tunbridge et al 2004a; Figure 5). Therefore, COMT activity is a significant factor in modulating performance on PFC-dependent cognitive tasks.

COMT and Cognition: Effect of PFC State

The putative inverted-U-shaped relation between dopamine levels and PFC function makes it likely that the relation between COMT activity and PFC function is more complex than simply "Met^{158} good, Val^{158} bad." The precise effect of COMT activity on PFC function will be dependent on precisely where on the inverted-U curve the individual in question lies in any given environmental or genetic context. This is likely governed by multiple factors, including both state factors, for example, the relative amount of stress that the individual is under, which is known to affect PFC dopamine levels (Thierry et al 1976), and trait factors, such as the complex genetic background on which the COMT genotype is expressed. Although studies of interactions between COMT genotype and other factors that might influence PFC function are in their infancy, research so far supports this hypothesis. For example, in patients with Parkin-

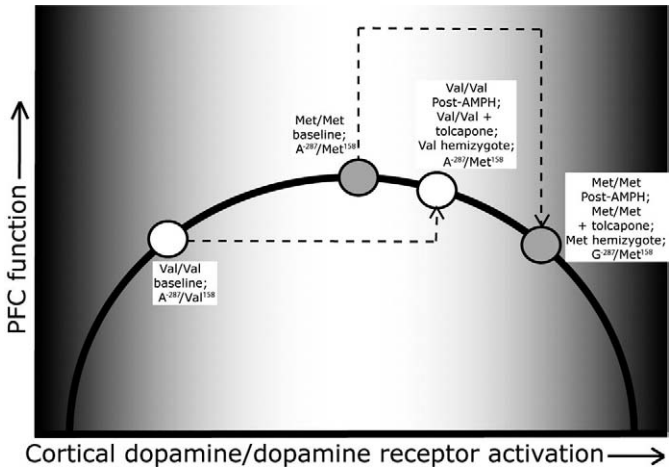

Figure 5. Effect of catechol-*o*-methyltransferase (COMT) activity on the inverted-U-shaped relation between dopamine and prefrontal cortex (PFC) function. At baseline, COMT activity in Val^{158} homozygotes is associated with suboptimal PFC dopamine, whereas Met^{158} homozygotes have near-optimal PFC dopamine levels. Val^{158} homozygotes can be pushed nearer to the peak of the inverted-U-shaped curve as a result of decreased COMT activity (e.g., by tolcapone treatment, the presence of the G^{-287} allele, or by hemizygosity at this locus, as in velo-cardio-facial syndrome) or by other causes of increased PFC dopamine transmission (e.g., by amphetamine [AMPH] treatment). The net effect is to improve PFC function. In contrast, decreasing COMT activity or increasing dopamine transmission in Met^{158} homozygotes results in superoptimal PFC dopamine levels, impairing PFC function.

son's disease (Foltynie et al 2004) or attention-deficit/hyperactivity disorder (Bellgrove et al 2005), both of which are associated with dopaminergic abnormalities, it is the Met^{158} rather than the Val^{158} allele that is linked with relatively impaired PFC performance, suggesting that the effect of the Val^{158}Met polymorphism is dependent on other factors that also affect dopaminergic tone. This was elegantly demonstrated by Mattay and colleagues (2003), who showed differential effects of amphetamine on COMT Val^{158}Met genotype groups of normal subjects: Val^{158} homozygotes show significant improvements in both PFC "efficiency" on fMRI and WCST performance, whereas Met^{158} homozygotes, the performance of which is normally superior to Val^{158} carriers, show decreased PFC "efficiency" and performance. These data are readily explained in the context of the inverted-U curve of dopamine and PFC function (Figure 5): Val^{158} homozygotes usually have suboptimal dopamine "tone," which is increased to more optimal levels by amphetamine, whereas Met^{158} homozygotes normally have near optimal dopamine "tone" and are pushed to supraoptimal levels by amphetamine administration. Thus, whether it is Met^{158} or Val^{158} that is associated with improved PFC performance depends in large part on the background on which the polymorphism exerts its effect.

Further evidence to support the hypothesis that the relation between COMT Val^{158}Met and cognition depends on the PFC background state comes from studies conducted in subjects with velo-cardio-facial syndrome (VCFS, also called DiGeorge syndrome; Shprintzen et al 1978). This developmental disorder is caused by hemizygous microdeletions of 22q11, with the COMT gene lying within the critical deletion region (Maynard et al 2002); thus, patients with VCFS are hemizygous for the COMT Val^{158}Met polymorphism. Interesting evidence that COMT may be a factor in the psychopathology associated with the VCFS syndrome is emerging, and this relationship is critically dependent on the age of the subject. In a longitudinal study, Gothelf and colleagues (2005) demonstrated that in childhood (mean age 13 years), Met^{158} hemizygotes significantly outperformed Val^{158} hemizygotes on tests of cognition and IQ, whereas during late adolescence (mean age 18 years) the Val^{158} hemizygotes performed better because of a significant decline in function in the Met^{158} hemizygote group. These findings clarify previous, apparently conflicting data: Bearden and colleagues (2004) showed better executive function in Met^{158} compared with Val^{158} hemizygotes in a childhood cohort (mean age 11 years), whereas Baker et al (2005) showed poorer neuropsychologic performance and frontal auditory mismatch negativity in Met^{158} hemizygotes compared with Val^{158} hemizygotes in an adolescent cohort (mean age 16 years). The contrast between the beneficial effect of the Met^{158} allele in childhood and the Val^{158} allele in adolescence (and possibly beyond) in VCFS subjects likely results from the protracted postnatal development of the PFC dopamine system. For example, pyramidal neurons in the PFC do not receive their full catecholaminergic innervation until adolescence (Rosenberg and Lewis 1995). The developmental relationship between PFC dopamine and COMT is further confounded by our finding that COMT activity increases in PFC during human postnatal development, peaking only in adulthood (Tunbridge et al 2005), making it difficult to predict precisely where Met^{158} and Val^{158} hemizygotes lie on the inverted-U-shaped curve of dopamine function during childhood. Nevertheless, the results obtained in late adolescence are consistent with the hypothesis of COMT's effect on the inverted-U relation (Figure 5). Presumably by early adulthood, the presence of the Val^{158} allele on a hemizygous 22q background produces COMT activity levels more akin to the optimal COMT enzyme activity levels of normal Met^{158} homozygotes. In contrast, Met^{158} hemizygotes are likely to have suboptimal COMT enzyme activity, resulting in superoptimal dopamine function and relatively impaired cognitive performance. In other words, allelic association with Val^{158}Met depends on an individual's dopamine-PFC inverted-U-shape curve, that is, hemizygosity rescues Val^{158} individuals by moving them toward the peak of the curve and impairs Met^{158} individuals by moving them to the downward slope of the curve (Figure 5).

COMT and Cognition: Effect of Task

The notion that increased dopamine flux in PFC will generically enhance function is an oversimplification. Rather, it appears that whether an individual's COMT genotype is beneficial or detrimental will depend not only on factors relating to PFC state (e.g., VCFS) but also on the nature of the task in question (Bilder et al 2004). Thus, the Met^{158} allele, which is generally beneficial to performance on tasks of working memory and executive function, may be associated with abnormal affective responses. The Met^{158} allele has been linked with a number of negative states that have an affective component, including increased pain sensitivity (Zubieta et al 2003), obsessive–compulsive disorder in men (Karayiorgou et al 1997), increased anxiety in women (Enoch et al 2003), and panic disorder (Woo et al 2004). Two recent fMRI studies suggest a neural mechanism for this effect. First, the Met^{158} allele was shown to be associated with greater reactivity of the limbic system, including the ventrolateral PFC, to unpleasant visual stimuli (Smolka et al 2005). These findings were extended by Drabant et al (in press), who also found a relation between Met^{158} allele dosage and limbic reactivity during an emotional face processing task; the Met^{158} allele was associated with exaggerated hippocampal and PFC activity, the opposite of the pattern of cortical activity associated with Met^{158} carriers during cognitive processing. In other words, Met^{158} carriers appear to be less efficient in processing emotionally arousing stimuli, perhaps because they have difficulty "dumping" or degrading the information. It is tempting to speculate that this might be mediated in part by altered dopamine neurotransmission in hippocampus, given the high expression of COMT in this region (noted earlier), and because we have found that administration of tolcapone alters hippocampal immediate early gene expression (EMT, T Sharp, and PJH, unpublished observations).

Thus, the effect of COMT genotype on cortical information processing is critically dependent on the nature of the information being processed. Under circumstances in which holding cognitive information in a stable state is beneficial (e.g., working memory), Met^{158} carriers are at an advantage; however, during certain emotional processing tasks that may depend on rapid disengagement of cortical states, Met^{158} carriers are deficient.

Preliminary data are supportive of the notion that COMT might modulate cognitive stability (Nolan et al 2004). Two hypotheses have been developed to integrate the role of COMT in the trade-off between cognitive stability and flexibility. Winterer and Weinberger (2004) emphasize the role of PFC dopamine in determining cognitive stability. They suggest that relatively low COMT activity, as a result of the Met^{158} allele, leads to elevated PFC dopamine, allowing it to diffuse further from the synaptic cleft and activate extrasynaptic D_1 receptors (Figure 3). Conversely, the high COMT activity encoded by the Val^{158} allele would limit diffusion from the synapse, favoring activation of intrasynaptic

D_2 receptors (Figure 3). It is proposed that D_1 stimulation enhances input-related pyramidal neuron excitability and increases inhibitory feedback to neurons not receiving input, thereby improving the local cortical signal-to-noise ratio and stabilizing the neural representation. In contrast, D_2 activation transiently reduces local inhibitory interneuron activity, resulting in a relatively nonspecific increased pyramidal neuron excitability, which might act to reduce local inhibition and cortical signal-to-noise ratio, thus interfering with the updating of neuronal representations. Thus, the D_1 activation state favored by the Met^{158} allele is anticipated to result in an improved cortical signal-to-noise ratio. Available empirical data support this hypothesis, indicating that the Met^{158} allele is associated with decreased event-related electrophysiologic response variability, thought to be a measure of PFC noise (Gallinat et al 2003; Winterer et al, in press).

An alternative model includes a role for the striatum, by considering how COMT might impact on the tonic-phasic model of striatal dopamine neurotransmission (Bilder et al 2004). Dopamine levels in the striatum are maintained via two processes: a tonic extracellular pool of dopamine and a brief phasic release, which follows neuron burst firing. The amplitude of phasic dopamine release is modulated by tonic dopamine levels, which in turn are regulated both by baseline striatal dopamine neuron firing and via corticostriatal feedback. Bilder et al (2004) proposed that the low activity Met^{158} COMT allele is associated with increased subcortical tonic dopamine transmission, with a concurrent decrease in phasic dopamine transmission, and increased cortical D_1 transmission, relative to the Val^{158} allele. Similar to the D_1-mediated state, this results in increased stability but decreased flexibility of the neuronal network activation states. Notwithstanding this theoretical formulation, the involvement of the striatum in mediating COMT's behavioural effects is currently unclear. As described earlier, altered COMT activity does not appear to affect gross catecholamine function in this region (Meyer-Lindenberg et al 2005); however, the possibility that altered COMT activity in the PFC leads to downstream adaptive changes in this region, similar to those seen in midbrain (Akil et al 2003; Meyer-Lindenberg et al 2005), is an interesting area for future investigation.

In summary, the Met^{158} COMT allele is associated with improved working memory and executive function compared with the Val^{158} allele, perhaps mediated by improved cortical signal-to-noise ratio, resulting in increased cognitive stability. There may be an associated cost, however, in that Met^{158} also appears to be associated with impaired emotional processing. Further complicating this story is emerging evidence that additional loci within the COMT also affect cognitive function.

COMT and Cognition: Effect of COMT Haplotypes

Although most genetic association studies of COMT have focused on the Val^{158}Met polymorphism because of its unequivocal functionality, recent evidence suggests that other sites within the gene may contain polymorphisms that also affect the function of the gene, and ultimately the enzyme. These effects may complicate clinical associations of Val^{158}Met. For example, a polymorphism near the 3′ untranslated region (UTR) was associated with differential expression of Val^{158}Met alleles (Bray et al 2003), and a polymorphism in the 5′ MB-COMT regulatory domain affects enzyme activity in brain and in lymphocytes (Chen et al 2004a). Several studies have found that subdividing the population of Val^{158} and Met^{158} chromosomes based on haplotypes comprising linked single nucleotide polymorphisms (SNPs) in these other domains of the gene may exert a more reliable effect on clinical phenotype than Val^{158}Met alone, but alleles vary across these haplotypes (O'Donovan et al, this issue). This suggests that different combinations of alleles at these sites can combine in various proportions and lead to similar functional states. A recent study using fMRI as a functional readout of the biological impact in PFC of genetic variation in COMT supports this proposition and offers a possible explanation for the complex pattern of clinical associations, based again on the inverted-U-shaped dopamine response curve. Meyer-Lindenberg et al (2005) found that various combinations of alleles at these loci combine to influence prefrontal efficiency and that no single allele at any locus guarantees an efficient or inefficient response. For example, the $A^{-287}G$ polymorphism in the 5′ upstream region of COMT (Figure 1), which also has a minor effect on COMT activity (Chen et al 2004a), interacts with Val^{158}Met to modulate PFC inefficiency during working memory. Based on the individual effects of the two polymorphisms, the predicted relative enzyme activities of the $A^{-287}G/Val^{158}$Met haplotypes are as follows: $A^{-287}/Val^{158} > G^{-287}/Val^{158} > A^{-287}/Met^{158} > G^{-287}/Met^{158}$. Neuroimaging demonstrated that greatest PFC efficiency was achieved by the A^{-287}/Met^{158} diplotype group, with worst PFC efficiency achieved by the A^{-287}/Val^{158} diplotype group, whereas diplotype groups including the G^{-287} allele showed intermediate PFC efficiency. These data are consistent with the hypothesis linking COMT activity, the dopamine inverted-U-shaped curve, and PFC function (Figure 5). The presence of the G^{-287} decreases COMT activity levels, relative to the A^{-287} allele. This is beneficial to PFC function in combination with the Val^{158} allele because it pushes COMT activity nearer to optimal levels; however, it is detrimental in combination with the Met^{158} allele because it decreases COMT activity to suboptimal levels, resulting in superoptimal PFC dopamine function. Adding effects at another SNP (rs165599; Figure 1) further modulated the functional readout. These data suggest that evolution has yielded a complex set of genetic variants within COMT that can balance or exaggerate effects across functional loci. To the extent that COMT is associated with variations in brain function and psychopathology, these data imply that it is the functional state of the gene and not any single allele or haplotype that accounts for this association across populations.

COMT and Schizophrenia

The COMT locus at chromosome 22q11 has been identified as a susceptibility locus for schizophrenia in several linkage studies (e.g., Coon et al 1994) and two meta-analyses (Badner and Gershon 2002; Lewis et al 2003) and is also implicated in schizophrenia by its role in VCFS. Of interest is the fact that VCFS patients demonstrate a greatly increased incidence of psychiatric disorders, particularly schizophrenia (Murphy et al 1999), leading to the suggestion that VCFS represents a genetic subtype of schizophrenia (Bassett and Chow 1999). Complementing these data, patients diagnosed with schizophrenia have an enhanced incidence of 22q11 deletions compared with the normal population (Bassett et al 1998; Gothelf et al 1997; Horowitz et al 2005; Karayiourgou et al 1995; Yan et al 1998). Furthermore, mice hemizygous for the VCFS region show sensorimotor gating abnormalities and deficits in learning and memory, which are reminiscent of impairments associated with schizophrenia (Paylor et al 2001).

As well as evidence linking 22q11 and schizophrenia, COMT

itself clearly represents an attractive candidate gene because schizophrenia is associated with dysfunction of the dopamine system and PFC (Goldman-Rakic et al 2001; Grace 1993; Weinberger et al 2001), and, as discussed earlier, COMT appears to be important in both regards.

A large number of studies have investigated whether the COMT gene is associated with schizophrenia. A full discussion of this controversial topic (Fan et al 2005; Munafo et al 2005; O'Donovan et al, this issue) is beyond the scope of this review; however, meta-analyses indicate that Val^{158} may be a weak risk factor for schizophrenia, at least in those of European ancestry (Glatt et al 2003). This conclusion is supported by the fact that the most supportive findings come from family studies, which lack the confounding effects of population stratification (e.g., Chen et al 2004b; Egan et al 2001; Li et al 2000). Furthermore, Val^{158} also appears to be linked with schizotypy in normal male subjects (Avramopoulos et al 2002; Stefanis et al 2004). It is also of interest that COMT, and particularly the Val^{158} allele, has been linked to psychosis in Alzheimer's disease (Borroni et al 2004; Sweet et al 2005).

Investigation of COMT expression in postmortem tissue indicates that there are no gross changes in mRNA expression or COMT activity in schizophrenia, at least in dorsolateral PFC (Chen et al 2004a; Matsumoto et al 2003b; Tunbridge et al 2004b). There are, however, alterations in the laminar distribution of COMT mRNA, with patients showing relatively increased layer IV/V expression and decreased layer II/III expression, unlike the comparable expression across laminae found in control subjects (Matsumoto et al 2003b). Because layer V neurons project to the brain stem, where they tonically inhibit dopaminergic neuronal activity, this alteration in COMT expression might result in a local reduction of dopamine in layer V, which may lead to reduced corticofugal output, resulting in disinhibition of striatal dopamine function (Akil et al 2003; Matsumoto et al 2003b; Meyer-Lindenberg et al 2005), contributing to the proposed corticostriatal imbalance in schizophrenia (Grace et al 2000; Weinberger 1987). There are also differences in schizophrenia in the relative abundance of the new variant form of COMT mentioned earlier, the identity of which is currently unknown (Tunbridge et al, in press); this isoform also appears to be relatively insensitive to the destabilizing effects of the Met^{158} allele, providing a further potential confounder for association studies of Val^{158}Met and schizophrenia.

COMT and Schizophrenia: Effect of State

Similar to its relationship with cognition, it is increasingly clear that the relationship between COMT and schizophrenia is more complex than simple association between the Val^{158} allele and schizophrenia per se. This is not surprising because schizophrenia is a complex, multifactorial illness, COMT does not act alone to modulate schizophrenia risk, and genetic variation in COMT is itself complex (vide infra). Thus, the impact of altered COMT enzyme activity on schizophrenia risk is likely to be highly dependent on the context in which it is expressed. This concept is supported by emerging data that find interactions between COMT and other genetic and environmental risk factors. A recent study demonstrated a striking interaction between Val^{158}Met genotype and cannabis use in a longitudinal study of schizophrenia risk (Caspi et al 2005). Specifically, Val^{158} carriers showed increased risk for developing schizophreniform disorder and exhibiting psychotic symptoms if they had used cannabis in adolescence (odds ratio: 10.9). It is possible that this effect is related to the relatively increased midbrain dopamine function associated with the Val^{158} allele (Akil et al 2003; Meyer-Lindenberg et al 2005), because cannabis causes dopamine release in the nucleus accumbens (Ameri 1999), and this effect might be enhanced in Val^{158} homozygotes, potentially resulting in subcortical hyperdopaminergia and psychosis. It is also conceivable that the interaction of COMT Val^{158} and cannabis occurs at the level of the cortex, with both factors acting to degrade the circuit architecture that subserves efficient processing of environmental information, elevating schizophrenia risk based on the cortical signal-to-noise risk scenario (Winterer and Weinberger 2004).

Val^{158}Met genotype may also interact with other genetic risk factors for schizophrenia. For example, genetic variation in GAD1, which encodes the enzyme required for GABA synthesis, appears to be associated with schizophrenia specifically in Val^{158} homozygotes (Nicodemus et al 2005). These data indicate that biological effects of genetic variation in GAD1 may combine with the relative deficiency in PFC dopamine that likely results from Val^{158} homozygosity to elevate schizophrenia risk, although it remains to be determined whether this statistical epistasis reflects a biological interaction.

Taken together, these various findings provide intriguing evidence that COMT Val^{158}Met genotype interacts with genetic and environmental factors to modulate schizophrenia risk. Such interactions might partially underlie the mixed findings of association studies investigating COMT Val^{158}Met genotype and schizophrenia because the genetic and environmental background on which the polymorphism is expressed will vary among populations.

COMT and Schizophrenia: Effect of Haplotypes

Because there are additional loci in the COMT gene that have an impact on the enzyme's function, independent of the Val^{158}Met polymorphism, it is likely that associations between COMT and schizophrenia are more complex than a linear relationship between allele dose at a given locus and schizophrenia risk. This concept is easiest to envisage in the case of the diplotypes formed by $A^{-287}G$ and Val^{158}Met polymorphisms. It might be anticipated that both superoptimal (A^{-287}/Val^{158}) and suboptimal (G^{-287}/Met^{158}) haplotypes, which are associated with relatively impaired PFC function, might increase risk for schizophrenia. If either single locus were examined, this association would clearly be missed because all alleles might be associated with schizophrenia under particular conditions. Although this hypothesis remains to be directly tested for the $A^{-287}G/Val^{158}$Met diplotypes, a three-marker COMT risk haplotype (including Val^{158}), shown to be highly significantly associated with schizophrenia (Shifman et al 2002; Figure 1), is associated with PFC inefficiency (Meyer-Lindenberg et al, unpublished data). The biological mechanism by which this haplotype alters COMT function is currently unknown because neither the rs737865 or rs165599 polymorphisms affect enzyme activity by themselves (Chen et al 2004a; although the risk haplotype affects COMT mRNA expression, Bray et al 2003). Thus, future genetic studies should consider the potential for interactions between multiple loci, both within COMT and likely other genes affecting PFC function. An understanding of the biology of COMT should be used to inform these studies, reducing the risk of false-positive associations.

Therapeutic Relevance of COMT

Given its roles in cognition, dopamine regulation, and perhaps schizophrenia, and because it is an enzyme for which inhibitors are already available, COMT is a promising and tractable therapeutic target for cognitive dysfunction in schizophrenia. Firstly, COMT Val^{158}Met genotype is associated with the "PFC response" to atypical antipsychotics (Bertolino et al 2004; Weickert et al 2004) and preclinical data suggest a pharmacologic mechanism for this interaction because reducing COMT activity potentiates clozapine-induced PFC dopamine release (Tunbridge et al 2004a). Additionally, preliminary data suggest that COMT inhibition can improve aspects of working memory and executive function in normal volunteers, and the effect of tolcapone on some of these measures is genotype dependent such that Val^{158} homozygote performance is significantly improved by tolcapone, whereas Met^{158} homozygote performance on some tests is worsened (Mattay et al, unpublished data). The deleterious effect of tolcapone on Met^{158} homozygote performance might result from excessive COMT inhibition resulting in superoptimal dopamine levels in PFC (Figure 5). It should be noted, however, that some of the measures affected by tolcapone (such as intradimensional set shifting) are not classically thought to be reliant on dopamine (see Tunbridge et al 2004a), and therefore these findings require replication and extension.

Thus, COMT might be relevant to schizophrenia treatment both in terms of pharmacogenetic background (because Val^{158} and Met^{158} carriers may respond differently to current antipsychotic medications) and as a direct drug target for treating the cognitive dysfunction associated with schizophrenia, a critical determinant of functional outcome. Clinical trials are underway to test the effects of COMT inhibition on cognition in schizophrenia.

Functional States of COMT: More Than Just Val^{158}Met

Taken together, the data described in this review are remarkably convergent in suggesting that the Val^{158}Met polymorphism acts to determine where on the inverted-U-shaped curve of prefrontal dopamine function an individual lies. It is also clear that whether the Val^{158}Met allele is beneficial or detrimental depends highly on a myriad of related factors. These include but are likely not limited to the following: other polymorphisms within the COMT gene (Meyer-Lindenberg et al, unpublished data), the nature of the task undertaken (Bilder et al 2004; Mattay et al 2002), and the current dopaminergic state of the PFC (Mattay et al 2002, 2003; Gothelf et al 2005; Figure 5). In addition, although beyond the scope of this review, sexually dimorphic effects have been reported for several aspects of COMT, including neurochemical and behavioral function in the COMT knockout mouse (Gogos et al 1998), COMT allele frequency (Shifman et al 2002), and associations between COMT and obsessive–compulsive disorder (Karayiorgou et al 1997) and anxiety (Enoch et al 2003), suggesting that gender may be a further confounder.

This concept of a modulatory role for the Val^{158}Met alleles, rather than their being "good" or "bad," may have far-reaching implications for the field of psychiatric genetics. The implication for our understanding of complex genetics in general is critical to note: an individual polymorphism in a risk gene does not act in isolation but in concert with a host of environmental (e.g., Caspi et al 2005) and genetic factors (e.g., Nicodemus et al 2005) to increase risk for disease. Thus, rather than considering whether an individual allele, or even haplotype, is associated with a disorder, it is more illuminating and likely necessary to examine synergism between multiple polymorphisms within a gene, between genes, and in the context of environmental factors. Although this notion is not revolutionary, the data for COMT provide some of the first empirical data and hence convergent validity for it.

In conclusion, nearly 50 years after its discovery (Axelrod and Tomchick 1958), COMT is experiencing a biological and clinical renaissance. Recent studies highlight its importance in cortical function and dysfunction but also the complexities of the association between molecular variations within COMT and its functional effects in brain. Thus, it is clear that COMT modulates cognition; however, the association between COMT Val^{158}Met genotype and PFC function is exquisitely sensitive to both state and trait factors. Similarly, recent data indicate significant interactions between COMT and other genetic and environmental risk factors for schizophrenia. Finally, on theoretical and practical grounds, COMT is a prime candidate for ameliorating the cognitive deficits of patients with schizophrenia, and empirical data to support this are beginning to emerge.

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