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Perspective

Catechol-*O*-Methyltransferase (COMT): A Gene Contributing to Sex Differences in Brain Function, and to Sexual Dimorphism in the Predisposition to Psychiatric Disorders

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Sex differences in the genetic epidemiology and clinical features of psychiatric disorders are well recognized, but the individual genes contributing to these effects have rarely been identified. Catechol-*O*-methyltransferase (COMT), which metabolizes catechol compounds, notably dopamine, is a leading candidate. COMT enzyme activity, and the neurochemistry and behavior of *COMT* null mice, are both markedly sexually dimorphic. Genetic associations between *COMT* and various psychiatric phenotypes frequently show differences between men and women. Many of these differences are unconfirmed or minor, but some appear to be of reasonable robustness and magnitude; eg the functional Val[158]Met polymorphism in *COMT* is associated with obsessive-compulsive disorder in men, with anxiety phenotypes in women, and has a greater impact on cognitive function in boys than girls. Sex-specific effects of COMT are usually attributed to transcriptional regulation by estrogens; however, additional mechanisms are likely to be at least as important. Here we review the evidence for a sexually dimorphic influence of COMT upon psychiatric phenotypes, and discuss its potential basis. We conclude that despite the evidence being incomplete, and lacking a unifying explanation, there are accumulating and in places compelling data showing that COMT differentially impacts on brain function and dysfunction in men and women. Since sex differences in the genetic architecture of quantitative traits are the rule not the exception, we anticipate that additional evidence will emerge for sexual dimorphisms, not only in COMT but also in many other autosomal genes.
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Sex is an important factor in neuroscience (Cahill, 2006) and psychiatry (Cosgrove *et al*, 2007). Many parameters of brain function and structure vary between men and women (eg Gur *et al*, 1995; Murphy *et al*, 1996; De Courten-Myers, 1999; De Bellis *et al*, 2001; Goldstein *et al*, 2001; Preece and Cairns, 2003; De Vries, 2004), and most psychiatric disorders show sex differences in one or more variables including incidence, age at onset, clinical features, and outcome (eg Lensi *et al*, 1996; Tamminga, 1997; Piccinelli and Wilkinson, 2000; Aleman *et al*, 2003; Baron-Cohen *et al*, 2005). These dimorphisms are usually ascribed primarily to the influence of sex hormones (Collaer and Hines, 1995; Rubinow and Schmidt, 1996; Seeman, 1997; Kelly *et al*, 1999), as well as to the actions of sex chromosome genes (Vawter *et al*, 2004; Cutter *et al*, 2006; Davies and Wilkinson, 2006). Sex differences in epigenetic mechanisms, such as DNA methylation and chromatin modifications, predisposing to these phenotypes may also play a major role (Kaminsky *et al*, 2006). In addition, there is evidence that autosomal genes contribute to sex differences in the genetic predisposition to psychiatric phenotypes. For example, chromosomal loci implicated in the vulnerability to major depression (Holmans *et al*, 2004; Nash *et al*, 2004), neuroticism (Fullerton *et al*, 2003), obsessive-compulsive disorder (OCD; Nestadt *et al*, 2000), and autism (Stone *et al*, 2004) differ between men and women. Such differences occur against a background of a sex difference in heritability estimates for some disorders; eg the heritability of major depression is greater in women than in men (Kendler *et al*, 2006). These indications that there are differences in the genetic factors contributing to psychiatric phenotypes in men and women is consistent with the fact—not always appreciated—that the genetic architecture of many, perhaps most, human traits is sexually dimorphic (Weiss *et al*, 2006).

Despite this diverse evidence for sex differences in the genetic basis of many psychiatric disorders and related phenotypes, the identity of the contributing genes is largely unknown. While perusing the literature and conducting studies of Catechol-*O*-methyltransferase (COMT), we were struck by several lines of evidence that suggest it may be one such gene. Here we review these data,

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consider the possible mechanisms, and discuss the broader implications.

CATECHOL-*O*-METHYLTRANSFERASE

Recent reviews discuss in detail the neurobiological and psychiatric implications of COMT (Weinberger *et al*, 2001; Craddock *et al*, 2006; Tunbridge *et al*, 2006a), and its pharmacology (Mannisto and Kaakkola, 1999). Briefly, COMT is an *S*-adenosylmethionine-dependent methyltransferase enzyme that methylates catechol substrates, notably catecholamines and catechol estrogens. It exists in two forms, soluble (S-COMT) and membrane-bound (MB-COMT), arising from different translation start sites. These isoforms differ in their affinity and capacity for substrates; in contrast to other tissues, MB-COMT predominates in brain, likely reflecting its higher affinity for the catecholamine neurotransmitters. The psychiatric relevance of COMT arises primarily from its role in cortical dopamine metabolism, although with regard to the sex differences, its role in methylating catechol estrogens should be borne in mind (see below). The *COMT* gene is located on chromosome 22q11. It contains several single nucleotide polymorphisms (SNPs) of known or suspected functional significance, notably rs4680, a 472G/A substitution at codon 158 in MB-COMT (codon 108 in S-COMT) that encodes either valine (Val) or methionine (Met), referred to here as $Val^{158}Met$. This SNP influences the thermal stability and activity of COMT; the key study is that of Chen *et al* (2004), who found COMT activity in human prefrontal cortex to be 35–50% lower in Met^{158} homozygotes than in Val^{158} homozygotes; prior studies had found even larger genotype differences in erythrocyte COMT activity (Lachman *et al*, 1996). In consequence, dopamine signaling is likely to be enhanced in Met^{158}- compared to Val^{158}-carrying individuals, consistent with pharmacological evidence (Tunbridge *et al*, 2004a). Following the landmark study of Egan *et al* (2001), a range of studies have shown that the $Val^{158}Met$ allele has a small but significant impact on prefrontal cognitive performance and efficiency, with Met^{158}-carrying individuals performing better and/or more efficiently than Val^{158}-carrying individuals (Barnett *et al*, 2007b). Conversely, the Val^{158} allele is associated with more 'flexible' cognitive responses (Bilder *et al*, 2004), especially during emotional processing (Smolka *et al*, 2005; Drabant *et al*, 2006). Apart from $Val^{158}Met$, other common *COMT* SNPs are noncoding (synonymous, intronic, or in the promoter or 3′-untranslated regions). As such, any functional impact they confer is presumably mediated by an effect on COMT expression; however, the evidence remains unclear (Bray *et al*, 2003; Chen *et al*, 2004; Tunbridge *et al*, 2004b; Dempster *et al*, 2006) and is likely complicated both by nonlinear interactions between the SNPs (Meyer-Lindenberg *et al*, 2006; Nackley *et al*, 2006), and by the range of molecular processes involved (Nackley *et al*, 2006). In any event, few studies that inform about sexual dimorphism and *COMT* have included any of these other SNPs, and hence it is $Val^{158}Met$ that is the major focus here.

COMT AND SEXUAL DIMORPHISMS

Catechol-*O*-methyltransferase exhibits sexual dimorphisms in the normal brain that set the scene for, and may contribute to, its differential involvement in psychiatric disorders in men and women. An important post-mortem study by Chen *et al* (2004), involving 118 subjects, showed COMT activity in prefrontal cortex to be 17% higher in men than women (independent of $Val^{158}Met$ and other SNPs), in agreement with earlier findings of 30% higher enzyme activity in men in liver (Boudikova *et al*, 1990) and also in most (Fahndrich *et al*, 1980; Floderus and Wetterberg, 1981; Philippu *et al*, 1981) but not all (Fitzgerald *et al*, 1980) studies of erythrocytes. It is not known at what stage in life the dimorphism in brain COMT activity manifests, since the sole developmental study was conducted almost entirely in men (Tunbridge *et al*, 2007a). Interestingly, the higher brain COMT activity in men occurs despite levels of COMT protein and mRNA being similar in both sexes (Bray *et al*, 2003; Chen *et al*, 2004; Tunbridge *et al*, 2004b) or higher in women (Dempster *et al*, 2006). This dissociation between expression and activity has implications for the likely mechanism underlying COMT sexual dimorphism, as discussed later.

The other main evidence for sexual dimorphism in normal COMT function comes from the *COMT* knockout mouse (Gogos *et al*, 1998). Tissue dopamine levels in the frontal cortex are increased almost threefold in male *COMT*−/− mice (and twofold in +/− mice) compared to wild-type mice, confirming the importance of COMT in cortical dopamine metabolism; conversely, in female *COMT*+/− and −/− mice, dopamine levels were unchanged. The lack of effect of *COMT* deletion on frontal cortex dopamine in female mice presumably reflects the existence of sex-specific compensatory mechanisms (such as a higher activity of dopamine or norepinephrine transporters), although this has not been determined. In contrast, female but not male *COMT* null mice showed greater anxiety compared to wild-type mice. Mechanistically, the basis for, and the relationship between, the male-only neurochemical effect and the female-only behavioral phenotype, remains to be explained. Further studies in the *COMT* knockout mice, using cocaine, GBR 12909 (a dopamine transporter inhibitor), levodopa, or amphetamine, showed that some but not all neurochemical and behavioral responses to these pharmacological challenges are sex specific (Huotari *et al*, 2002a, b, 2004; see also O'Tuathaigh *et al*, 2007). For example, *d*-amphetamine administration affected dopamine metabolism equally in male and female knockout mice (Huotari *et al*, 2004), whereas hyperactivity in response to GBR 12909 was attenuated only in male mice (Huotari *et al*, 2002b).

A final COMT sexual dimorphism worthy of mention concerns allele frequencies. In 4014 Ashkenazi Jews (control subjects participating in a genetic association study of schizophrenia discussed below), Shifman *et al* (2002) found that the frequency of the A allele of the 3′-untranslated region SNP rs165599 was higher in women than men (65 *vs* 61%, $p = 0.0009$); they state that a similar difference was seen in a second sample, giving a combined *p*-value of 0.00009 (see also Shifman *et al*, 2004). The authors speculate that the finding may be due to a reduced viability of female fetuses carrying this allele. However, to our knowledge, a sex difference in rs165599 allele frequency has not been replicated (eg Sweet *et al*, 2005; see also Molero *et al*, 2007)—albeit no other study has reported on such a large sample—and so its significance remains unclear.

SEXUALLY DIMORPHIC EFFECTS OF *COMT* GENOTYPE ON PSYCHIATRIC DISORDERS AND RELATED PHENOTYPES

Table 1 is an extensive but not exhaustive list of the studies that have reported a sex difference in the impact of *COMT* genotype on a psychiatric phenotype. The studies vary in the robustness and plausibility of the finding with regard to sex, in several respects. Few have been statistically convincing, eg by demonstrating a sex-by-genotype interaction (eg Kates *et al*, 2006; Lang *et al*, 2007). Many studies simply found an association that reached significance in one sex but not in the other, without demonstrating an interaction between sex and genotype (eg Enoch *et al*, 2006), an approach further compromised by the fact that the nonsignificant sex often had a smaller sample size and less power than did the significant one (eg Nolan *et al*, 2000; Ono *et al*, 2004; Stein *et al*, 2005). Other studies discuss sex-related effects despite reporting a nonsignificant sex-by-genotype interaction (eg Olsson *et al*, 2005; Zinkstok *et al*, 2006), while a final category of studies, not included in the table, provide only trend-level findings of sex-related effects of *COMT* genotype (eg Eley *et al*, 2003; Sazci *et al*, 2004; Woo *et al*, 2004). A further consideration is that some phenotypic associations with a *COMT* allele are in the opposite direction in the two sexes, rather than just being limited to one sex (eg Dauvilliers *et al*, 2001; Rybakowski *et al*, 2006); such findings may be correct, but in the absence of a prior hypothesis, or replication, may well be false positives.

These issues and limitations mean that most of the studies in Table 1 are merely suggestive and do not, in isolation, provide convincing evidence that *COMT* genetic variation has a sexually dimorphic influence on the phenotype in question. Nevertheless, the number of studies showing at least some evidence for sexual dimorphisms is intriguing, especially as among the studies are several more striking and robust findings of this kind. It is the latter results that we focus upon here.

Karayiorgou *et al* (1997) were the first to report a sex difference in the role of *COMT* in the genetic predisposition to a psychiatric disorder. They showed that the low-activity (Met^{158}) allele was associated with OCD in men, but not in women. The finding was replicated in a family-based study (Karayiorgou *et al*, 1999), and in three out of four subsequent case control studies (Poyurovsky *et al*, 2005; Denys *et al*, 2006; Pooley *et al*, 2007). The sex-selective effect of *COMT* in OCD was confirmed in a meta-analysis (Pooley *et al*, 2007); the odds ratio associated with the Met^{158} allele in men was 1.88 ($p<0.001$), with no effect in women (odds ratio 0.98, $p=0.83$), and with a significant sex difference between the odds ratios ($p<0.0001$). The *COMT* OCD data are arguably the clearest evidence to date for a sexually dimorphic autosomal genetic association with a psychiatric disorder.

Another demonstration of a sexually dimorphic role for *COMT* is that of Barnett *et al* (2007a), who genotyped the $Val^{158}Met$ SNP in over 5000 participants in a longitudinal study of child development, and in whom a range of cognitive tests, including IQ, attention, and working memory had been conducted between ages 8 and 10. The Met^{158} allele was found to be associated with better function in several domains, with these effects greater in, or limited to, boys. For example, in boys, Met^{158} homozygotes had a verbal IQ 3 points higher than Val^{158} homozygotes, whereas the difference in girls was less than 1 point. The data also showed that the *COMT* effect on verbal IQ was greater in pubertal than prepubertal boys (increasing to a 10-point difference between homozygote groups), suggesting that its influence increases with sexual maturation. An interaction with developmental stage is consistent with COMT $Val^{158}Met$ data in a longitudinal study of velo-cardio-facial syndrome (VCFS or 22q11 hemideletion syndrome, in which one copy of *COMT* is deleted; Gothelf *et al*, 2005). There are also significant maturational increases in COMT expression and activity in prefrontal cortex, albeit these occur postadolescence not peri-pubertally (Tunbridge *et al*, 2007a). Kates *et al* (2006) also studied children with VCFS. Their finding, though in a small sample, is noteworthy because it concerns brain structure, and also because the dimorphism is statistically robust—a sex-by-genotype interaction ($p<0.001$), with an opposing effect of $Val^{158}Met$ allele on frontal cortical volumes in boys and girls. These data, together with those of Zinkstok *et al* (2006), raise the possibility of a complex interaction between *COMT* genotype, sex, brain structure, and development.

Shifman *et al* (2002) reported that homozygosity for the G allele at rs165599 of *COMT* was strongly associated with schizophrenia in women ($p=6.8\times10^{-6}$) but not in men ($p=0.09$), with the sex difference in genotype effect being significant ($p<0.01$). The authors concluded that there may be a sex-specific genetic component to schizophrenia, while acknowledging that twin studies had not predicted this. Moreover, a sex difference in the genetic association with schizophrenia was not present for the other *COMT* SNPs they analyzed, nor was it observed for haplotypes (that included rs165599), and, as noted by Craddock *et al* (2006), it was driven by the dimorphic allele frequency in the control group mentioned above. Hence, despite the statistical significance, the result remains difficult to interpret *vis-à-vis* schizophrenia, and in need of replication, especially as Sazci *et al* (2004) reported a female-predominant association (of Met^{158}) with schizophrenia, and the meta-analyses of *COMT* $Val^{158}Met$ with schizophrenia find no sex effect (Glatt *et al*, 2003; Fan *et al*, 2005).

A sex-by-genotype interaction ($p<0.0005$) was seen by Lang *et al* (2007) who showed that the Val^{158} allele was associated with the personality trait of sensation-seeking in women. This finding is the latest in a line of studies that show relationships between *COMT* genotype and personality traits in women but not in men. In particular, anxiety-related phenotypes (such as harm avoidance or neuroticism) have been repeatedly (though often weakly) associated in women with the Met^{158} allele (Eley *et al*, 2003; Enoch *et al*, 2003; Olsson *et al*, 2005; Stein *et al*, 2005), with similar findings in anxiety disorder (Domschke *et al*, 2004; Woo *et al*, 2004; Rothe *et al*, 2006). A recent meta-analysis of the panic disorder studies (Domschke *et al*, 2007) confirmed this sex difference, but also revealed an additional complexity, in that the relationship interacted with ethnicity such that panic disorder was associated with the Met^{158} allele in Caucasian women but with the Val^{158} allele in Asian women. The latter result is consistent with that of Kim *et al* (2006), who showed a Val^{158} association with harm avoidance in

Table 1 Chronological List of Studies Reporting Sexually Dimorphic Effects of *COMT* Genotype on Psychiatric Disorders and Allied Phenotypes[a]

Authors	Phenotype/parameter	Males/ females	Finding related to sex
Karayiorgou *et al*, 1997[b]	OCD	117/104	Met^{158} allele associated in men ($p=0.0002$) not women ($p=0.066$)
Nolan *et al*, 2000	Suicide attempts in schizophrenia	117/31	Met^{158} allele associated in men ($p=0.028$) not women ($p>0.5$)
Dauvilliers *et al*, 2001	Sleep latency in narcolepsy	59/38	Longer latency associated with Met^{158} allele in men, Val^{158} allele in women
Shifman *et al*, 2002[b]	Schizophrenia	3980/1643	G allele of rs165599 associated in women ($p<0.00001$) not men ($p=0.1$). Sex difference $p=0.01$
Enoch *et al*, 2003	Harm avoidance	160/241	Met^{158} homozygosity associated in women ($p<0.03$) not men ($p>0.79$)
Domschke *et al*, 2004	Panic disorder	82/148	Val^{158} allele associated in women ($p=0.01$) not men ($p=1.0$)
Ono *et al*, 2004	Suicide	112/51	Val^{158} homozygosity protective in men ($p=0.016$) not women ($p=0.96$)
Olsson *et al*, 2005	Persistent episodic anxiety	340/473	Met^{158} homozygosity associated in women ($p=0.02$) not men ($p=0.38$). No genotype × sex interaction
Poyurovsky *et al*, 2005	OCD	109/141	Met^{158} allele associated in men ($p=0.029$) not women ($p=0.78$)
Stein *et al*, 2005	Low extraversion	154/343[c]	Met^{158} homozygosity associated in women ($p=0.001$) not men ($p=0.6$)
Sweet *et al*, 2005	Psychosis in Alzheimer's disease	130/243[c]	Val^{158} allele associated in women ($p=0.005$) not men ($p=0.383$)
Kates *et al*, 2006[b]	Dorsal and orbital frontal volumes	25/26	Opposite effects in boys and girls with VCFS. Sex × genotype interaction ($p<0.001$)
Beuten *et al*, 2006[b]	Nicotine dependence	668[d]/1369[c,d]	Met^{158} allele associated in women. Sex × genotype interactions ($0.006<p<0.02$)
Denys *et al*, 2006	OCD	135/170	Met^{158} allele associated in men ($p=0.036$) not women ($p=0.23$)
Enoch *et al*, 2006	Alcoholism and smoking	141/201	Val^{158} allele associated in women ($p=0.011$) not men ($p=0.186$)
Kim *et al*, 2006	Harm avoidance	138/148	Val^{158} allele associated in women ($p=0.003$) not men ($p=0.36$)
O'Hara *et al*, 2006	Delayed verbal recall tests	62[e]/101[e]	Val^{158} allele associated with 8-point WMS-R advantage in men. Sex × genotype interaction on BNT
Rothe *et al*, 2006	Panic disorder	60/118[d]	Val^{158} allele associated in women ($p=0.008$) not men ($p=0.272$)
Rybakowski *et al*, 2006	WCST in schizophrenia	43/36	Val^{158} homozygosity associated with fewer errors by men ($p=0.044$), more errors by women ($p=0.042$)
Zinkstok *et al*, 2006	Gray and white matter volumes	57/97	Aging effects related to genotype in women only. No genotype × sex interactions
Barnett *et al*, 2007a[b]	IQ and executive function	2650[f,g]/2650[f,g]	Effects in boys only. Genotype × sex interactions on attention and verbal IQ
Domschke *et al*, 2007[b]	Panic disorder	209/319	Meta-analysis. Association in women only: Val allele in Caucasians, Met allele in Asians
Lang *et al*, 2007[b]	Sensation-seeking	214/218	Val^{158} homozygosity associated in women ($p>0.005$) not men[h]. Sex × genotype interaction ($p=0.005$)
Pooley *et al*, 2007[b]	OCD	580/718	Meta-analysis. Met^{158} allele associated in men ($p=0.001$) not women ($p=0.83$). Sex difference $p=0.0001$

Abbreviations: BNT, Boston Naming Test; OCD, obsessive-compulsive disorder; IQ, intelligence quotient; VCFS, velo-cardio-facial syndrome (22q11 deletion syndrome); WCST: Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale (Revised).
[a]All findings relate to Val^{158}Met polymorphism except where stated.
[b]Key studies, discussed in the text.
[c]Haplotypes containing Val^{158}Met were also studied.
[d]Calculated from their Table 1.
[e]Elderly adults.
[f]Representative number; exact sample size differed between tests.
[g]Children.
[h]*p*-value not stated.

Korean women. Two main explanations come to mind for the genotype-by-ethnicity interaction. First, given that the resulting subgroups are quite small and the *p*-values modest ($p=0.04$ in Caucasians, $p=0.02$ in Asians; Domschke *et al*, 2007), the findings may be false positives. Second, if true, the finding may relate to ethnic differences in the genetic background of the Val^{158}Met polymorphism, such that the opposing allelic associations with panic disorder are both genuine (Lin *et al*, 2007).

Parenthetically, the data reviewed here show that the Met^{158} allele is associated with anxiety phenotypes in (Caucasian) women but with OCD—usually considered to be a type of anxiety disorder—in men. One interpretation is that Met^{158} is a risk factor for a predisposition to anxiety in both sexes, but that this manifests itself as different anxiety phenotypes in men and women because of other influences that are themselves sexually dimorphic, whether genetic, epigenetic, or environmental in origin.

MECHANISMS OF SEXUAL DIMORPHISM IN COMT EFFECTS AND ASSOCIATIONS

Estrogens are usually implicated to explain the sex differences related to COMT. Contemporary interest can be traced to the work of Xie *et al* (1999), although many years previously Axelrod had reported that 17-β-estradiol (E2) administration decreased COMT activity in rat liver (Cohn and Axelrod, 1971). Xie *et al* (1999) showed that there are two estrogen response elements in the *COMT* promoter, and that E2 at physiological concentrations inhibits COMT mRNA expression in cells expressing estrogen receptors but not in those which do not. The same group later showed that the estrogen-mediated decrease in COMT mRNA was accompanied by a proportional decrease in COMT immunoreactivity and activity (Jiang *et al*, 2003). This inhibitory regulation by estrogens is consistent not only with the normal sex differences in COMT activity noted above, but with evidence that women with high estrogen states (eg on the combined oral contraceptive, or in the third trimester of pregnancy) have higher COMT activity than other women (Briggs and Briggs, 1973). In postmenopausal women, estrogen levels fall dramatically, to substantially below that of men of the same age (Bjornerem *et al*, 2004); it would be of interest to know if sexual dimorphisms in COMT activity (or its genetic associations) present in younger adults are lost or reversed in the elderly.

Complementing the estrogenic regulation of COMT, COMT plays an important role metabolizing catechol estrogens and thereby lowering levels of these potential carcinogens (Creveling, 2003). Notably, there is both *in vivo* (Worda *et al*, 2003) and *in vitro* (Dawling *et al*, 2001; but see Goodman *et al*, 2002) evidence that the Val^{158}Met SNP influences this pathway, with greater E2 metabolism in those with the high-activity Val^{158} allele; this may also explain the associations reported in some studies between the *COMT* Met^{158} allele and estrogenic cancers (see Goodman *et al*, 2002). These reciprocal, and partly genotype-influenced, interactions between COMT and estrogens may both be relevant to the question of sexual dimorphism: *COMT* genotype may modulate the role that estrogens play in brain function and dysfunction (Seeman, 1997), while estrogens affect COMT activity and its pathophysiological sequelae by virtue of their influence on COMT gene expression.

Despite the focus on estrogenic regulation of COMT gene expression, it is probably only a partial explanation for COMT sexual dimorphisms. Cohn and Axelrod (1971) found that E2 did not affect rat brain COMT activity despite its robust downregulation in the liver, and Jiang *et al* (2003) found estrogenic regulation of COMT in a breast cancer cell line but not in a glioblastoma cell line, again suggesting that this relationship may not pertain in the brain. The suggestion that estrogenic regulation of COMT may be less important in the brain than in the periphery is supported by several recent human brain studies showing that COMT activity is higher in men (Chen *et al*, 2004) even though women express COMT at the same (Tunbridge *et al*, 2004b; Chen *et al*, 2004) or higher (Dempster *et al*, 2006) levels. Hence, for a given level of COMT expression, COMT activity in the male brain is higher than it is in females, and therefore the sexual dimorphism cannot be explained by transcriptional regulation. This fact also bears upon potential explanations for sexual dimorphism in COMT based upon epigenetic regulation (Kaminsky *et al*, 2006); in any event, there is no evidence for a sex difference in COMT methylation status (Abdolmaleky *et al*, 2006). Furthermore, the finding that COMT protein and activity levels rise considerably in men between the third and fifth decade of life (Tunbridge *et al*, 2007a), despite steady estradiol levels across this period (Bjornerem *et al*, 2004) emphasizes that estrogens are not the only factor responsible for regulating COMT in the brain.

The basis for a sex difference in COMT activity without an accompanying difference in COMT abundance is unknown. It may be that the discrepancy is in fact spurious, since localized or phasic sex differences in mRNA or protein abundance in brain—eg in specific cell types, or in relation to menstrual cycle—have not been ruled out. However, the fact that a robust sex difference in COMT enzyme activity was seen with no hint of a sex difference in COMT protein measured in the same samples (Chen *et al*, 2004), suggests that it is genuine. As such, one possibility is that it reflects a sex difference in the relative abundance of novel mRNA (Tunbridge *et al*, 2007b) or protein (Tunbridge *et al*, 2006b) isoforms of COMT, which might differ in their enzyme activity and would not affect the amount of total COMT transcript or protein. Or, there could be a sex difference in the abundance of cofactors, endogenous inhibitors (eg *S*-adenosylhomocysteine; Zhu, 2002), or interacting proteins that modulate COMT activity.

Broadening the perspective, sexual dimorphisms in COMT occur against a background of sex differences in biochemical pathways, not only of the catechol estrogens, but also pertaining to dopamine, and the interactions between them (Morissette and Di Paolo, 1993; Becker, 1999; Andersen and Teicher, 2000; Carroll *et al*, 2004). For example, compared with men, women have higher striatal [^{18}F]fluorodopa uptake, suggestive of greater presynaptic dopamine synthesis (Laakso *et al*, 2002), and a lower D2 receptor affinity (Pohjalainen *et al*, 1998) which the authors hypothesized reflects their higher dopamine levels. Women also have lower amphetamine-stimulated dopamine release (Munro *et al*, 2006), and a greater dopamine transporter uptake (Mozley *et al*, 2001). Thus, compared with men, women appear to have elevated basal, but decreased stimulated, striatal dopamine levels. However, estrogenic state (eg phase of menstrual cycle) has not been fully taken into account and may be a significant confounder: rodent studies have shown marked fluctuations in multiple dopaminergic parameters in the striatum across the estrus cycle (Jori and Cecchetti, 1973; Favis *et al*, 1977; Crowley *et al*, 1978; Fernandez-Ruiz *et al*, 1991; Morissette and Di Paolo, 1993; Xiao and Becker, 1994). Sex differences in dopamine function are less well studied outside the striatum, in cortical regions wherein COMT is likely to play its major role (Karoum *et al*, 1994; Gogos *et al*, 1998). Cortical tissue dopamine concentrations are similar in men and women (Robinson *et al*, 1977), although women may have a higher extrastriatal D2 receptor-binding potential (Kaasinen *et al*, 2001). In summary, there are diverse data indicating sex differences in central dopaminergic parameters (see Cosgrove *et al*, 2007). However, it is not clear what their net effect is upon the dopamine system in men compared to women, nor how the dopaminergic sexual

dimorphisms impinge upon the inverted U-shaped relationship between dopamine activity and prefrontal function (Goldman-Rakic *et al*, 2000) nor the modulatory effect that COMT has upon this relationship (Mattay *et al*, 2003; Tunbridge *et al*, 2006a; Williams-Gray *et al*, 2007).

CONCLUSIONS

Genetic epidemiological and other studies show that sex differences in the genetic architecture of many human traits, and of psychiatric disorders, are common. There is also a substantial literature attesting to male–female differences across many domains of brain function, structure, and development. The data reviewed here suggest that *COMT* is one of the genes that contribute to these sexual dimorphisms. As well as a difference in COMT enzyme activity between men and women, there is evidence that the involvement of *COMT* in predisposition to OCD and anxiety phenotypes is sex specific, and weaker evidence for sex differences in its roles in several other phenotypes.

Not all *COMT* genotypic associations are demonstrably sexually dimorphic; eg on any risk for schizophrenia that it confers (Glatt *et al*, 2003; Fan *et al*, 2005), or its influence on Wisconsin Card Sort Test performance (Barnett *et al*, 2007b) and on homocysteine metabolism (Tunbridge *et al*, 2007c). Neither is *COMT* the only autosomal gene for which sexually dimorphic genetic associations with psychiatric phenotypes have been reported; eg *HTR2A* with OCD in women (Enoch *et al*, 2001), *MTHFR* with schizophrenia in men (Sazci *et al*, 2005; Kempisty *et al*, 2006), and *ACVII* with depression in women (Hines *et al*, 2006). However, the data do appear more extensive, and in places statistically more convincing, for *COMT* than for any other autosomal gene we could determine, especially as the findings are complemented by the sexual dimorphism in COMT activity and by a plausible, if incomplete, mechanistic explanation in terms of estrogenic regulation. As such, *COMT* may well contribute to the genetic basis for sexual dimorphisms in human brain, behavior, and its disorders. However, it is clearly but one of many genes acting in this way, and in isolation explains only a tiny proportion of the variance. Future studies are needed not only to establish the range and magnitude of the COMT-related sexual dimorphisms, but also to identify other genes, their epistatic and gene–environment interactions, and the underlying biological mechanisms.

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DECLARATION OF INTERESTS

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