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Molecular genetics support Gray's personality theory: the interaction of COMT and DRD2 polymorphisms predicts the behavioural approach system

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Abstract

The present study provides the first direct molecular genetics support for Gray's Reinforcement Sensitivity Theory (RST), which is one of the most influential biologically oriented personality theories. It was investigated whether the DRD2 *TaqIA* and the COMT polymorphisms were related to the dimensions of Gray's personality theory, as measured by the Carver and White BIS/BAS scales. In a sample of 295 healthy subjects results revealed significant DRD2 $\times$ COMT interactions (i.e. epistasis) for the total BAS scale (related to positive emotionality) and for the subscales Drive (D) and Fun Seeking (FS). High BAS scores were observed if the catabolic enzyme activity and the D₂ receptor density as indicated by the two polymorphisms were in disequilibrium, i.e. in the presence of the Val⁻/A1⁻ (low enzyme activity/high receptor density) or the Val⁺/A1⁺ (high enzyme activity/low receptor density) alleles. In a random subsample ($n=48$), it could be demonstrated that those allele combinations of COMT and DRD2 associated with high BAS scores also had significantly lower prolactin levels under resting conditions, indicating high dopamine activity, compared to those allele combinations with low BAS scores. Furthermore, two-way interactions of DRD2 *TaqIA* $\times$ smoking status and of the Met allele of COMT $\times$ smoking status on FS and Met $\times$ gender on BIS could be shown.

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Introduction

Jeffrey Gray's Reinforcement Sensitivity Theory (RST) is an influential biological personality theory originally derived from studies in animals and extrapolated to humans where it has been extensively tested. In the original version of the theory, Gray (1970, 1982) postulated three personality dimensions: the behavioural approach system (BAS), the behavioural inhibition system (BIS), and the fight-flight system (FFS). The BAS was hypothesized to be sensitive to conditioned appetitive stimuli, forming a positive feedback loop, activated by stimuli associated with reward and the termination/omission of signals of

punishment – this system was related to the state of positive affect and the trait of impulsivity. The BIS was hypothesized to be sensitive to conditioned aversive stimuli (i.e. signals of both punishment and the omission/termination of reward), extreme novelty, high-intensity stimuli, and innate fear stimuli (e.g. snakes, blood) – this system was related to the state of negative affect and dispositional anxiety. The FFS was hypothesized to be sensitive to unconditioned aversive stimuli (i.e. innately painful stimuli), mediating the emotions of rage and panic – this system was related to the state of negative affect (associated with pain) and Eysenck's trait of psychoticism.

These trait dimensions were postulated to have a neuroanatomical basis. According to Gray (1987), dopaminergic pathways in limbic circuits function as a behavioural approach system; the BIS is constituted by a set of circuits involving the hippocampus, the subiculum, the septum and related structures; and

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the neuroanatomical basis of the FFS systems are the basolateral and centromedial nuclei of the amygdala, the ventromedial nucleus of the hypothalamus, the central grey region of the midbrain, and the somatic and motor effector nuclei of the lower brain stem.

Although the RST could be validated by experimental studies from many disciplines, including psychopharmacology, psychophysiology, or traditional experimental psychology (for a review, see Corr, 2004), to date, there exists no evidence for the validity of Gray's theory from molecular genetics. Findings from behavioural genetics which demonstrate the high heritability (up to 60%) of personality traits (e.g. Bouchard et al., 1990; Bouchard, 1994; Lander and Schork, 1994) have stimulated the search for the specific genes underlying personality (for a review, see Benjamin et al., 2002; Reif and Lesch, 2003). Genes coding for enzymes, transporters or receptors of neurotransmitter systems are especially the focus of interest because several personality theories postulate a biochemical basis for their major traits (e.g. Cloninger, 1987). However, most of the studies from molecular genetics which are concerned with personality focus on single gene loci without considering gene interactions, although epistasis (i.e. gene-gene interactions) is thought to be important in behavioural phenotypes (Benjamin et al., 2002).

The aim of the present study was to look at such an interaction between two gene loci: the dopamine D₂ receptor polymorphism (DRD2 *TaqIA*) and the catechol-O-methyltransferase (COMT) polymorphism (COMT Val158Met). Both polymorphisms are related to the activity of the dopamine (DA) system. COMT is an enzyme which has a crucial role in the metabolism of catecholamines by inactivating them in the synaptic cleft. A single nucleotide polymorphism (SNP), a G→A transition in codon 158 of the *COMT* gene located at the q11 band of human chromosome 22, results in a 3- to 4-fold difference in COMT enzyme activity (Lachman et al., 1996) by coding for the synthesis of the amino acid methionine (Met) instead of valine (Val). According to the literature homozygosity for the high-activity allele (Val/Val genotype) and for the low-activity allele (Met/Met genotype) is found in ~25% of Caucasians respectively. Heterozygotes (Val/Met genotype) have intermediate levels of COMT activity (Lachman et al., 1996; Syvänen et al., 1997).

In the literature there already exist association studies attempting to relate the COMT polymorphism to personality traits. Each prominent personality theory encompasses at least one trait representing negative emotionality (NEM) and one trait

representing positive emotionality (PEM). Examples for NEM are Gray's BIS, Cloninger's harm avoidance (HA; Cloninger, 1987) and Eysenck's neuroticism (N; Eysenck and Eysenck, 1991) which all share aspects of sensitivity, irritability, anxiety and low activation. Traits associated with PEM are, for example, Gray's BAS, Cloninger's novelty seeking (NS), and Eysenck's extraversion (E), which are all characterized by positive mood and high activation. Findings attempting to relate the COMT polymorphism to personality traits suggest that it is primarily associated with NEM.

For the COMT polymorphism Val158Met, an association to HA was reported with the highest HA scores in subjects with the Met/Met genotype (Enoch et al., 2003). This finding was corroborated by Eley et al. (2003) who reported a higher prevalence of the Met allele in female subjects with high scores in neuroticism. Rujescu et al. (2003) reported that COMT homozygotes could differentiate between facets of aggressive personality traits although they did not find any differences in allele/genotype frequency between patients and control subjects. They found higher outwardly directed anger in the Met/Met carriers and more inwardly expressed anger in Val/Val carriers.

The DRD2 *TaqIA* polymorphism is a restriction fragment polymorphism (RFLP) on chromosome 11 at q22-q23 which is also caused by a mutation in a single nucleotide. The prevalence of the mutated A1 allele is 28% and that of the A1A1 genotype is ~3% in healthy Caucasians (Noble, 2000). Due to the small prevalence of the A1A1 genotype carriers of the A1 allele are often contrasted with carriers without the A1 allele by classifying the A1A1 and the A1A2 carriers as A1+ and carriers of the A2A2 genotype as A1-. Although the DRD2 *TaqIA* polymorphism is located in the 3' untranslated region of the *DRD2* gene it seems to have functional consequences resulting either from linkage disequilibrium with another functional DRD2 variant, or from being located in an as yet unidentified coding or regulatory region downstream of DRD2. In individuals with the A1 allele a 30-40% reduction in D₂ dopamine receptor density compared to those homozygous for the A2 allele could be demonstrated (Ritchie and Noble, 1996), a result which could be confirmed by others (Jonsson et al., 1999; Pohjalainen et al., 1998; Ritchie and Noble, 2003; Thompson et al., 1997). We only tested the DRD2 *TaqIA* polymorphism although other DA receptor polymorphisms like DRD4 would be of interest. However, due to the clear functional associations between DRD2 and receptor density this

gene locus seemed likely to influence DA activity in interaction with COMT.

Genetic association studies trying to relate the DRD2 *TaqIA* polymorphism were far from conclusive because the DRD2 *TaqIA* polymorphism was sometimes related to traits of PEM and sometimes to traits of NEM. For example, the less frequent A1 allele of the DRD2 *TaqI* polymorphism was reported to be associated with higher reward dependence (RD) scores on the RD4 subscale (dependence vs. independence) in females in a Korean population (Lee et al., 2003) and was associated with schizoid/avoidant behaviour (Blum et al., 1997). In a sample of adolescent boys ($n=203$), Berman et al. (2002) reported significantly higher novelty seeking (NS) scores in A1+ allelic boys than in A1- allelic boys. Interestingly they found a significantly positive correlation between NS and HA in the subgroup of A1+ carriers and a significantly negative correlation between NS and HA in the group of A1- carriers. Berman et al. (2002) concluded that the negative association between NS and HA in the A1- group is consistent with the traditional view that NS provides positive reinforcement, or the fulfilment of appetitive drives and that in contrast the positive correlation between NS and HA in the A1+ group indicates that for the A1+ carriers NS includes a negative reinforcement or self-medication function. Also Noble et al. (1998) reported higher NS scores in boys with the A1 allele. Other authors did not find associations between the DRD2 polymorphism and personality traits as measured by Cloninger's Temperament and Character Inventory (TCI; Cloninger et al., 1993) (Gebhardt et al., 2000; Katsuragi et al., 2001).

Using a quite different approach, positron emission tomography (PET) studies also related the D_2 receptor density or binding capacity to differences in personality traits. Farde et al. (1997) reported a substantial negative correlation between D_2 receptor density and Detachment scores of the 'Karolinska scales of personality'. Subjects with high scores on the Detachment scale described themselves as cold, socially aloof and vindictive in their relationships. The authors conclude that these trait characteristics resemble negative symptoms that commonly characterize patients with schizophrenia and that the negative symptoms are caused by a loss of DA function. The results by Farde et al. (1997) could be replicated by Breier et al. (1998). In another PET study Suhara et al. (2001) revealed a significant negative correlation between NS and D_2 receptor binding potential values in the right insular cortex, a region which is important for the processing of emotions (for a review see

Murphy et al., 2003). Suhara et al. (2001) interpret this finding as being in line with the assumption that NS is related to a highly active DA system. They conclude that the low binding potential of the radioactive ligand [^{11}C]FLB457 resulted from increased endogenous DA due to competitive binding (Dewey et al., 1993; Volkow et al., 1994).

It is evident that a possible gene interaction of the DA-catabolizing enzyme COMT and a receptor, to which DA binds and whose density varies dependent on its polymorphic loci, may allow us to learn more about the proportions between the amount of neurotransmitters and receptor density. The interdependence of these two gene loci is probable, at least from a pharmacological viewpoint. Certainly one crucial question remains open: Is high COMT activity indeed related to low levels of DA – if high rates of DA are catabolized it can be assumed that this results in low levels of DA – or is it possible that the high enzyme activity is the result of a large amount of substrate in the sense of an adaptation of the enzyme activity to high demands? The same debate has been made with respect to Zuckerman's Sensation Seeking (SS) where low levels of norepinephrine (Zuckerman, 1985) as well as low levels of monoamine oxidase (MAO) (Zuckerman et al., 1980) were related to SS and where the 'adaptation hypothesis' is best suited to explain this apparent contradiction.

The question arises how personality is influenced if a high or low DA level is confronted with a disposition for high or low receptor density. Apart from Gray, other personality theorists have also related the DA system to traits in PEM. Based on findings from a pharmacological challenge test with a D_2 receptor agonist, Depue et al. (1994) claimed that DA functional activity is positively related to PEM. He explicitly denies that the strong hormone responses to the D_2 agonist were the consequence of low DA levels with an ensuing elevated receptor density (Depue et al., 1994). Cloninger, in contrast, postulated low levels of DA in high novelty seekers (Cloninger, 1987). NS is a trait which also encompasses facets of PEM. The low activity in the DA system should be the reason why novelty seekers permanently search for sensations which yield an elevation of DA levels – in other words, low basal DA provides the motivation to seek (tonic DA-enhancing) reward. In line with Cloninger (1987), Gerra et al. (1999) reported a positive correlation between NS and prolactin (Prl) levels indicating low levels of DA in high novelty seekers. The debate whether PEM is related to low or high DA activity is still ongoing. Presumably controversies result from the fact that experimental results are

theoretically explained by alternatively using the terms 'DA activity', 'amount of DA', 'receptor sensitivity' and 'receptor density'. Therefore, the simultaneous investigation of genes coding for a rate-limiting enzyme and an indicator of DA density yields at least information on two of these aspects.

In summary, the principal aim of the present study (Study 1) was to investigate the association between the BIS and BAS (as measured by standardized questionnaire) and the DRD2 *TaqIA* and the COMT polymorphisms. As outlined above, possible interaction effects yield information about D₂ receptor density and DA catabolism in the synaptic cleft and their relationship to personality. However, the actual amount of DA can only be inferred under the prerequisite that either high enzyme activity of COMT results in low DA levels or that the enzyme activity of COMT is adapted to the amount of DA. But it is also possible that the COMT enzyme activity alone does not give precise information on the DA levels. It is conceivable that the mechanisms influencing the actual amount of DA are more complex. In an attempt to clarify this problem we obtained blood samples in a subgroup of our sample (Study 2) and analysed them for levels of Prl under resting conditions (baseline) and related them to COMT and DRD2 polymorphisms. Because DA is the principal inhibiting hormone of Prl, low Prl levels indicate high DA levels and vice versa (for a review see Ben-Jonathan and Hnasko, 2001). The additional measurement of Prl levels offers the possibility to conclude the actual amount of DA of groups defined by genotypes/alleles which were related to BIS/BAS dimensions.

Materials and methods

Sample

For genotyping (Study 1) the sample consisted of 295 healthy Caucasian subjects of German origin ($n=143$ men and $n=152$ women; age: mean = 25.49 yr, S.D. = 5.79 yr). In a subgroup of 48 healthy male volunteers, aged between 20 and 34 yr, blood samples were drawn between 15:00 and 17:00 hours for analysis of Prl levels (Study 2). Only males were selected for Study 2 to avoid a confounding of Prl levels by hormonal contraceptives or variations in the menstrual cycle. All subjects were fully informed about the study objectives, and the requirements for blood sampling. Subjects were paid for their participation and gave informed consent. Both aspects of the study (genotyping and blood sampling) were

approved by the Ethics Committee of the German Association of Psychology.

Psychological measurements

The Carver and White BIS/BAS scales (Carver and White, 1994) provide direct measures of the two main systems underlying Gray's RST. They are a self-report instrument consisting of a total of 24 items to be rated on four-point Likert scales. The 13 items assessing the BAS are divided into the three subscales fun-seeking (FS), reward responsiveness (RD) and drive (D). The BIS is represented by seven items and the remaining four items are dummy items. The BAS is positively correlated to traits of PEM like extraversion and NS and the BIS is positively correlated to traits of NEM like HA and neuroticism. The psychometric properties of the German BIS/BAS scales meet all standards of a reliable instrument and are reported elsewhere (Strobel et al., 2001).

Recent studies have provided biological evidence for the validity of the Carver and White BIS/BAS scales: Reuter et al. (2004) performed the first fMRI study to investigate the validity of Gray's personality theory. It was seen that the BIS/BAS scales had the highest discriminate validity to predict haemodynamic brain responses to emotional stimuli compared to other personality dimensions, for example extraversion or neuroticism. Another fMRI study (Gray and Braver, 2002) that examined working-memory performance after pre-exposure to emotional stimuli, also found evidence for BAS. For the caudal anterior cingulate, personality scores explained variance in the task-related activity after emotional pre-exposure that was not explained by activity in the neutral condition. Although this study did not examine emotional reactivity directly, it nonetheless supports the validity of the Carver and White scales to measure neurologically accessible individual differences. These scales are now widely used in experimental studies of RST, and with considerable success (Corr, 2004).

Subjects completed the BIS/BAS scales (Carver and White, 1994). Smoking status was checked by the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991). The rationale to include smoking status as a control variable was based on findings that subjects with high scores on personality traits related to impulsivity, extraversion, and SS have a higher proclivity to become addicted to nicotine (e.g. Lejuez et al., 2003; Reuter and Netter, 2001; Zuckerman et al., 1990) and nicotine addiction in turn is mediated by the DA system (e.g. Caskey et al., 2002;

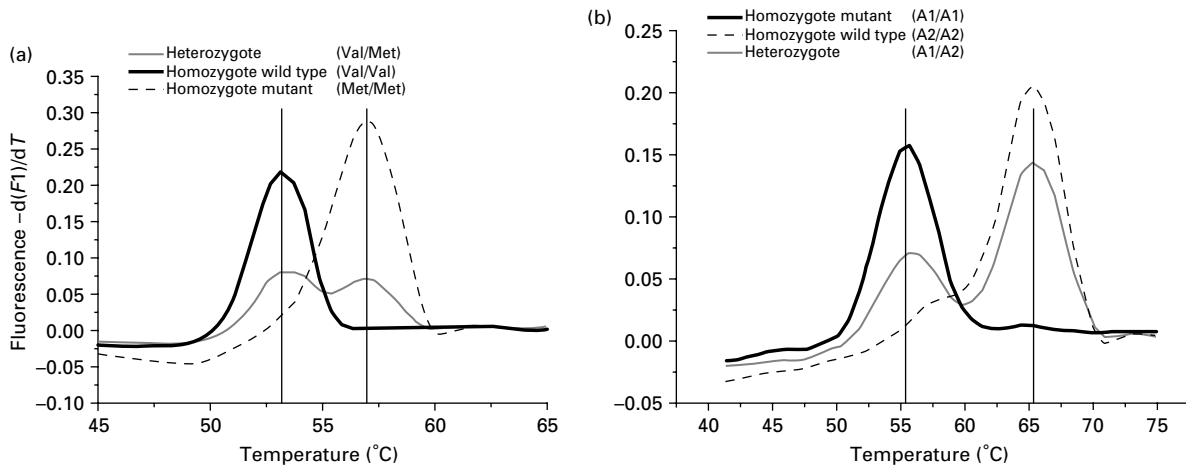


Figure 1. Results of the melting-curve analyses of the COMT and the DRD2 *TaqIA* polymorphisms. Melting temperature (T_m) is calculated by taking the first negative derivate ($-dF/dT$) of the melting curve. The heights of the amplitudes (fluorescence) of the curves are irrelevant. Only of relevance is the temperature of the peak of the curves (T_m). (a) A single late peak indicates a mutation on both alleles (Met/Met genotype). A single early peak indicates the homozygote wild type (Val/Val genotype). Two peaks indicate a heterozygote sample (Val/Met genotype). (b) A single early peak indicates a mutation on both alleles (A1/A1 genotype). A single late peak indicates the homozygote wild type (A2/A2 genotype). Two peaks indicate a heterozygote sample (A1/A2 genotype).

Reuter et al., 2002). Therefore, possible mediator effects of smoking on possible associations between personality and polymorphisms will be controlled.

Genetic analyses

DNA was extracted from buccal cells to avoid a selective exclusion of subjects with blood and injection phobia. The subjects completed a health questionnaire containing questions on psychiatric illnesses. However, a great proportion of healthy subjects had a mild form of blood phobia which could have resulted in a selective drop-out, if blood samples were taken. To avoid this we used buccal swabs.

Purification of genomic DNA was performed with a standard commercial extraction kit (High Pure PCR Template Preparation kit; Roche Diagnostics, Mannheim, Germany). Genotyping of the COMT and the DRD2 *TaqIA* polymorphisms was performed by real-time PCR using fluorescence melting-curve detection analysis by means of the Light Cycler System (Roche Diagnostics). By means of melting-curve analyses SNPs could be detected without conducting gel electrophoresis and ensuing sequencing after amplification. Moreover, the precision of the technique yields PCR results with a reliability of 1.0. The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) and the PCR protocols were as follows. For COMT – forward

primer: 5'-GGGCCTACTGTGGCTACTCA-3'; reverse primer: 5'-GGCCCTTTTCCAGGTCTG-3'; anchor hybridization probe: 5'-LCRed640-TGTGCATGCCT-GACCCGTTGTCA-phosphate-3'; sensor hybridization probe: 5'-ATTTCGCTGGCATGAAGGACAAG-fluorescein-3'. For DRD2 *TaqIA* – forward primer: 5'-CGGCTGGCCAAGTTGTCTAA-3'; reverse primer: 5'-CAAATGTCCACGCCCCGCA-3'; anchor hybridization probe: 5'-LCRed640-TGAGGATGGCTGTGTT-GCCCTT-phosphate-3'; sensor hybridization probe: 5'-CTGCCTCGACCAGCACT-fluorescein-3'. The PCR runs comprised 55 cycles of denaturation (95 °C, 0 s, ramp rate 20 °C/s), annealing (57 °C for COMT and 63 °C for DRD2, 10 s, ramp rate 20 °C/s) and extension (72 °C for both polymorphisms, 10 s, ramp rate 20 °C/s) which followed an incubation period of 10 min to activate the FastStart *Taq* DNA polymerase of the reaction mix (Light Cycler FastStart DNA Master Hybridization Probes; Roche Diagnostics). After amplification a melting curve was generated by holding the reaction time at 40 °C for 2 min and then heating slowly to 95 °C with a ramp rate of 0.2 °C/s. The fluorescence signal was plotted against temperature to yield the respective melting points (T_m) of the two alleles. COMT: T_m for the Val allele was 59.00 °C and 64.50 °C for the Met allele (see Figure 1a). DRD2: T_m for the A1 allele was 55.00 °C and 64.80 °C for the A2 allele (see Figure 1b).

Table 1. Genotype and allele frequencies of the COMT and DRD2 polymorphisms ($n=295$, Study 1)

COMT		DRD2 <i>TaqIA</i>	
Val/Val	79 (26.78%)	A1A1	8 (2.71%)
Val/Met	133 (45.08%)	A1A2	100 (33.90%)
Met/Met	83 (28.14%)	A2A2	187 (63.39%)
		A1+	108 (36.61%)
		A1–	187 (63.39%)
Val	291 (49.32%)	A1	116 (19.66%)
Met	299 (50.68%)	A2	474 (80.34%)

Prolactin

Samples were taken from an in-dwelling catheter 1 h after venepuncture to avoid stress effects on the endocrine parameter. Blood samples were centrifugated (10 min at 4000 g). Plasma was taken and stored at -30°C until Prl levels were measured with a commercial enzyme immunoassay (EIA) (DRG, Marburg, Germany). All analyses were performed fully automatically by use of the Labotech II (Biochem, Freiburg, Germany) yielding very low intra- and inter-assay variations (both CV <5%).

Results

Study 1

Molecular genetics

The distribution of genotype and allele frequencies of the COMT and the DRD2 *TaqIA* polymorphisms are shown in Table 1. The genotype distribution for both gene loci was in Hardy–Weinberg equilibrium (COMT: $\chi^2 = 2.94$, d.f. = 1, $p = 0.086$; DRD2: $\chi^2 = 1.51$, d.f. = 1, $p = 0.220$). With respect to the COMT SNP, the proportion of the Val allele was 49.32% and of the Met allele 50.68% and for the DRD2 SNP, the proportion of the less common A1 allele was 19.66% and for the more common A2 allele 80.34%. To control for linkage disequilibrium between COMT and DRD2 SNP, Burrows' composite measure of linkage disequilibria between pairs of loci was estimated and tested by means of χ^2 test for significance for single populations (Weir, 1979). No linkage disequilibrium between DRD2 *TaqIA* and COMT was observed.

Effects of gender and smoking status on personality

The only significant difference was an effect of gender on BIS [$F = 8.44$, d.f. = 1, $p = 0.004$, $\eta^2 = 0.028$;

men: (mean $\pm$ S.E.M.) 18.85 ± 0.18 , women: 19.62 ± 0.19], a finding that is consistent with many other studies of gender and NEM.

Associations between gender or smoking status and gene loci

There were no significant associations between gender or smoking status and the genotype and allele frequencies of COMT and DRD2 as indicated by χ^2 tests.

Associations between personality and gene loci

For none of the BIS/BAS scales was there a main effect of DRD2 or COMT, irrespective whether independent groups were defined by genotypes or by alleles. However, there were significant interactions of DRD2 $\times$ Val for the total BAS scale (DRD2 $\times$ Val: $F = 7.35$, d.f. = 1, $p = 0.007$, $\eta^2 = 0.025$) as well as for the Drive (DRD2 $\times$ Val: $F = 5.26$, d.f. = 1, $p = 0.023$, $\eta^2 = 0.018$) and FS (DRD2 $\times$ Val: $F = 4.08$, d.f. = 1, $p = 0.044$, $\eta^2 = 0.014$) scales. For all three scales, BAS scores were high in A+/Val+ and in A–/Val– carriers and low in A+/Val– and in A–/Val+ carriers (see Table 2). That is, BAS scores were low if the D₂ receptor density and the COMT activity are low or if the D₂ receptor density and the COMT activity are high, and BAS scores were high if the D₂ receptor density is low and the COMT activity is high or if the D₂ receptor density is high and the COMT activity is low.

Although there were no main effects for smoking or for gender on personality (with the exception of a gender effect on BIS, see above) we tested all possible two-way-interactions (gene loci $\times$ gender and gene loci $\times$ smoking status) and all possible three-way-interactions (DRD2 $\times$ COMT $\times$ gender and DRD2 $\times$ COMT $\times$ smoking status) to pinpoint possible interactions with gender and smoking.

Results showed a significant two-way interaction for Met $\times$ gender on BIS ($F = 4.28$, d.f. = 1, $p = 0.040$, $\eta = 0.014$) indicating that in men carriers of the Met allele (mean $\pm$ S.E.M. = 18.63 ± 0.22) had lower BIS scores than men without the Met allele (mean $\pm$ S.E.M. = 19.47 ± 0.37) and that in women the Met+ group (mean $\pm$ S.E.M. = 19.72 ± 0.21) had higher BIS scores than the Met–group (mean $\pm$ S.E.M. = 19.34 ± 0.35). There was also a significant two-way interaction (Met $\times$ smoking status) on FS ($F = 6.90$, d.f. = 1, $p = 0.009$, $\eta = 0.023$) indicating that in smokers carriers of the Met–allele (genotype Val/Val) had higher FS scores than those smokers who are carriers of the Met+ allele while the opposite was true for

Table 2. Means and S.E.M. of the BIS/BAS scales dependent on alleles of the COMT and the DRD2 polymorphisms ($n=295$, Study 1)

DRD2	COMT	<i>n</i>	Mean	S.E.M.
BAS total				
DRD2 $\times$ Val:				
$F=7.35$, d.f. = 1, $p=0.007$				
A1–	Val–	50	41.14	0.57
	Val+	137	40.31	0.35
A1+	Val–	33	39.58	0.71
	Val+	75	41.68	0.47
BAS drive				
DRD2 $\times$ Val:				
$F=5.26$, d.f. = 1, $p=0.23$				
A1–	Val–	50	12.56	0.26
	Val+	137	12.23	0.16
A1+	Val–	33	11.73	0.32
	Val+	75	12.53	0.22
BAS fun seeking				
DRD2 $\times$ Val:				
$F=4.08$, d.f. = 1, $p=0.44$				
A1–	Val–	50	11.82	0.27
	Val+	137	11.66	0.16
A1+	Val–	33	11.33	0.33
	Val+	75	12.19	0.22
BAS reward responsiveness				
DRD2 $\times$ Val: n.s.				
A1–	Val–	50	16.76	0.27
	Val+	137	16.42	0.16
A1+	Val–	33	16.52	0.33
	Val+	75	16.96	0.22
BIS				
DRD2 $\times$ Val: n.s.				
A1–	Val–	50	19.08	0.32
	Val+	137	19.12	0.20
A1+	Val–	33	19.09	0.40
	Val+	75	19.65	0.26

BIS, Behavioural inhibition system; BAS, Behavioural approach system.

non-smokers (see Table 3, upper part). There was also a significant two-way interaction seen for DRD2 $\times$ smoking status on FS ($F=3.95$, d.f. = 1, $p=0.048$, $\eta^2=0.013$). A1– carriers did not differ in FS scores whereas in A1+ carriers smokers had significantly higher FS scores than non-smokers ($F=7.27$, d.f. = 1, $p=0.008$, $\eta^2=0.064$) (see Table 3, lower part).

Study 2

The random sample of Study 2 showed similar genotype frequencies to the total sample of Study 1. There

Table 3. Means and S.E.M. of the BAS-FS scale dependent on the Met allele of the COMT polymorphism, the DRD2 polymorphism and on smoking status ($n=295$, Study 1)

Smoking status	<i>n</i>	Mean	S.E.M.
BAS-FS			
Met $\times$ smoking status:			
$F=6.90$, d.f. = 1, $p=0.009$			
COMT			
Met– Non-smokers	50	11.34	0.26
Smokers	29	12.76	0.35
Met+ Non-smokers	120	11.72	0.17
Smokers	96	11.81	0.19
BAS-FS			
DRD2 $\times$ smoking status:			
$F=3.95$, d.f. = 1, $p=0.48$			
DRD2			
A1– Non-smokers	108	11.67	0.18
Smokers	79	11.76	0.21
A1+ Non-smokers	62	11.50	0.24
Smokers	46	12.50	0.28

BAS, Behavioural approach system – Fun Seeking.

Table 4. Means and S.E.M. of prolactin baseline levels (ng/ml) dependent on alleles of the COMT and the DRD2 polymorphisms ($n=48$, Study 2)

DRD2	COMT	<i>n</i>	Mean	S.E.M.
Prolactin baseline				
DRD2 $\times$ Val:				
$F=5.02$, d.f. = 1, $p=0.30$				
A1–	Val–	8	4.25	0.89
	Val+	19	6.37	0.58
A1+	Val–	4	7.23	1.26
	Val+	17	5.41	0.61
Prolactin baseline				
DRD2/Val:				
$F=4.19$, d.f. = 1, $p=0.46$				
A1– /Val–		25	5.04	0.50
A1+ /Val+				
A1– /Val+		23	6.52	0.52
A1+ /Val–				

were no main effects of COMT or DRD2 but a significant interaction effect for DRD2 $\times$ COMT on baseline Prl levels ($F=5.02$, d.f. = 1, $p=0.030$, $\eta^2=0.102$; see Table 4, upper part). In order to prevent low cell frequencies, groups marked by allele combinations which were related to high BAS scores in Study 1 (A– /Val– and A+ /Val+) and those groups which had low BAS scores in Study 1 were collapsed. The groups which had higher BAS scores in Study 1 had significantly lower Prl levels than those with

Table 5. Means and S.E.M. of BAS total scores dependent on alleles of the COMT and the DRD2 polymorphisms ($n=48$, Study 2)

DRD2	COMT	<i>n</i>	Mean	S.E.M.
BAS total				
DRD2 $\times$ Val: n.s.				
A1–	Val–	8	43.13	1.53
	Val+	19	41.32	0.99
A1+	Val–	4	42.00	2.49
	Val+	17	42.35	1.05
BAS total				
DRD2/Val: n.s.				
DRD2/Met				
A1–/Val–		25	42.60	0.84
A1+/Val+				
A1–/Val+		23	41.41	0.90
A1+/Val–				

BAS, Behavioural approach system.

low BAS scores ($F=4.19$, d.f. = 1, $p=0.046$, $\eta^2=0.083$; see Table 4, lower part). Although A–/Val– and A+/Val+ groups also had higher BAS scores in the sample of Study 2 this effect was not significant (see Table 5). Furthermore, there was no significant correlation between Prl levels and BAS scores.

Discussion

Study 1 tested the hypothesis that the COMT and DRD2 *TaqIA* polymorphisms are related to Gray's behavioural approach/activation system (BAS) which was postulated to have its biological basis in dopaminergic structures of the limbic system. The two polymorphisms COMT and DRD2 *TaqIA* influence DA activity either by catabolizing the neurotransmitter itself or by determining the receptor density of the D₂ receptor subtype. For this reason they are candidate genes to test the validity of Gray's RST.

Results of Study 1 indicated that both gene loci have an influence on BAS. Although there was no main effect observed for each of the gene loci it was seen that the interaction of both significantly predicts differences in the total BAS scale and in the two subscales of the BAS, FS and Drive. For all of the three BAS scales high scores were seen in A+/Val+ and in A–/Val– carriers and low scores in A+/Val– and in A–/Val+ carriers. This gene interaction is of high relevance for the activity of the DA system, because it implies that it is not the receptor density itself or the COMT activity that influences the phenotype of BAS but it is

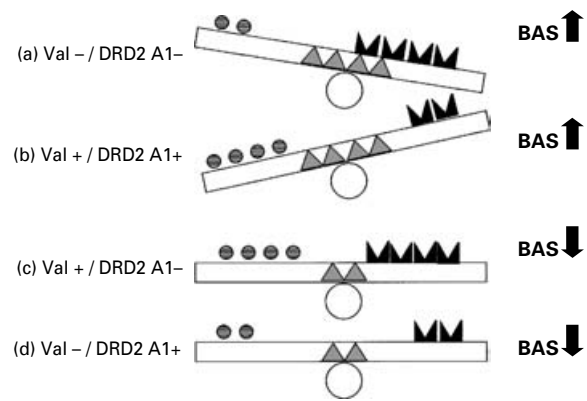


Figure 2. COMT-DRD2 Equilibrium Model of Positive Emotionality. *Disequilibrium* between catabolic enzyme activity of COMT and D₂ receptor density is associated with high DA levels and predicts high BAS scores: (a) low enzyme activity, high D₂ receptor density and high DA levels. (b) High enzyme activity, low D₂ receptor density and high DA levels. *Equilibrium* between catabolic enzyme activity of COMT and D₂ receptor density is associated with low DA levels and predicts low BAS scores. (c) High enzyme activity, high D₂ receptor density, and low DA levels. (d) Low enzyme activity, low D₂ receptor density, and low DA levels. Circles indicate COMT, triangles indicate DA, and black figures indicate DA receptors.

disequilibrium between catabolic enzyme activity and receptor density that is crucial. High DA receptor density (A1–) and low COMT enzyme activity (Val–) or low receptor density (A1+) and high COMT enzyme activity (Val+) predict high BAS scores (see Figure 2). Such gene–gene interactions may, in part, be the reason for failures to replicate gene–personality associations.

As mentioned above, based on the findings of Study 1, we cannot give an answer to the question whether high COMT activity is related to high or low DA activity. A combination of endocrinological markers of DA activity with genetic markers of the DA system provides deeper insight. Study 2 addressed this problem. Results of Study 2 indicated exactly that those groups of subjects defined by DRD2 and COMT alleles (A1–/Val– and A1+/Val+) as having high BAS scores had significantly lower baseline Prl concentrations than those groups with an allele combination (A1–/Val+ and A1+/Val–) predicting low BAS scores. This finding indicates that COMT enzyme activity alone does not predict DA activity – in the same way as the D₂ receptor density does not allow us to infer DA activity – but that the interaction of D₂ receptor density and the catabolic enzyme activity of COMT seem to determine

it. The low Prl levels in the A1+/Val+ and A1-/Val- subjects indicate high DA activity (Ben-Jonathan and Hnasko, 2001). Therefore, high BAS subjects are marked by high DA activity which is in line with Gray (1994) and Depue et al. (1994). Although there was no association between BAS scores and Prl levels in Study 2 ($n=48$), the A1+/Val+ and A1-/Val- subjects again had – at least on a descriptive level – higher BAS scores compared to the A1-/Val+ and A1+/Val- subjects. Due to the small sample size the power was too low to get a significant result. However, another study by our group revealed that low Prl levels are associated with NS (Stuettgen et al., in press). This trait shares a substantial amount of variance with the BAS.

The question remains as to why high D₂ receptor density (A1-) and low catabolic enzyme activity of COMT (Val-), as well as low receptor density (A1+) and high catabolic enzyme activity (Val+) are equally associated with high DA activity as indicated by low Prl levels (see Figure 2a,b). The results can be explained by a COMT-DRD2 Equilibrium Model of Positive Emotionality (see Figure 2). It seems that both patterns of alleles which were associated with high BAS scores in Study 1 are adaptive in the sense of having sufficiently high DA activity for behavioural approach and PEM and that both groups have high DA levels as indicated by their low Prl levels.

In A1-/Val- subjects low catabolic enzyme activity leads to high levels of DA but the D₂ receptor density is also high, resulting in a balanced state between receptor density and transmitter availability (Figure 2a). In A1+/Val+ subjects a high catabolic enzyme activity meets high DA levels counterbalancing the DA surplus and, therefore, the low D₂ receptor density is again in congruence with the DA activity (Figure 2b). Whereas in A1-/Val+ and A1+/Val- subjects low DA levels do not allow a compensation process (see Figure 2c,d). A1+/Val- subjects have low DA levels, a low enzyme activity of COMT and in addition their D₂ receptor density is low indicating a completely down-regulated DA system (Figure 2d). Therefore, it is not surprising that A1+/Val- subjects had the lowest BAS scores. In A1-/Val+ subjects the high COMT activity further reduces DA leading to an extreme imbalance between the high receptor density and the low DA levels (Figure 2c). It can be assumed that a high receptor density is already an adaptation to low DA synthesis rates and high catabolic enzyme activity. The phenomenon of high D₂ receptor density is reminiscent of clinical findings reporting a receptor up-regulation in depressed patients suffering from

monoamine deficiency (Yates et al., 1990). Although this mechanism clearly denotes an adaptive process in patients to compensate for a monoamine deficiency it is obvious that compensation breaks down if COMT activity is also high. The same imbalance between receptor density and the amount of monoamines available is present in normal subjects scoring lowest on BAS (A1-/Val+). Therefore, the present results once more corroborate the assumption that personality traits within a normal range and psychopathological personality disorders have one common underlying dimension (Donnelly, 1998).

Thus, it is only possible to compensate for either a high enzyme activity or a low receptor density if high DA levels are available. Obviously neither the theory that high COMT activity results in lower DA levels nor the adaptation theory implying an elevated COMT activity in the presence of high DA activity seem to be valid in the light of the present data.

Further studies are needed to investigate the linkage between personality and gene loci that determine DA synthesis, DRD2 and COMT. Furthermore, due to the fact that COMT is not the only factor influencing the catabolism of DA, the activity of MAO has also to be taken into account. MAO is an additional candidate to play a role in the above-mentioned interaction between COMT activity and D₂ receptor density. It cannot be ruled out that COMT and MAO interact to maintain an optimal level of DA activity.

Additional analyses yielded a two-way interaction (Met $\times$ gender) on BIS. In general men had significantly lower BIS scores than women but men carriers of the Met- allele (genotype Val/Val) had higher BIS scores than carriers of the Met+ allele (genotypes Val/Met and Met/Met) while in women the opposite was true. Further research is necessary to test if there is a gonosomal linkage with the COMT gene in the expression of the phenotypic BIS as indicated by the data. Moreover, results stressed the importance of FS for smoking behaviour. Although the main effect of smoking status on FS missed statistical significance ($F=3.71$, d.f.=1, $p=0.055$) there were two-way interactions of smoking status and COMT and of smoking status and DRD2 on FS. Smokers who are carriers of the Met- allele (genotype Val/Val) had higher FS scores than those smokers of the Met+ allele, the opposite being true for non-smokers. In the light of the principal findings of the present study, that COMT activity does not allow the prediction of actual DA levels (the A+/Val+ as well as the A-/Val- groups had low Prl levels and, therefore, high DA levels), this result cannot be explained by classical

addiction theories which assume that either high levels of DA lead to drug addiction (incentive theory) or that low levels of DA trigger the search for drugs to compensate a DA deficiency (reward theory) (Reuter et al., 2002). For this reason we just conclude that high Fun Seekers differ in COMT activity dependent on their smoking status. Smokers who are high Fun Seekers have high COMT enzyme activity and non-smokers who are high Fun Seekers have low COMT enzyme activity.

The interaction between DRD2 and smoking status on FS was markedly smaller than the interaction of Met $\times$ smoking status on FS. It was seen that in A1-carriers smokers and non-smokers did not differ in FS scores whereas in A1+ carriers smokers had significantly higher FS scores than non-smokers. The results of both interactions suggest that high COMT activity and low D₂ receptor density is associated with high FS scores in smokers.

Finally we make a crucial comment on the interpretation of the main finding of the paper: Despite the significant interaction effects of COMT and DRD2 TaqIA on personality it has to be pointed out that these gene polymorphisms determine only the disposition for enzyme activity and receptor density. In the living organism regulatory processes in confrontation with environmental effects or in response to gene-environment interactions determine the actual activity of the DA system in concert with the inherited genetic make-up. Nevertheless, results demonstrate that a genetic disposition, located on the COMT and DRD2 genes, has a significant effect on Gray's personality dimensions as measured by the Carver and White scales (Carver and White, 1994) and on the actual DA levels as indicated by the baseline Prl levels. In testing Gray's RST, the coincidence of positive findings in neurophysiological studies as indicated by fMRI (Gray and Braver, 2002; Reuter et al., 2004) and in a study from molecular genetics, the ecological validity of the Carver and White scales (Carver and White, 1994) is demonstrated.

However, due to the fact that association studies are prone to produce false-positive effects the present results have to be corroborated by an independent sample. However, the risk to obtain positive findings due to multiple testing was not very high in this study because no other genes were tested than COMT and DRD2 and because the subscales of BAS are highly correlated and showed similar associations. The Prl results must also be investigated in female subjects. In this initial study we restricted the analyses to males to avoid the influence of the menstrual cycle on Prl levels.

Further studies investigating the effects of the COMT and DRD2 polymorphisms on Prl levels after a challenge with dopaminergic substances will further elucidate the neurochemical basis of the BAS dimension, especially if further polymorphisms involved in DA metabolism and their interactions are also considered. Nevertheless, the present study is the first to provide evidence from molecular genetics for the validity of Gray's theory and which also combined genetic and endocrinological data to contribute substantially to the search for an answer to the question of how DA is related to personality traits of PEM.

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None.

Statement of Interest

None.

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