

## Genetically determined dopamine availability predicts disposition for depression

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### Abstract

Although prominent personality theories postulate orthogonality between traits of positive emotionality (PEM) and negative emotionality (NEM), empirical evidence often demonstrates the opposite indicating a negative relationship. Therefore, it is not surprising that dopaminergic (DA) gene loci have been related to traits of positive and of NEM. The present genetic association study investigates the influence of two functional DA gene polymorphisms on Sadness as defined by the Affective Neuroscience Personality Scales (ANPS) in healthy Caucasians ( $n = 1041$ ). We observed a significant interaction effect between the 10-repeat (10R) allele of the dopamine transporter (DAT1) gene and the methionine (Met) allele of the catechol-O-methyltransferase (COMT) Val158Met polymorphism ( $F_{(1,1018)} = 11.11$ ;  $P < 0.001$ ). Carriers of the 9R/9R and the Val/Val genotype showed dramatically reduced Sadness scores in comparison to the other three genotype configurations. Both the 9R/9R and the Val/Val genotypes characterized by reduced transporter density and high dopamine catabolism, respectively, have been separately related to personality traits of PEM and externalizing behavior in the past. The present findings indicate that gene variations of the DA system previously associated with PEM are at the same time protective against high NEM and can therefore constitute a resilience factor against depression.

### Introduction

Dopaminergic (DA) neurotransmission plays a crucial role for human personality with implications for affective disorders. With respect to the DA system it has been shown that the same biological basis is related to variability in personality and psychopathology (Dunlop and Nemeroff 2007). Thus, personality traits and also the vulnerability for and the severity of psychopathological disorders can be interpreted as variations of a common underlying dimension. This implies a natural continuum between high and low levels of a certain personality trait dimension and only extreme variations at the end of trait scales result in symptoms of psychiatric illness (Donnelly 1998). Moreover, DA neurotransmission is implicated in the regulation of reward and cognitive processes (Bressan and Crippa 2005; Yacubian and Buchel 2009). Most relevant for the present study, there is mounting evidence that the DA system plays a role in the processing of

positive emotionality (PEM) as well as of negative emotionality (NEM) (Reuter and Hennig 2005; Montag et al. 2010) leading to the hypothesis that PEM and NEM constitute a unidimensional bipolar construct and that the position of an individual on this continuum is characterized by the amount of DA availability in the central nervous system. In other words, DA can be described as the “Yin and Yang principle of personality.” In personality psychology, there is still a debate on the question if PEM and NEM are orthogonal constructs or represent—as hypothesized in the present study—a unidimensional bipolar construct. In this context, it is stressed that the thought of a continuum model to personality traits is in particular observable in traits linked to approach (PEM) and avoidance behavior (NEM—see supplementary material for further explanations). This hypothesis is corroborated by studies in humans, where dopamine D2 receptor (DRD2) blockade results in an impaired recognition of emotionally negative stimuli (Mehta et al. 2005). DA antagonists also

reduce motivation and mood and induce states of depression (Bressan *et al.* 2002; Verhoeff *et al.* 2003). On the other side data from human pharmacological imaging studies demonstrate that an increase of extracellular dopamine in the striatum is correlated with the experience of positive mood states (Drevets *et al.* 2001; Laruelle *et al.* 1995). Furthermore, genetically influenced differences in DA transmission contribute to individual differences in reward-seeking behavior during functional magnetic resonance imaging (fMRI) suggesting that variation in DA availability modulates affective states (Dreher *et al.* 2009). In general, the association between DA activity and depression (Dunlop and Nemeroff 2007) is based on the fact that the neurotransmitter DA is involved in approach behavior (Schultz 1998) and depression is related to deficits in the approach system associated with reduced positive affect (see Shankman and Klein 2003 for a review).

To sum up, contrary to empirical findings mentioned above prominent personality theories postulate orthogonality of personality dimensions, but growing empirical evidence indicates a negative correlation between traits of positive and NEM (for an overview see Reuter 2008). Heritability estimates for personality traits as well as for psychopathologies are rather high indicating that the genetic background (genotype) of a person accounts substantially for individual differences in behavior and the predisposition to psychiatric disorders. Genetic association studies provide considerable evidence that DA genes are associated with personality traits and a range of psychiatric phenotypes. For instance, for the well-studied DA candidate genes coding for catechol-O-methyltransferase (COMT) and DRD2, a significant interaction for the total Behavioral Activation System (BAS) scale related to PEM and also higher scores on extraversion and PEM for COMT valine (Val) allele carriers have been reported (Reuter and Hennig 2005; Reuter *et al.* 2006). In line with the “Yin and Yang principle of dopamine” results for the COMT polymorphism showed an association of the methionine (Met) allele with personality traits primarily related to NEM (Enoch *et al.* 2003; Eley *et al.* 2003; Rujescu *et al.* 2003). Despite this convergent evidence, the proportion of variance accounted for by a single polymorphism is rather low. Complex phenotypes of high heritability such as personality traits are influenced by the interplay of many different genes (Reif and Lesch 2003), resulting in a wide variance of individual behavioral dispositions. In order to investigate the role of the DA system for personality, we have to keep in mind that DA genes interact to determine the efficacy of the DA system by influencing the expression and distribution of the gene products within the brain. In particular, DA activity depends on synthesis rates, catabolism, and receptor density but also on further enzymes and proteins regulating DA neurotransmission (see Opmeer *et al.* for an overview). Numerous polymorphisms in the corresponding genes can have major influence on DA metabolism and neurotrans-

mission. A vast body of evidence from studies in humans as well as animals illustrates the pivotal role of COMT and the dopamine transporter (DAT1) in DA neurotransmission. Since both polymorphisms are well studied and shown to be functional, the present theory-based study of COMT  $\times$  DAT1 gene interaction takes a pharmacologically relevant interaction into account. Both COMT, as a catecholamine catabolizing enzyme, and the DA transporter, DAT1, work together to clear extracellular DA from the synaptic cleft. In doing so, they regulate synaptic DA concentrations in the brain mainly in cortical and subcortical regions. A contribution of both the COMT and the DAT1 polymorphisms to the activity of the DA system and an interaction (epistasis effect) of these genes is quite likely, at least from a pharmacological viewpoint.

In humans, the COMT gene contains a functional nonsynonymous single nucleotide polymorphism (SNP), a guanine to adenine transition in codon 158 of the COMT gene located at the q11 band of human chromosome 22 (rs#4680). The substitution of the amino acid Val by Met results in decreased thermostability of the protein leading to a three- to fourfold reduced COMT enzyme activity at physiologically relevant temperatures. The COMT alleles are codominant with three genotypes possible: carriers of the Val/Val genotype have highest, carriers of the Met/Met genotype have lowest, and heterozygotes (Val/Met genotype) have intermediate levels of COMT enzyme activity (Lachman *et al.* 1996; Chen *et al.* 2004; Weinshilboum *et al.* 1999). Consistently, the number of Met alleles is positively related to prefrontal DA levels (Tunbridge *et al.* 2006). The involvement of the COMT Val158Met polymorphism in emotional processing is supported by numerous association studies relating the Met allele or the Met/Met genotype to anxiety disorders (Enoch *et al.* 2003; Domschke *et al.* 2004; McGrath *et al.* 2004; Woo *et al.* 2004; Olsson *et al.* 2005; Montag *et al.* 2008), anxiety-related traits including high neuroticism, and low sensation seeking and low extraversion (Reuter and Hennig 2005; Stein *et al.* 2005; Lang *et al.* 2007) and obsessive-compulsive disorder (Pooley *et al.* 2007). A diminished stress resilience and emotional regulation for the Met allele (Goldman *et al.* 2005) is in line with an association with increased pain sensitivity (Zubieta *et al.* 2003). In addition, the Met allele is associated with the onset of mood disorders after exposure to adverse life events (Mandelli *et al.* 2007). These findings suggest that the COMT Val158Met polymorphism and especially the Met/Met genotype leads to increased predisposition to emotional disorders, with anxiety and depression as the most common ones. However, it must be noted that despite of this high convergent validity that relates the Met allele to NEM and the Val allele to PEM, there are also some studies reporting conflicting results.

The human dopamine transporter (DAT1/SLC6A3) gene localized on chromosome 5p15.3 contains a 40 base pair (bp) variable number of tandem repeats (VNTR) polymorphism

in its 3'-untranslated region (3'UTR) with repeat numbers ranging from 3 to 11. The two most frequent alleles in the population are the nine- and 10-repeat (9R and 10R) alleles (Vandenberg et al. 1992). An increased level of DAT1 expression is most common associated with the 10R allele than with the 9R allele (Heinz et al. 2000; Fuke et al. 2001; Mill et al. 2002; VanNess et al. 2005), although some studies reported the opposite (Jacobsen et al. 2000; Van Dyck et al. 2005) or no differences between genotypes and DAT1 expression rates (Martinez et al. 2001; Krause et al. 2006; Costa et al. 2011). The functional DAT1 VNTR polymorphism directly alters DAT1 density and activity in the brain mainly in the striatum. Individuals carrying two copies of the 10R allele have higher DAT1 density and therefore less dopamine in the synaptic cleft than 9R carriers (Heinz et al. 2000). Hence, the presynaptic neuronal membrane protein DAT1 plays a pivotal role in terminating DA neurotransmission, as it mediates active reuptake of DA into the presynaptic nerve terminals (Giros and Caron 1993). DAT1 is implicated in DA-related personality, emotional processing, and pathologies associated with dysregulation of DA transmission such as depression, attention deficit-hyperactivity disorder (ADHD), Parkinson's disease, schizophrenia, cocaine-induced paranoia, tobacco smoking, and alcohol dependence (Greenwood et al. 2002; Mehler-Wex et al. 2006; Samochowiec et al. 2006; Haeffel et al. 2008; Garcia-Garcia et al. 2010). Garcia-Garcia et al. (2010) reported a DAT1-dependent enhancement of novelty processing in a negative emotional context. Individuals with at least one 9R allele (associated with larger striatal DA levels) showed larger distraction as 10R/10R individuals (associated with less striatal DA levels). Further studies reported a lower risk of smoking addiction for 9R allele carriers (Lerman et al. 1999; Sabol et al. 1999). Recently Guo et al. (2010) showed that the 9R/9R genotype exerts a general protective effect against a spectrum of risky behaviors in comparison to the 10R/9R and 10R/10R genotypes. Lower scores on neuroticism are associated with carriers of at least one copy of the 9R allele in combination with the Met allele of the Brain-derived neurotrophic factor (BDNF) gene (Huennerkopf et al. 2007). In addition, a role of the DAT1 gene in the development of depression was reported (Haeffel et al. 2008; Brunswick et al. 2003). However, similar to the COMT Val158Met polymorphism, the DAT1 VNTR polymorphism have been examined in several psychiatric studies with heterogeneous results dependent on phenotype and grouping of DAT1 alleles (Opmeer et al.; Huang et al. 2011).

To date, only a few studies have explored the genetic interaction between COMT and DAT1. Previous studies reported an interaction between both genes in cortical regions in relation to schizophrenia (Prata et al. 2009), on reward processing and cognition (Bertolino et al. 2006; Caldu et al. 2007; Yacubian et al. 2007; Bertolino et al. 2008; Alexander et al. 2011) reported epistasis between COMT Met and DAT1 10R

resulting in elevated cortisol reactivity and impaired stress recovery. Moreover, an interaction between both polymorphisms was observed in Alzheimer patients, in which carriers of the DAT1 10R without COMT Val allele exhibit significantly lower agitation levels (Proitsi et al. 2010).

The aim of the present study was to examine the existence of a nonadditive/epistatic interaction between two functional polymorphisms COMT Val158Met and DAT1 3'UTR VNTR in a large cohort of healthy Caucasian subjects. Especially, we wanted to explore potential associations between risk alleles/genotypes of both genetic polymorphisms for NEM as measured by the Affective Neuroscience Personality Scales (ANPS) questionnaire. The ANPS was chosen for this study because, unlike personality questionnaires derived from a lexical approach, this scale has been constructed to reflect most directly emotional neuronal circuits of the mammalian brain (Davis et al. 2003). We hypothesized that the association of DAT1 with NEM is dependent on genetic variation of the COMT gene because the Met allele of COMT has been previously associated with NEM and the Val/Val genotype with PEM. DA variation should influence vulnerability to negative emotions, possibly due to changes in DA availability. We hypothesized that carriers of the 9R/9R and Val/Val genotype configuration would show lowest scores on NEM, as assessed by the ANPS scales Sadness, Anger, and Fear.

## Material and Methods

### Participants

A total of 1041 healthy Caucasians of German origin filled in a paper-and-pencil version of the ANPS. In addition, all participants provided buccal swabs for genotyping of COMT rs#4680 and DAT1 rs#28363170 polymorphisms. The sample consisted of 358 males and 683 females. Mean age was 25.42 years (SD = 7.86, age range: 18–76 years). Participants were recruited at the University of Bonn, Germany. The presence of exclusion criteria or former ICD-10 diagnosis of psychopathology was assessed by a self-constructed screening questionnaire. The report of any present or former psychiatric or neurological disorders led to an exclusion from the study. The study protocol adheres to the ethical principles of the Declaration of Helsinki of the World Medical Association and was approved by the local ethics committee at the University of Bonn. All participants gave written informed consent to participate in this study.

### Self-report questionnaire

Participants completed the German version of the ANPS personality questionnaire (Davis et al. 2003; Davis and Panksepp 2011). This self-report measure of behavioral dispositions was used because the construction of this inventory was biologically motivated by a theory of basic emotional

systems that was validated across mammalian species (Panksepp 1998). Each scale of the ANPS has been built in analogy to the existence of basic emotional neuronal circuits of the mammalian brain. The ANPS consists of 110 items, scaled on a four-point Likert scale ranging from “strongly disagree” to “strongly agree.” The questionnaire measures six personality dimensions, three of positive (Play, Seek, Care) and three of negative (Fear, Anger, Sadness) experience. Moreover, a scale measuring Spirituality is included in the questionnaire, due to its potential importance for the treatment of alcoholics. The Sadness dimension that is relevant to this study refers to feelings of loneliness and distress, thinking about loved ones and frequent crying.

## Genotyping

DNA was extracted from buccal mucosa cell samples. Automated purification of genomic DNA was conducted by means of the MagNA Pure LC system using a commercial extraction kit (MagNA Pure LC DNA isolation kit; Roche Diagnostics, Mannheim, Germany).

The VNTR polymorphism of the DAT1/SLC6A3 gene (rs#28363170) was amplified from genomic DNA using polymerase chain reaction (PCR) and the primers 5'-TGTGGTGTAGGGAACGGCCTGAG-3' and 5'-CTTCCTGGAGGTCACGGCTCAAGG-3'. In brief, after an initial denaturation for 3 min at 94°C, 39 cycles of denaturing at 94°C for 45 sec, annealing at 62°C for 30 sec, and extension at 72°C for 30 sec were followed by a final extension at 72°C for 5 min. PCR amplification was carried out in a final volume of 20  $\mu$ l consisting of 50 ng genomic DNA, 0.2 mM of each deoxyribonucleotide, 1 pmol of sense and antisense primers, 1 U of GoTaq-Polymerase (Promega, Mannheim, Germany), and the enzyme supplier's buffer. Amplification products were analyzed by 2% agarose gel electrophoresis. The sizes of the 8, 9, 10, and 11 repeats were 360, 400, 440, and 480 bp, respectively.

Genotyping of COMT Val158Met SNPs (rs#4680) was performed by real time PCR (RT-PCR) using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). Details of the PCR protocol are described elsewhere (Reuter et al. 2006). The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) were as follows: forward primer: 5'-GGGCCTACTGTGGCTACTCA-3'; reverse primer: 5'-GGCCCTTTTCCAGGTCTG-3'; sensor hybridization probe: 5'-ATTTTCGCTGGCATGAAGGACAAG-fluorescein-3'; anchor hybridization probe: 5'-LCRed640-TGTGCATGCCTGACCCGTTGTCA-phosphate-3'.

## Statistical analysis

We investigated the influence of COMT and DAT1 on ANPS personality dimensions by means of analysis of variance

(ANOVA). On the genotype levels, the independent factors had three levels each (COMT: Val/Val, Val/Met, and Met/Met; DAT1: 9R/9R, 9R/10R, and 10R/10R). For statistical analyses focusing on gene  $\times$  gene interactions, COMT and DAT1 genotypes were dichotomized to enhance statistical power. Individuals with the COMT Met/Met and Val/Met genotypes were combined (Met+ and Met- for Val/Val) based on findings that the Val/Val genotype is associated with PEM (Reuter and Hennig 2005) and the Met allele with NEM (Enoch et al. 2003). The DAT1 10R/10R and 10R/9R genotypes were dichotomized for the presence (10R+) or absence (10R-) of the DAT1 10R allele as DAT1 expression is higher in the presence of the 10R allele (Fuks et al. 2001; Mill et al. 2002). Age was negatively correlated with Sadness ( $r = -.113$ ,  $P < 0.001$ ) and positively with Seek ( $r = .088$ ,  $P = 0.005$ ) and was therefore included as covariate into all ANOVA models. In order to test and to control for possible gender effects, an ANOVA with gender as fixed factor and the ANPS subscales as independent variables was conducted. Since no significant association between gender and ANPS scores was observed, gender was not included in further analyses. All statistical tests were conducted at a  $P < 0.05$  threshold and significant results were corrected for multiple testing according to the Bonferroni correction. All analyses were carried out using SPSS 18.0.0 (SPSS Inc., Chicago, IL).

## Results

### Sample characteristics

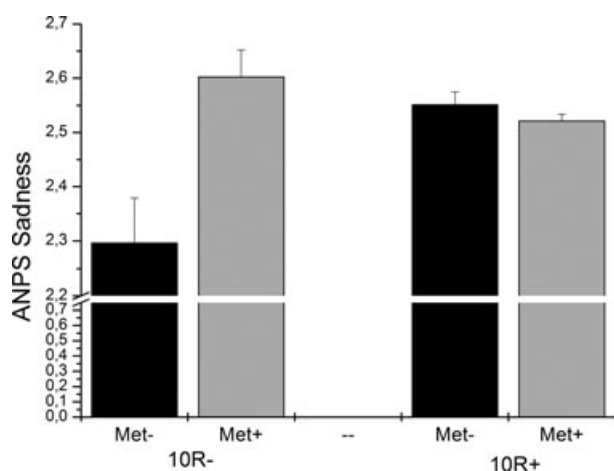
Genotype frequencies of the COMT and the DAT1 polymorphisms were as follows: For COMT Val158Met Val/Val:  $n = 251$ , Val/Met:  $n = 498$ , Met/Met:  $n = 292$  and for DAT1 VNTR 9/9:  $n = 72$ , 9/10:  $n = 381$ , 10/10:  $n = 570$ , 10/11:  $n = 13$ , 9/11:  $n = 4$ , and 8/10:  $n = 1$ . The genotype distributions for both gene loci were in Hardy-Weinberg equilibrium (COMT:  $\chi^2 = 1.81$ ,  $df = 1$ , ns; DAT1:  $\chi^2 = 0.58$ ,  $df = 1$ , ns) and did not differ between gender groups (COMT:  $\chi^2 = 3.05$ ,  $df = 2$ , ns; DAT1:  $\chi^2 = 0.10$ ,  $df = 2$ , ns). In our analyses, we focused solely on individuals with DAT1 genotypes homozygous for 10R and 9R and heterozygous 9R/10R ( $N = 1023$ ). The individuals with rare genotypes (1.7%) were excluded from the analyses. Allele frequencies were as follows: COMT: 48% Val and 52% Met alleles, DAT1: 25% 9R and 73% 10R alleles. There were no differences in allelic distributions between both gender groups ( $\chi^2 = 3.71$ ,  $df = 1$ , ns). The resulting sample distribution over the four allelic configurations of interest is depicted in Table 1.

### COMT, DAT1, and the personality dimension of Sadness

There was no main effect for the DAT1 VNTR polymorphism on any of the ANPS subscales. The COMT Met allele showed a significant association with the subscales Sadness

**Table 1.** Number of participants in the allelic configurations of interest ( $N = 1023$ ).

DAT1	COMT	<i>n</i>
10R-	Met-	19
	Met+	53
10R+	Met-	229
	Met+	722

**Figure 1.** Means and Standard errors of means (SEM) of the ANCOVA for the Sadness dimension of the ANPS dependent on the significant interaction of COMT Met and DAT1 10R. Age was inserted as covariate into the ANOVA.

( $F_{(1,1018)} = 7.55, P = 0.006$ ) and Anger ( $F_{(1,1019)} = 4.19, P = 0.04$ ). Moreover, we found a significant interaction between COMT Met and DAT1 10R on Sadness ( $F_{(1,1018)} = 11.11, P < 0.001$ ). Lowest Sadness scores were observed in carriers of the genotype configuration 10R- and Met- (9R/9R and Val/Val). Results are depicted in Figure 1. Post hoc tests using the Bonferroni method revealed that COMT Met-/DAT1 10R- carriers had significantly lower Sadness scores than carriers of the other three configurations: COMT Met-/DAT1

10R+ ( $P = 0.016$ ), COMT Met+/DAT1 10R- ( $P = 0.007$ ), and COMT Met+/DAT1 10R+ ( $P = 0.038$ ). No other comparisons reached significance. Furthermore, none of the other interactions between the two polymorphisms were significant (all  $P$ -values  $> 0.05$ ; Table 2). Only Fear, a construct highly correlated with Sadness ( $r = .685, P < 0.001$ ; correlation matrix in supplementary material) that also reflects NEM, showed a tendency for significance ( $F_{(1,1019)} = 2.88, P = 0.06$ ). After Bonferroni correction for multiple testing, only the main effect of the COMT Met allele and the interaction of COMT Met with DAT1 10R on the Sadness dimension remained significant, whereas the COMT Met effect on Anger could not hold after adjusting the statistical threshold.

## Discussion

In a large, healthy sample, we assessed the effects of functional polymorphisms in the COMT and the DAT1 gene, which regulate synaptic levels of DA in the brain and modulate central DA function. We hypothesized an interaction of the two prominent polymorphisms COMT Val158Met and DAT1 VNTR on individual differences in NEM as represented by the subscales Sadness, Anger, and Fear of the ANPS. This hypothesis was confirmed by a significant interaction of COMT Met and DAT1 10R leading to lowest scores on the personality dimension Sadness in carriers of the Val/Val and 9R/9R genotype configuration. The interaction on the dimension Fear was not significant but on a descriptive level a trend toward lower Fear levels of Val/Val and 9R/9R carriers was observed.

Previous studies supporting the “Yin and Yang principle of COMT Val158Met” showed that the Val/Val genotype, characterized by high enzyme activity leading to efficient dopamine clearance from the synaptic cleft (Chen et al. 2004), is associated with PEM (e.g., Bressan et al. 2002) whereas the Met allele is related to NEM (e.g., Drevets et al. 2001) and lower enzyme activity, resulting in elevated DA levels in the synaptic cleft. Also in the present study the observed significant main effect of the Met/Met genotype on Sadness supports the association of the Met allele with NEM. The

**Table 2.** ANCOVA results of COMT Met and DAT1 10R on all dimensions of the ANPS.

Personality Dimension of the ANPS	COMT Met		DAT1 10R		Interaction of COMT Met and DAT1 10R	
	$F(1,1018)$	$\eta^2$	$F(1,1018)$	$\eta^2$	$F(1,1018)$	$\eta^2$
Sadness	$F(1,1018) = 7.55, P = 0.006$	0.007	$F(1,1018) = 2.97, P = 0.085$	0.003	$F(1,1018) = 11.11, P < 0.001$	0.011
Fear	$F(1,1018) = 2.72, P = 0.10$	0.003	$F(1,1018) = 1.60, P = 0.21$	0.002	$F(1,1018) = 3.56, P = 0.06$	0.003
Anger	$F(1,1019) = 4.19, P = 0.04$	0.004	$F(1,1019) = 1.04, P = 0.31$	0.001	$F(1,1019) = 1.91, P = 0.17$	0.002
Seek	$F(1,1017) = 0.91, P = 0.34$	0.001	$F(1,1017) = 0.00, P = 0.97$	0.000	$F(1,1017) = 0.08, P = 0.78$	0.000
Care	$F(1,1017) = 0.49, P = 0.50$	0.000	$F(1,1017) = 0.03, P = 0.86$	0.000	$F(1,1017) = 0.22, P = 0.64$	0.000
Play	$F(1,1017) = 1.26, P = 0.26$	0.001	$F(1,1017) = 0.32, P = 0.57$	0.000	$F(1,1017) = 0.66, P = 0.42$	0.001
Spirituality	$F(1,1018) = 1.20, P = 0.27$	0.001	$F(1,1018) = .10, P = 0.75$	0.000	$F(1,1018) = 1.29, P = 0.26$	0.001

Degrees of freedom vary in the table, because not for all participants all questionnaire data of the ANPS subscales were available. Age was included as covariate.  $\eta^2$  = partial eta squared.

DA availability is further modulated through the occurrence of the individual DAT1 variant. The 9R/9R genotype corresponding to lower transcription rate and therefore lower amount of DAT1 protein results in higher DA levels through a slower reuptake of DA into the presynapse (VanNess *et al.* 2005). However, it has to be mentioned that a recent meta-analysis by Costa *et al.* (Costa *et al.* 2011) did not corroborate a significant association between the DAT1 VNTR and DAT1 availability in the striatum. Despite the heterogeneity between studies and the unknown mechanism how the polymorphism influences DAT1 expression affecting cognition and emotionality, the investigated genetic variants impact the personality dimension Sadness in the investigated sample. Interestingly, dependent on the rare 9R/9R genotype (10R-carriers), the Val/Val genotype (Met-carriers) influences personality toward less NEM. By contrast, the presence of at least one 10R allele seems to suppress the beneficial effect of the Val-allele on NEM. In order to illustrate this effect in terms of the explained variance of the Sadness scores, it is of interest that the main effect of the COMT SNP alone explains 0.7% of the variance. For the DAT1, no significant main effect was observed but at least a trend. Both effects like hypothesized, reduced Sadness in Met-carriers as well as in 10R-carriers. As postulated, the accumulation of both resilience factors for depression results in lowest Sadness scores and was visible in an interaction effect of both polymorphisms increasing the explained variance to 1.1%. This led us to the suggestion that only the combination of the previously independent with PEM-associated alleles (Met-/10R-) results in decreased NEM.

From a theoretical point of view, the genotype configuration 9R/9R (10R-) and Val/Val (Met-) that is related to the lowest Sadness scores, results in balanced DA levels due to lower reuptake (more DA in the synaptic cleft) in combination with faster degradation of DA (leading to an adaptation to the DAT1 10R-induced increase in synaptic DA levels). Of course, it is in general problematic to conclude on DA levels by taking into account only two DA polymorphisms even if COMT and DAT1 have great impact on DA levels due to their function in DA clearance. However, a balanced DA level as inferred from the DA transporter density and DA catabolism cannot be an explanation for the present results. The genotype configuration Met+/10R+ (low DA catabolism and high DA reuptake) that is related to high Sadness scores would theoretically result in balanced DA levels, too. This problem can be solved if we take the distribution of the proteins within the different brain regions into consideration. DAT1 is most abundantly expressed in the striatum and midbrain and COMT in the prefrontal cortex (PFC), where DAT1 is only marginally present (Sesack *et al.* 1998; Lewis *et al.* 2001). This raises the question if a direct interplay of both proteins in the regulation of DA neurotransmission with a strong dampening effect on NEM is dependent on a balanced DA level with

low DA levels in the PFC (Met-) and high DA levels in the striatum (10R-). This idea is corroborated by neuroimaging studies demonstrating the importance of DA gene variations in regulating brain circuitry involved in processing negative emotional stimuli (Prata *et al.* 2009). Several lines of evidence indicate that both cortical and subcortical regions are activated during the presentation of emotional stimuli (Zubieta *et al.* 2003) and are associated with Sadness and depression (Haber and Brucker 2009). A recent fMRI-study by Prata *et al.* (Prata *et al.* 2009) demonstrated significant epistasis between DAT1 and COMT genes on cortical activation during task-tapping executive functions in relation to schizophrenia, whereas the epistatic effect of DAT1 and COMT varied in different brain areas. For this reason they speculated that their findings possibly reflect expression and activity levels of the two proteins in different brain areas.

The present association study of COMT and DAT1 genetic variants on Sadness explains 1.1% of variance. To gain deeper insight into the contribution of DA genes on NEM, further work will focus on additional polymorphisms within these genes or others contributing to variability in DA function. A potential candidate is the DA catabolizing enzyme Monoamine Oxidase B (MAOB) that has also been associated with NEM before (Dlugos *et al.* 2009). Despite the high number of participants in this study, three-way interaction analyses of variance were not possible because they require an even larger sample size.

However, personality traits appear to be shaped by many genetic variants each making a small contribution. The issue of the relationship of genetic effects on personality variables to clinical conditions is well established for personality traits such as neuroticism (being shy, moody, anxious, and sad) representing a vulnerability factor for depression (Kendler and Myers 2010). Therefore, it is likely that this is also true for the Sadness dimension of the ANPS. Moreover, the question arises whether the continuum model for Sadness is applicable to a clinical relevant sample of depressed patients. In that case, carriers of the Val/Val and 9R/9R genotype configuration should show lower severity of depression in analogy to lower expression of Sadness in healthy subjects. We suggest that genotype configurations related to PEM are protective against NEM and therefore constitute a resilience factor against depression. Additionally, the postulated distribution of COMT and DAT1 variants resulting in balanced DA levels could be analyzed by fMRI studies in healthy and depressed subjects. The detection of functional and structural connectivity between the PFC and striatal areas dependent on the proposed genotype configurations would further support our findings. Differences between depressed patients and healthy controls reflecting alterations in DA function will shed light on the contribution and impact of COMT and DAT1 interaction in regional brain activation and implications for depression.

In conclusion, we found a significant interaction of COMT  $\times$  DAT1 on human personality. Thereby, the genotype constellation COMT Val/Val and DAT1 9R/9R showed lowest Sadness levels and therefore might consequently contribute to individual differences in risk and resilience for depression. Nevertheless, further research using molecular genetics and genetic imaging techniques will give insights into the precise neural mechanisms underlying the interaction of COMT and DAT1.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Correlation matrix for the dimensions Fear, Anger, Sadness, Seek, Care, and Play of the Affective Neuroscience Personality Scales.

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