

# COMT Genetic Variation Affects Fear Processing: Psychophysiological Evidence

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Emotional dysregulation is a core characteristic of many psychiatric diseases, including the anxiety disorders. Although heritable influences account for a significant degree of variation in risk for such disorders, relatively few candidate susceptibility factors have been identified. A coding variant in one such gene, encoding the dopamine catabolic enzyme catechol-O-methyltransferase (COMT Val158Met), has previously been associated with anxiety and with anxiety-related temperament and altered neural responses to affective stimuli in healthy individuals. In 96 healthy women recruited from a sample of 800 participants according to genotype, the authors tested for an association between the DRD2/ANKK1 Taq Ia, the COMT Val158Met, and a psychophysiological measure of emotion processing, the acoustic affective startle reflex modulation (ASRM) paradigm, and found that COMT genotype significantly affected startle reflex modulation by aversive stimuli, with Met158 homozygotes exhibiting a markedly potentiated startle reflex compared with Val158 carriers. A trait measure of anxiety (Gray's Behavioral Inhibition System; J. A. Gray & N. McNaughton, 2000) was also associated with ASRM. The functional polymorphism in the dopamine D2 receptor (DRD2/ANKK1 Taq Ia) had no effect on startle modulation. The findings support prior genetic and neuroimaging associations of the COMT 158Met allele to affective psychopathology and alterations in neural systems for emotional arousal and regulation.

*Keywords:* affective startle reflex modulation, DRD2/ANKK1 Taq Ia, COMT Val158Met, anxiety, BIS

Anxiety disorders—including panic disorder, generalized anxiety disorder, and phobias—are relatively common psychiatric diseases with significant negative consequences for quality of life and economic productivity in those afflicted (Breslau, Kendler, Su, Gaxiola-Aguilar, & Kessler, 2005; Hoffmann, Dukes, & Wittchen, 2006; Kessler et al., 1994). Furthermore, they show considerable comorbidity and, possibly, shared genetic liability with mood (Kendler et al., 1994; Moffitt et al., 2007; Roy, Neale, Pedersen, Mathe, & Kendler, 1995) and substance abuse disorders (Conway,

Compton, Stinson, & Grant, 2006; Ducci et al., 2007; Grant et al., 2004), making the anxiety disorders critical targets for both clinical intervention and susceptibility gene identification. Although evidence of heritability for anxiety disorders is modest to moderate (estimates range from 0.3 to 0.4; Hettrema, Neale, & Kendler, 2001), the identification and verification of specific genes that likely contribute to risk has been slow.

One promising, well-studied candidate is the gene *COMT*, encoding the dopamine catabolic enzyme catechol-O-methyltransferase (COMT). COMT is the major clearing step for dopamine in the prefrontal cortex (Gogos et al., 1998; Tunbridge, Bannerman, Sharp, & Harrison, 2004)—owing to the paucity of synaptically localized dopamine transporters in this region (Lewis et al., 2001; Sesack, Hawrylak, Matus, Guido, & Levey, 1998)—but it is also found subcortically, with high expression levels in the hippocampal formation (Matsumoto et al., 2003). *COMT* contains a common functional polymorphism resulting from a nonsynonymous G→A base pair substitution in the coding sequence of the gene, producing a valine→methionine substitution at position 158 of the membrane-bound allozyme that predominates in the brain (MB-COMT; position 108 of the soluble allozyme S-COMT; see review by Tunbridge, Harrison, & Weinberger, 2006). The 158Met form is less thermo-

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stable than the Val158 form and thus has lower activity at physiologically relevant temperatures (Lachman et al., 1996); in the brain, Met158 homozygotes have an approximate one-third diminution in activity compared with Val158 homozygotes (Chen et al., 2004).

Lowered COMT activity, resulting in higher concentrations of dopamine (Tunbridge et al., 2004), may have a salutary effect on cortical function: The Val158 (higher activity) allele is associated with prefrontal inefficiency during working memory and cognitive control as measured by neuroimaging (Blasi et al., 2005; Egan et al., 2001; Winterer, Egan, et al., 2006) and electroencephalography (Winterer, Musso, et al., 2006), with relatively poorer performance on prefrontally mediated tasks (Barnett, Jones, Robbins, & Muller, 2007; Goldberg et al., 2003; Jooper et al., 2002; Malhotra et al., 2002), and with schizophrenia—particularly in interaction with other schizophrenia risk genes (Nicodemus et al., 2007; Tunbridge et al., 2006). However, as both alleles are maintained at high levels in populations worldwide, it has been proposed that each confers an environment-specific selective advantage—representing a trade-off between cognitive efficiency and emotional resiliency (Goldman's "warrior/worrier" model; Goldman, Oroszi, & Ducci, 2005). This model has developed from findings that suggest that the Met158 allele is linked to poor emotion regulation: in particular, associations of the Met158 allele to anxiety disorders (Domschke et al., 2004; Enoch, Xu, Ferro, Harris, & Goldman, 2003; McGrath et al., 2004; Olsson et al., 2005, 2007; Woo et al., 2004), anxiety-related traits including high neuroticism and low sensation seeking and extraversion (U. E. Lang, Bajbouj, Sander, & Gallinat, 2007; Reuter & Hennig, 2005; Reuter, Schmitz, Corr, & Hennig, 2006; Stein, Fallin, Schork, & Gelernter, 2005), obsessive-compulsive disorder (Pooley, Fineberg, & Harrison, 2007), and increased pain sensitivity (Diatchenko et al., 2005). However, it must be noted that such associations are not entirely consistent, with negative findings reported for each.

Effect sizes for single genetic variants associated with psychiatric illnesses are generally small; however, penetrance tends to increase as one studies quantitative biological traits that are closer to the level of a variant's putative direct physiological effect (Meyer-Lindenberg & Weinberger, 2006). Therefore, one promising approach is the interrogation of candidate risk variants using neuroimaging and psychophysiological intermediate phenotypes. Such tools may allow a preliminary understanding of the specific neural mechanisms by which risk variants exert their deleterious effects. Three neuroimaging studies to date have shown that the COMT Val158Met genotype affects functional activation and connectivity within critical neural circuits for affective arousal and regulation. Smolka et al. (2005) found that the Met158 allele was associated in an allele dose-dependent manner with exaggerated limbic and prefrontal engagement in response to aversively valenced pictures. This same group found an additive interaction between genotypes at the COMT Val158Met locus and the serotonin transporter-linked promoter polymorphism (5HTTLPR) on an functional MRI measure of aversive emotion processing (Smolka et al., 2007). The Met158 allele is also associated with increased hippocampal and ventrolateral prefrontal activation while viewing angry and fearful facial expressions; these regions showed augmented functional connectivity in Met158 homozygotes, the magnitude of which negatively predicted scores on a

temperamental measure of flexibility (Cloninger's Novelty Seeking; Drabant et al., 2006).

Here, we use a psychophysiological paradigm (affective startle reflex modulation, or ASRM) to characterize the impact of genetic variation in COMT on emotion processing. The startle reflex involves a set of involuntary responses to a sudden, intense stimulus (often a high-intensity white noise of very short duration), measured in humans by recording the amplitude of the eyeblink reflex, consisting of a rapid contraction of the orbitalis oculi muscle (Anthony, 1985; Berg & Balaban, 1999). ASRM describes a well-replicated phenomenon (see Grillon & Baas, 2003, for review) whereby the amplitude of the startle reflex is modified by the presentation of affective stimuli, often slides depicting scenes of different emotional valence. Such modulation is valence specific, with aversive scenes potentiating and appetitive scenes attenuating startle amplitude compared with neutral scenes (Bradley, Codispoti, Cuthbert, & Lang, 2001; Bradley, Cuthbert, & Lang, 1993; Vrana, Spence, & Lang, 1988). Lang and colleagues have suggested that startle is a protective reflex produced by a defensive motivational system. In this scheme, aversive pictures—particularly those depicting fear or threat (Balaban & Taussig, 1994)—induce an emotional state that acts to prime this defensive system, enhancing the startle reflex (P. J. Lang, Bradley, & Cuthbert, 1990, 1997).

Mounting evidence has suggested that ASRM may index individual differences in emotion processing, particularly with respect to both clinically diagnosed anxiety and temperamental traits associated with risk for anxiety disorders. Two groups have found exaggerated startle responses to unpleasant pictures in patients with anxiety (Kaviani et al., 2004; Larson, Nitschke, & Davidson, 2007). In addition, potentiated startle to aversive pictures has been shown in individuals scoring low on trait measures of sensation seeking (Lissek & Powers, 2003) and those scoring high on measures of behavioral inhibition (Caseras et al., 2006; Hawk & Kowmas, 2003), neuroticism (Chan, Goodwin, & Harmer, 2007), and fearfulness (Cook, Davis, Hawk, Spence, & Gautier, 1992; Cook, Hawk, Davis, & Stevenson, 1992).

In this study, we examined the impact of the COMT Val158Met polymorphism on ASRM. Given prior associations of the Met158 allele to anxiety, anxiety-related traits, and augmented limbic response to unpleasant stimuli, we hypothesized that individuals carrying a Met158 allele would show greater startle (i.e., larger startle amplitude) relative to individuals carrying a Val158 allele during the presentation of aversive pictures. We also tested for a main effect of the DRD2/ANKK1 Taq Ia polymorphism (a polymorphism that turned out to be located <10 kb downstream of DRD2 within a protein-coding region, exon 8, of the adjacent ANKK1 gene [Neville, Johnstone, & Walton, 2004]; the DRD2/ANKK1 Taq Ia single nucleotide polymorphism was associated with reduced D2 receptor density [Jonsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003]) on our measure of ASRM, and for an epistatic interaction between COMT Val158Met and DRD2/ANKK1 Taq Ia, previously demonstrated to be associated with behavioral measures of cognitive function (Reuter et al., 2005) and aspects of temperament (Reuter et al., 2006) on affect-modulated startle. Last, we examined the impact of individual differences on a measure of behavioral inhibition (Gray's Behavioral Inhibition System; Gray & McNaughton, 2000), a trait previously linked to individual differences in the

structure and function of brain regions implicated in affective response and affect-modulated startle (Barros-Loscertales et al., 2006), on ASRM.

## Method

### Participants

Ninety-six Caucasian female participants of German origin were recruited out of a genetic data bank (the Giessen Gene Brain Behavior Project, or GGBBP) of more than 800 healthy participants. The GGBBP is a project of the University of Giessen investigating the molecular basis of individual differences in behavior (e.g., processing of emotions, cognitive functioning, and personality). At the core of the project is a gene data bank that allows recruitment of participants according to polymorphisms on candidate genes for experimental testing. After entry into the GGBBP, every participant is routinely genotyped for several candidate gene loci including COMT Val158Met and DRD2/ANKK1 Taq Ia. There are no principal exclusion criteria for participation in GGBBP, although some studies, like this one, exclude participants with psychopathological symptoms. The largest part of the gene data bank (about 80%) consists of students. The remaining 20% are participants from the normal population who were recruited for specific studies within the framework of the GGBBP. Recruitment of participants for the present study was conducted in psychology classes of the University of Giessen.

Ninety-six Caucasian female participants of German origin (mean age = 22.11 years,  $SD = 3.29$ , range = 17–38 years) were recruited according to their genotype/allele pattern, resulting in six independent groups (COMT: VAL/VAL, VAL/MET, and MET/MET  $\times$  DRD2/ANKK1 Taq Ia: A1- or A1+) of 16 participants each. Participants were considered to be healthy when they did not report having a psychopathological or neurological disease on a simple self-report questionnaire (which we set up), which was administered along with the German version of the Carver and White (1994) Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) questionnaire (Strobel, Beauducel, Debener, & Brocke, 2001; for more information on the questionnaire, see below). In addition, this questionnaire asked about recent sleep irregularities, drug abuse, and menstrual cycle. All participants of the study were inconspicuous as to sleep, drug abuse, or psychotropic medication. Smoking status, alcohol intake, and age had no influence on the results of our study.

Effects of the menstrual cycle on the startle reflex were controlled by selectively inviting the participants who were within the range of the 2nd to 4th day after onset of menstruation. In this time window, concentrations of sex steroids and their releasing hormones is extremely low and therefore the influence on the startle reflex should be smallest.

Because most GGBBP participants are female psychology students, we invited only female participants. Otherwise, many more participants would have been needed to control for possible gender effects. Before participating in the experiment, participants were genotyped for the COMT Val158Met and DRD2/ANKK1 Taq Ia polymorphisms. Participants were invited to the experiment after this a priori genotyping, were informed about the general aims of the study (“processing of emotions anxiety/fear depending on candidate gene loci”), and gave written consent. The study was

approved by the ethics committee of the German Psychological Association. After the experiment, all participants were informed in detail about the paradigm used in the study and received course credit for joining the study. In Germany, students have to participate in approximately 15 experiments besides writing tests and attending classes before getting admission to their final exams. This “testing after a priori genotyping” approach increases the statistical power and guarantees a balanced cell frequency in the study design, which is advantageous if the prevalence of certain gene-allele configurations is seldom in the population (Reuter et al., 2006). In total, 101 participants were originally recruited but 5 participants—showing an inadequate startle reflex (nondetectable amplitudes)—were excluded from analyses. We refer to these 5 participants as nonresponders. Their detectable amplitude in reflex to the pulse was near 0  $\mu$ V.

### Procedure

Participants were seated in a chair in front of a computer. For electromyographic measures, electrodes were attached under the left eye over the musculus orbicularis oculi. A ground electrode was attached to the left mastoid. The participants were instructed to watch pictures alternating in valence on a 17-in. (43.2-cm) computer screen. The distance between the participant’s head and the computer screen was 1 m. Participants wore earphones (Sennheiser HD 201), over which the startle probes and the pre-pulses were binaurally administered.

The experiment began with five test startles, used to check the correct functioning of the electrodes. Conditions were administered in randomized order. The pulse-alone condition consisted of 12 startle probes (white noise, 106 dB, 35 ms duration, 5 ms risetime) with an interstimulus interval of 15–25 s. The ASRM paradigm consisted of 12 pleasant, 12 unpleasant, and 12 neutral pictures (duration 6 s, onset of startle probe randomized 2.5–5.5 s after onset of the pictures) and an interstimulus interval of 15–25 s. The onset of the startle probe was balanced over the different picture conditions.

Pictures used in the emotional startle paradigm were taken from the International Affective Picture System (P. J. Lang, Bradley, & Cuthbert, 1999). The affectively valenced pictures were chosen on the basis of affective valence and arousal ratings by a normative sample. Animal, baby, and family photos were chosen as pleasant stimuli. Neutral stimuli were, for example, a photo of a power outlet or a hair dryer. Unpleasant stimuli consisted of pictures depicting fear or threat, such as weapons or injured victims at a crime scene.

### Apparatus

The eyeblink elicited by the startle pulse was measured with the module V75-04 isolated bioamplifier with band pass filter from the device LabLink V System (Coulbourn Instruments, Allentown, PA). The electromyograph signal was digitized at a 1000-Hz rate and band pass filtered (13–1000Hz). Impedance level was kept below 10 k $\Omega$ . Ag-AgCL electrodes with 4-mm inner diameter were used to measure the startle reflex of the eyelids. The startle was produced via the soundcard Creative Labs CT4810. Windaq software (DATAQ Instruments, Akron, OH) was used to record and analyze the eyeblink data.

### Data Reduction and Analysis

The intensity of the startle reflex in microvolts was read off the graphs in Windaq. The minimum and maximum peaks of the startle amplitude in a time window of 20–140 ms after the pulse were identified. Participants with a startle reflex lower than 0.1  $\mu$ V were excluded from further analyses ( $n = 5$ ). To minimize the chance of contaminated ASRM values through overall startle magnitude, we calculated not only the raw startle reflex but also the percentage modulation scores, considered to be the gold standard (Hawk & Kowmas, 2003; Ison, Bowen, Pak, & Gutierrez, 1997). Percentage ASRM was computed as [(pulse with pleasant picture – pulse alone)/pulse alone]  $\times$  100. The same was conducted for the neutral and unpleasant picture condition.

Analyses of variance (ANOVAs) were calculated to test the effect of picture condition on startle reflex. Pairwise contrasts between conditions were tested via  $t$  tests. The influence of the two polymorphisms on ASRM was calculated by multivariate analyses of variance (MANOVAs). The influence of Gray's personality dimensions BIS/BAS on both paradigms was investigated by Pearson correlations. Potential interactions between polymorphisms and personality variables on ASRM were also computed by MANOVAs. For interaction analyses, we divided participants into "high" and "low" BIS and BAS groups using a median split. To correct for multiple comparisons (Bonferroni), we set alpha equal to .008 (.05/6 [2 polymorphisms  $\times$  3 experimental conditions]). All statistical analyses were conducted by using SPSS 11.5 for Windows, and the graphics were made with Origin 7.5 for Windows.

### Measurement of BIS/BAS

Participants completed the German version of the BIS/BAS questionnaire that has been shown to have good psychometric criteria (Strobel et al., 2001). This self-report measure consists of 20 items, scaled on a 4-point Likert scale. The BIS is measured by 7 items and the BAS by 13 items. The BIS scale is associated with negative emotionality and builds the core of Gray's reinforcement sensitivity theory, investigating the genesis of anxiety. The BAS scale reflects individual differences in the behavioral activation system, a motivational approach system located in the dopaminergic mesolimbic system, which is associated with positive emotionality. The BAS scale consists of three subscales measuring one's intrinsic drive to achieve things, differences in looking for pleasure activities and responsiveness to reward.

### Genetic Analyses

DNA was extracted from buccal cells to avoid a selective exclusion of participants with blood and injection phobias. 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 two single nucleotide polymorphisms was performed by real-time polymerase chain reaction using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). Details of the polymerase chain reaction protocols are described elsewhere (Reuter et al., 2006). The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) were as follows:

For COMT VAL158MET,

Forward primer: 5'-GGGCTACTGTGGCTACTCA-3'

Reverse primer: 5'-GGCCCTTTTCCAGGTCTG-3'

Anchor hybridization probe: 5'-LCRed640-TGTGCATGCC TGACCCGTTGTCA-phosphate-3'

Sensor hybridization probe: 5'-ATTTCGCTGGCATGAAG GACAAG-fluorescein-3'

For DRD2/ANKK1 Taq Ia,

Forward primer: 5'-CGGCTGGCCAAGTTGTCTAA-3'

Reverse primer: 5'-AGCACCTTCCTGAGTGTATCA-3'

Anchor hybridization probe: 5'-LCRed640-TGAGGATGGC TGTGTTGCCCT-phosphate-3'

Sensor hybridization probe: 5'-CTGCCTCGACCAGCACT-fluorescein-3'

## Results

### ASRM

All picture–pulse conditions in ASRM showed a significant increase in the startle response in contrast to the pulse-alone condition: pulse alone versus unpleasant picture condition,  $t(95) = -3.29$ ,  $p < .001$ ; pulse alone versus pleasant picture condition,  $t(95) = -2.51$ ,  $p < .02$ ; and pulse alone versus neutral picture condition,  $t(95) = -3.47$ ,  $p < .001$ . There was no significant difference between picture–pulse conditions,  $F(2, 285) = 0.371$ ,  $p = .69$ .

### COMT Val158Met, DRD2/ANKK1 Taq Ia, and ASRM

With respect to the dopaminergic gene loci, results revealed a significant influence of the COMT genotype on the startle reflex in response to the unpleasant picture condition,  $F(2,93) = 6.38$ ,  $p < .003$  (Figure 1). Contrasting COMT allele groups, we found that Met/Met individuals had an exaggerated startle response compared with Val-allele-carrying participants,  $F(1,94) = 12.59$ ,  $p < .0006$ . Moreover, Met-allele homozygotes showed a trend for potentiated startle response during the presentation of neutral pictures,  $F(1, 94) = 4.89$ ,  $p < .029$ ; however, this effect did not survive correction for multiple comparisons. COMT had no effect on the startle modulation in the pleasant condition. There was no main effect of DRD2/ANKK1 Taq Ia and no interaction between DRD2/ANKK1 Taq Ia and COMT on ASRM regardless of the affective condition.

### Personality and ASRM

The BIS dimension correlated significantly negative with ASRM in the unpleasant picture condition ( $r = -.28$ ,  $p < .006$ ) and in the pleasant picture condition ( $r = -.24$ ,  $p < .02$ ). No significant correlations between BAS and ASRM were found.

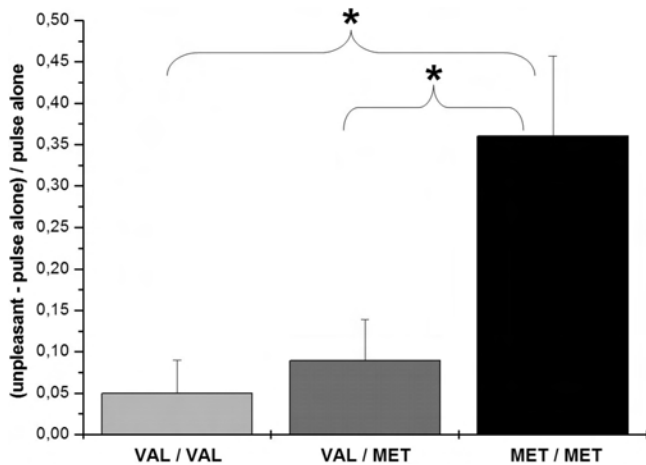


Figure 1. COMT Val158Met and the affective startle reflex modulation in the unpleasant condition. The x-axis is divided up into the three different genotypes of the COMT Val158 Met polymorphism. On the y-axis, the magnitude of the startle reflex (defined as [unpleasant condition – pulse alone condition]/pulse alone condition) is scaled in microvolt units. In contrast to the Val+ group (Val/Val or Val/Met), the Val– group (Met/Met) responds with a significantly potentiated startle to the pulse in the unpleasant picture condition: genotype level,  $F(2, 93) = 6.38, p < .003$ ; Val allele level,  $F(1, 94) = 12.59, p = .001$ . Post hoc comparisons: \*  $p < .05$ .

#### Personality, COMT Val158Met, DRD2/ANKK1 Taq Ia, and ASRM

MANOVA revealed no interaction effects between BIS/BAS score and genotype on ASRM.

#### Post Hoc Analyses

Given prior associations of the Met158 allele to negative affect and our current finding that COMT genotype and BIS score both have an impact on startle, we wondered whether Val158Met genotype was specifically associated with BIS score in our sample. To answer this question, we dichotomized participants into high (BIS+) and low (BIS-) BIS groups on the basis of a median split and used a chi-square test. In accordance with our hypothesis and the findings of Reuter and Hennig (2005), the frequency of BIS+ was higher in the Val– group (genotype Met/Met) than in the Val+ group, but the chi-square test barely missed significance,  $\chi^2(1, N = 96) = 3.19, p = .058$  (Figure 2), presumably due to a lack of power.

Analysis of variance revealed that COMT and BIS score exert additive effects on startle magnitude while viewing aversive pictures. Both factors together accounted for 13.6% of the variance in ASRM: COMT variation explained 8.9% of the variance and BIS explained 4.7%.

#### Conclusions

The aim of this study was to explore individual differences in the regulation of emotions by using a molecular genetic approach combined with a well-established psychophysiological measure of fear processing, the ASRM. Given prior findings that have suggested that genetic variation in dopamine signaling is a significant

risk factor for affective psychopathology and negative emotionality, our first hypothesis investigated the influence of two functional polymorphisms in dopamine signaling pathway genes (COMT Val158Met and DRD2/ANKK1 Taq Ia) on ASRM. Second, we tested for an association between ASRM and individual differences on a measure of behavioral inhibition (Gray's BIS), a trait that is strongly correlated with neuroticism, negative affect, and anxiety symptom severity (Campbell-Sills, Liverant, & Brown, 2004); has been linked to individual differences in the structure and function of the prefrontal cortex, amygdala, and hippocampus (Barros-Loscertales et al., 2006; Cools et al., 2005); and predicts psychophysiological responsiveness to affectively arousing stimuli (Keltikangas-Jarvinen, Kettunen, Ravaja, & Naatanen, 1999).

We found a significant effect of COMT genetic variation on innate fear processing. Met158-allele homozygotes demonstrated markedly greater probe responses in the unpleasant picture condition compared with Val-allele carriers. The DRD2/ANKK1 Taq Ia polymorphism did not significantly affect ASRM in any of the picture conditions. The positive association between COMT and ASRM accords with several recent studies that have demonstrated a link between the Met158 allele and alterations in neural circuitry for affective response (Drabant et al., 2006; Smolka et al., 2005, 2007). For example, using functional MRI, Drabant and colleagues (2006) found an exaggerated response in Met homozygotes to fearful and angry facial expressions in the hippocampus, a region that highly expresses COMT mRNA and protein (Chen et al., 2004; Matsumoto et al., 2003). In that study, Met/Met individuals also demonstrated elevated functional connectivity between hippocampus and ventrolateral prefrontal cortex; the degree of

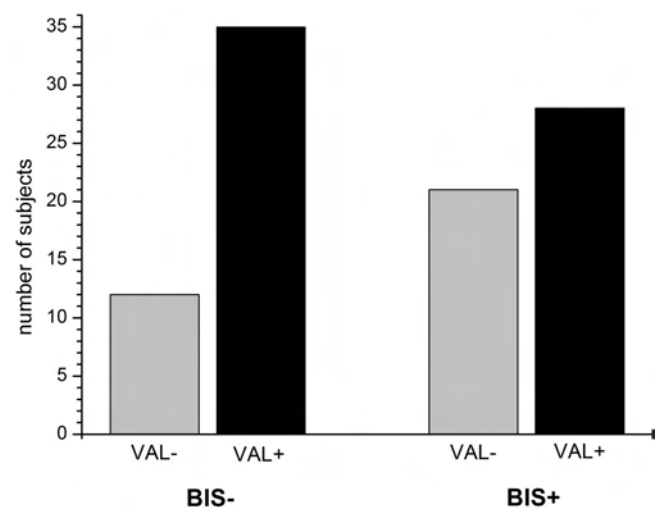


Figure 2. Distribution of the genotype frequencies of Val– (Met/Met) and Val+ (Val/Met and Val/Val) in the dichotomized groups of participants scoring low (BIS–) and high (BIS+) on the BIS measured by Carver and White's (1994) BIS/BAS questionnaire ( $N = 96$ ). On the x-axis, the different genotypes of COMT Val158Met polymorphism are depicted according to BIS– or BIS+ group membership. The y-axis presents the number of participants. Carriers of the homozygous Met/Met genotype (Val–) scored on BIS more often high than carriers of the Val allele (Val+). Presumably due to a lack of power, the chi-square test barely missed significance,  $\chi^2(1, N = 96) = 3.19, p = .058$ . BIS = Behavioral Inhibition System; BAS = Behavioral Activation System.

connectivity in turn negatively predicted scores on a trait measure of emotional rigidity.

On the basis of these and other findings, we propose that the potentiated startle reflex seen here in Met/Met participants may reflect the impact of relatively increased limbic dopamine levels on affective processing. Although the neural mechanisms underlying ASRM are not well elaborated, preclinical, pharmacological, and neuroimaging findings suggest that dopamine signaling in limbic structures may critically regulate affect-modulated startle. One functional imaging study to date has examined the neuroanatomical substrates of ASRM: Using positron emission tomography, Pissioti et al. (2003) found amygdala/hippocampal activation during the modulation of startle by aversive stimuli. In addition, damage to the medial temporal lobe diminishes startle potentiation to negative pictures (Buchanan, Tranel, & Adolphs, 2004; Funayama, Grillon, Davis, & Phelps, 2001). This accords well with a wealth of studies that have shown that the amygdala critically mediates the link between perceiving fearful, anxiogenic, or otherwise aversive stimuli and the organization and execution of defensive behaviors, including the startle reflex (Grillon & Baas, 2003; Phelps & LeDoux, 2005; Zald, 2003). It is well known from preclinical work that the response of this region to affective stimuli is modulated by dopamine (Grace & Rosenkranz, 2002; Kroner, Rosenkranz, Grace, & Barrionuevo, 2005; Rosenkranz & Grace, 1999, 2002); furthermore, limbic response to unpleasant stimuli is amplified in humans following the administration of the nonspecific dopaminergic agonist amphetamine (Hariri et al., 2002) and diminished in individuals with Parkinson's disease (Tessitore et al., 2002). Of note, a recent report by Bowers and colleagues (2006) found attenuated startle responses to aversive stimuli in Parkinson's patients.

With respect to COMT genotype, putatively elevated hippocampal and amygdala dopamine in Met158 homozygotes may enhance the salience of environmental threat cues, as we suggest is evidenced in their potentiated startle response to the aversive stimuli presented in the current study. This conclusion could be derived from findings of genetic imaging studies (Drabant et al., 2006; Smolka et al., 2007) investigating the neuronal response to emotional stimuli depending on the COMT Val158Met polymorphism. Met/Met carriers showed an augmented corticolimbic connectivity, which also encompasses the structures amygdala and hippocampus.

Alternatively or in addition, elevated dopamine in the prefrontal cortex could result in an inflexible attentional focus on aversive stimuli. Bilder, Volavka, Lachman, and Grace (2004) have made the intriguing proposal that risk for affective illness in Met158 homozygotes stems from a derangement in the balance of tonic and phasic dopamine signaling in prefrontal cortex. According to this model, attenuated clearing of extrasynaptic dopamine may strengthen the stability of prefrontal representations while diminishing cognitive flexibility. Diminished capacity to update and shift attentional focus may lead to affective perseveration, whereby inappropriate prefrontal representations of threat persist in spite of newer information signaling safety. Thus, a bias in affective processing, combined with augmented cognitive stability and diminished cognitive flexibility associated with the Met158 allele (Nolan, Bilder, Lachman, & Volavka, 2004; Winterer & Weinberger, 2004), may impair disengagement of attentional resources from perceived sources of threat. This notion is supported by Drabant and colleagues' (2006) finding that augmented corticolimbic con-

nectivity in Met/Met participants predicted higher temperamental rigidity. Such a mechanism might underlie clinical associations of the Met158 allele to anxiety and aggression (Enoch et al., 2003; Jones et al., 2001; Rujescu, Giegling, Hartmann, & Moller, 2003; Strous et al., 2003; Volavka, Bilder, & Nolan, 2004).

Our second hypothesis concerned the influence of individual differences in behavioral inhibition on ASRM. We found that BIS scores were negatively correlated with startle amplitude in both picture conditions. This finding supports the revised reinforcement sensitivity theory (RST; Gray & McNaughton, 2000). The RST was revised to account for animal learning data that suggested a critical role for the septohippocampal system in the development and expression of anxiety. In its original formulation, RST consisted of a reward system (BAS) sensitive to conditioned signals of reward, a punishment system (BIS) that reacts to conditioned signals of punishment and frustrative nonreward, and a threat response system (the fight/flight system, or FFS). The revision of the model in Gray and McNaughton (2000) construed BAS as responding to all appetitive stimuli and FFS (in the revised model, the fight/flight/freezing system, or FFFS) as responding to all aversive stimuli. The BIS was reconceived as sensitive to signals that engender conflict or uncertainty, interrupting ongoing behavior and calling the BAS (to approach) or FFFS (to avoid) the stimulus on the basis of further evaluation of its reinforcement value. Thus, BIS can be conceived of as a conflict-detection and resolution system, with uncertainty arising from the activation of this system by ambiguous stimulus leading to the expression of anxiety.

In our study, participants scoring high on a trait measure of BIS showed startle potentiation in the positive and the negative picture conditions. The revised RST may offer an explanation for this finding. We suggest that the organization of our ASRM paradigm created a scenario of high uncertainty, as highly arousing novel pictures were presented at random. Alternatively, the simultaneous presentation of an aversive pulse and a negative picture might have created an avoidance-avoidance conflict, whereas presentation of the pulse during positive picture viewing may have led to an approach-avoidance conflict. Both kinds of conflict activate the BIS and have been suggested to engender a state of anxiety (Gray & McNaughton, 2000; Smillie, Pickering, & Jackson, 2006). Startle reflex modulation has been proposed to reflect the activity of a defensive (fear) system (Bradley et al., 2001). However, given the association between BIS score (putatively reflecting individual differences in an anxiety system) and startle shown here, we suggest that separable aspects of both fear and anxiety are involved in the startle response.

In summary, using a well-validated psychophysiological measure in a large sample of healthy individuals, we show the COMT Val158Met polymorphism critically regulates innate fear processing. The present data accord well with prior studies that have shown an association between the Met158 allele and anxiety-related psychopathology. In line with previous findings, we show here that Met-allele carriers are characterized by an exaggerated reaction to aversive stimuli. The potentiation of negative emotion processing in these individuals may underlie their increased risk for developing anxiety disorders. The personality dimension BIS, which indexes heritable variation in anxious temperament, responds to both appetitive and aversive stimuli, supporting a revised RST that postulates a distinct brain circuit for the processing of

stimuli eliciting conflict and uncertainty. Together, these findings show that genetic variation in COMT underlies individual differences in affective arousal and validates the use of ASRM as an endophenotype measure in future studies of genetic risk for anxiety. A limitation of this study is the rough screening for psychopathological disorders, which could be improved by a structural interview with guidelines by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994).

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