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Interaction Effects of the *COMT* and *DRD4* Genes with Anxiety-Related Traits on Selective Attention

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Abstract. The study investigated whether the *DRD4* and *COMT* genes can modify relations between trait anxiety and selective attention. Two hundreds and sixty-six subjects performed a visual search task in which they had to find words looking through a sheet with rows of letters. After finishing the first sheet the subject was presented the second one, this time with an instruction to perform the task as quickly and accurate as possible. To study top-down attention, the number of correctly identified words (accuracy) and the time for completion of each trial were analyzed. To study bottom-up attention, the letters 'o' and 'n' were written in green, whilst the others were in black, and subjects were asked whether they had noticed that 2–3 minutes after the task completion. Genotypes for the *COMT Val158Met* and *DRD4 VNTR-48* polymorphisms and TCI Harm Avoidance and MMPI Depression scales' scores were obtained as well. High anxious individuals showed a more pronounced increase in accuracy in the second trial and more profound processing of irrelevant stimuli (colored letters). There was a significant interaction effect of *DRD4* and Harm avoidance on the accuracy dynamics $F(1, 210)$, = 7.65, p = .006, η^2 = .04. Among *DRD4* long allele carriers, high anxious subjects significantly improved accuracy (p = .013) and tended to slow speed, while those with lower Harm avoidance demonstrated the opposite trend. These effects were more robust in less educated individuals. It was concluded that the *DRD4* polymorphism may modify the influence of trait anxiety on the speed-accuracy tradeoff.

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There is a wealth of studies documenting anxiety effects on cognitive functions. Anxiety has been shown to be associated with a tendency to interpret ambiguous information in a mood-congruent manner, which in turn may produce biases in estimating the likelihood of future events and finally in decision making. Behind such a cascade of events lay anxiety effects on basic cognitive processes. In particular, the central executive component of working memory, especially its inhibition and shifting functions, and spreading activation in semantic memory have been proposed to play a key mediating role in relations between anxiety and the higher level cognitive processes (see Blanchette & Richards, 2010; Derakshan & Eysenck, 2010; Gable & Harmon-Jones, 2010 for reviews). According to the attentional control theory (ACT) and its antecedent - the processing efficiency theory (Eysenck, Derakshan, Santos, & Calvo, 2007; Eysenck & Calvo, 1992), anxiety alters the balance between goal-directed (top-down) and stimulus-driven (bottom-up) attention in favor of the latter. It is also assumed that anxiety diminishes processing efficiency, i.e. increases brain costs of task performance, but may not influence performance effectiveness, if individuals allocate additional processing resources (effort) and use compensatory strategies to maintain a desirable level of performance. However, there is a lack of empirical data concerning a difference between state and trait anxiety impact on cognitive processes. It has been recently argued that trait anxiety is related to deficiencies in the executive control attentional network, while state anxiety is associated with hyperactivity of the alerting and orienting networks (Pacheco-Unguetti, Acosta, Callejas, & Lupianez, 2010).

Consistent with ACT, neuroimaging studies demonstrated that high-anxious individuals had to invest more cognitive (compensatory) efforts in task performance which manifested itself as an increased task-related activation of the prefrontal cortex (PFC) (Ansari & Derakshan, 2011; Basten, Stelzel, & Fiebach, 2011; Eisenberger, Lieberman, & Satpute, 2005). At the same time, the reduced sustained activity of the PFC in high-anxious individuals was reported. This was interpreted as an aversive effect of trait anxiety on brain mechanisms of attentional control (Bishop, 2009; Fales et al., 2008). It may be assumed that the discrepancies between studies are explained partly by baseline individual differences in prefrontal functioning. These differences depend, to a considerable degree, on genetic

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polymorphism of the dopaminergic system regulating PFC neuronal activity. In particular, prefrontal functions are influenced by polymorphism of the gene coding for catechol-O-methyltransferase (COMT). This enzyme catalyzes dopamine degradation to 3-methoxytyramine thereby inactivating dopamine after its release in the synaptic cleft. COMT is thought to be particularly critical for regulating dopamine signaling in the PFC due to the scarcity of dopamine transporter in this region.

The human COMT gene is located on the chromosomal region 22q11.1-q11.2. Among polymorphic markers lying within this site, a polymorphism commonly known as *Val158Met (rs4680)*, which corresponds to a G to A transition at nucleotide 472 in exon 4 of the *COMT* gene and results in a valine to methionine substitution at the 158 locus of the peptide sequence, has received the most attention. The substitution causes alterations in COMT enzymatic activity by influencing enzyme thermostability. The *Met* allele is associated with lower COMT activity and is therefore thought to lead to higher extrasynaptic dopamine levels in the PFC than the *Val* allele (Lachman et al., 1996; Tunbridge, Harrison, & Weinberger, 2006). There is evidence that the *Met* allele is related to superior performance in PFC-dependent tasks including measures of working memory and sustained attention and is associated with higher IQ (Barnett, Scoriels, & Munafo, 2008; Blasi et al., 2005; Egan et al., 2001; Tunbridge et al., 2006). Neuroimaging data indicate that *Met*-carriers exhibit lower PFC activity during cognitive tasks compared to Val-carriers, suggesting more efficient processing in the former group (Blasi et al., 2005; Egan et al., 2001).

A *DRD4* gene polymorphism may represent another important factor of variability of dopaminergic signaling in the brain. D4 receptors are widespread in the PFC, including regions of the anterior cingulate cortex related to error-monitoring and inhibition control, as well as in some limbic structures involved in motivation. The *DRD4* gene is located on the chromosomal region 11p15.5. A *VNTR*-polymorphism in exon 3 of the gene is represented by a variable number of 48-bp repeated sequences. Allelic variants with 2–11 imperfect copies of the repeat have been reported. In European populations, the most prevalent alleles are those with 4 (67%) and 7 (12%) repeats (Petronis, Van Tol, Lichter, Livak, & Kennedy, 1993). Shorter alleles (2–5 repeats) are considered to be more efficient with regard to transcription and DRD4-mediated inhibitory postsynaptic effects (Ebstein, 2006). Association studies indicate that longer alleles (6 or more repeats), and the *7R* allele in particular, are related to extraversion, novelty seeking, and impulsivity, i.e. to domain of approach-related traits, although a recent meta-analysis does not provide support for significant associations between the *DRD4 VNTR* polymorphism and this personality dimension (Munafo, Yalcin, Willis-Owe, & Flint, 2008). Moreover, there is evidence that the *7R* allele is associated with attention deficit hyperactivity disorder (Li, Sham, Owen, & He, 2006). It is therefore expected that carriers of the *7R* allele compared to those without this allele should show greater cognitive impulsiveness manifesting as faster and less accurate responses in attention tasks (Kieling, Roman, Doyle, Hutz, & Rohde, 2006; Langley et al., 2004).

The data reviewed above suggest that the *COMT* and *DRD4* genes could modify anxiety impact on attentional control. We hypothesized that their influence would show itself in effects of interaction with anxiety-related traits on top-down and bottom-up attention during visual search.

Method

Participants

A total of 266 participants, aged between 16 and 67 years (M = 30.8 years; SD = 11.3; 157 females and 109 males, 184 subjects having or receiving higher education and 82 subjects with secondary education), took part in the study. All subjects were ethnically Russians from Moscow and the surrounding region. Exclusion criteria were psychiatric, neurologic and other serious medical conditions, and education less than 9 grades. Each subject gave written informed consent to take part in the study. The research was approved by the Ethics Committee of the Mental Health Research Centre.

Anxiety and attention measures

Subjects were asked to donate biological samples for DNA extraction and to undergo examination which included assessment of cognition and personality (see Alfimova et al., 2009 for more detailed description of the assessment battery). As part of the cognitive session, subjects completed a selective attention task, which was a modified Munsterberg test. In this test, the subject had to find and name words looking through sheets with rows of letters, initially at any desired rate and then at the highest possible one (Figure 1). In contrast to the original version of the task, each row contained a different number of words, and words' length varied from 2 to 8 letters. The letters 'o' and 'n' were written in a dark-green color, whilst the others were in black. After finishing the first sheet (Trial 1), the subject was shown 2–3 words he/she had missed as a negative feedback. Then he/she was presented the second sheet with an instruction to perform the task as quickly and accurate as possible (Trial 2). Two-three minutes after completion of the second sheet, the subject was asked if he/she had noticed what colors the letters were. Where there was a correct answer, he/she was asked to remember which letters exactly were in green.

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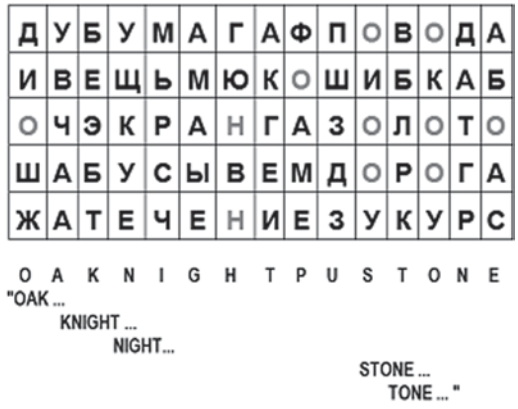

Figure 1. The modified version of Munsterberg's test, in which subjects have to search for words among letters.

To assess top-down attention, we used the number of correctly identified words during each trial (Accuracy 1 and Accuracy 2) and the time for completion of each trial (Time 1 and Time 2). Errors were not analyzed as they were rare. To study bottom-up attention, answers about green letters were assessed in points (0 - *did not notice the color*, 1- *noticed that some letters were green*, 2 - *named the color and one of the green letters*, 3- *named the color and both letters*).

Anxiety related traits were assessed with the Harm Avoidance (HA) scale of Cloninger's Temperament and Character Inventory-125 (TCI-125) and the Depression scale of the Minnesota Multiphasic Personality Inventory (MMPI). According to Cloninger, individuals who score higher on HA manifest anticipatory worry and pessimism, shyness with strangers, fear of uncertainty, fatigability and asthenia (versus Optimism, Confidence, and Vigor; Cloninger, Przybeck, Svrakic, & Wetzel, 1994). Twenty hundreds and eighteen of the subjects completed the TCI-125. The MMPI Depression scale reflects symptoms of depression or anxiety depending on a whole MMPI-profile configuration. Its items concern a lack of confidence and pessimism (Berezin, Miroshnikov, & Rozhanec, 1976). Valid MMPI data were available for 259 of the subjects.

DNA extraction and Genotyping. DNA was extracted from blood or mouthwash samples using phenol-chloroform method. The primer sequences for the *COMT Val158Met* polymorphism were: forward 5'-CTG ACA ACG GGT CAG GCA TG- 3' and reverse 5'-CTG ACA ACG GGT CAG GCA TG- 3'. PCR reaction was carried out in a reaction volume of 15 μL containing 100 ng of genomic DNA, 10 pmoles of each primer, 0.5 U Taq polymerase (Helicon, Russia), 200 μM of each dNTP and 1M betaine hydrochloride. After an initial denaturation at 94°C for 2 min, amplification was performed as follows: 30 cycles of denaturation at 94°C for 30 sec, annealing at 57°C for 30 sec and extension at 72°C for 30 sec with a final extension for 4 min at 72°C. PCR products were cleaved by the restriction endonuclease Fat I (Sibenzyme, Russia) and separated on an 8%-polyacrylamide gel electrophoresis (PAGE). The resulting fragments were 87 and 22 bp for the *Val* allele and 69, 18 and 22 bp for the *Met* allele.The primer sequences for the *DRD4 VNTR* polymorphism were: forward 5'- CGACTACGTGGTCTACTCG -3'and reverse 5'- AGGACCCTCATGGCCTTG -3'. PCR conditions were the same as for the *COMT Val158Met* polymorphism. The reaction mixture was electrophoresed on an 8%-polyacrilamide gel with ethidium bromide to screen for alleles. Fragments representing different numbers of repeats (2, 3, 4, 5, 6, 7, 8, and 9) were identified.

Statistical Analysis

Distribution of the accuracy and anxiety measures did not substantially deviate from normality. The time measures were skewed to the right and were subjected to square-root transformation. Then the anxiety and top-down attention measures were analyzed with parametric statistics (t-test for independent samples, Pearson's correlations, ANCOVA). To test the study hypothesis, eight 2x2x2x2 repeated-measures ANCOVAs were conducted, where genotype, anxiety and education were the between-subjects factors, Trial was the within-subject factor, and age served as a covariate. Dependent variables were either Accuracy or Time. To run ANCOVAs, genotypes were grouped and encoded as follows: *COMT ValVal* (1) vs. at least one *Met* allele (2); at least one *DRD4 L* allele (6 or more repeats) (1) vs. *SS* (2). Genotype groups for both polymorphisms did not differ with regard to sex, age and education. Participants were divided into low-anxious and high-anxious individuals using a median split on the HA and Depression scales. Belonging to the lower anxiety group (HA < 11 scores; Depression < 49 T-scores) was encoded as 1, and to the higher anxiety group as 2; secondary education was encoded as 1, higher education was encoded as 2. A separate ANCOVA was run for each gene and each anxiety measure. Where significant main or interaction effects of genes and anxiety took place, post hoc analyses were conducted using Newman-Keuls test.

The bottom-up attention, measured with ordering scale, was analyzed using nonparametric statistics (Mann–Whitney U-test, Spearman's correlations). To assess influence of genotypes and anxiety on the bottom-up attention variable, logistic regressions were conducted. For the logistic regression analysis, the subjects were classified into those who did not identified color letters (0) and those who identified at least one of the letters (1). Age and education were entered in the equations as additional independent variables. Data analysis was performed using Statistica 6.0 for Windows.

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Results

Allele and genotype frequencies

Genotyping was successful in 250 subjects for *COMT* and in 266 subjects for *DRD4*. The relative frequencies of the *COMT ValVal, ValMet*, and *MetMet* genotypes were .24, .52, and .24; the relative frequency of each allele was .5. The distribution of *COMT* genotypes did not deviate from Hardy-Weinberg equilibrium, $\chi^2(1, N=250) = 0.4$, $p > .5$. Among *DRD4* alleles, the four-repeat allele was the most common (.72), followed by the seven-repeat (.16) allele. Frequencies of the other alleles were .7 for *2R*, .3 for *3R*, less than .2 for *5R*, less than .1 for *6R, 8R*, and *9R*. These were similar to allele frequencies reported for other white samples.

Influence of demographic factors on attention and anxiety

The attention measures did not differ by sex. Accuracy was related to education, being higher in individuals with higher education (Accuracy 1, $M = 17.09$, $SD = 4.43$; Accuracy 2, $M = 17.74$, $SD = 3.40$) than in those with secondary education (Accuracy 1, $M = 15.27$, $SD = 4.31$; Accuracy 2, $M = 16.30$, $SD = 3.50$), $t(264) = 3.12$, $p = .002$, $d = 0.41$ and $t(264) = 3.16$, $p = .002$, $d = 0.41$ for Accuracy 1 and Accuracy 2 respectively. Time was positively correlated with age ($r = .13$, $p = .030$ and $r = .14$, $p = .023$ for Time 1 and Time 2 respectively), while the bottom-up attention measure was negatively correlated with age ($r_s = –.23$, $p = .001$). Analysis of relations between the top-down and bottom-up attention measures revealed a negative correlation of bottom-up attention with Time 1 ($r_s = –.16$, $p = .009$).

HA and Depression were correlated with each other ($r = .45$, $p = .001$), but were related differently to demographic variables. Women had higher HA scores ($M = 10.38$, $SD = 4.34$) compared to men ($M = 8.72$, $SD = 4.61$), $t(216) = 2.65$, $p = .009$, $d = 0.37$. Individuals with secondary education had higher Depression scores ($M = 52$, $SD = 11$) than those with higher education ($M = 48$, $SD = 12$), $t(259) = 2.36$, $p = .019$, $d = 0.31$. In addition, Depression scores were positively correlated with age ($r = .21$, $p = .001$). These data were taken into account when selecting independent variables for the ANCOVAs and logistic regression models.

Influence of genotypes and anxiety on top-down attention

We did not reveal any significant main effect of genotypes and anxiety on Accuracy and Time. However, there were significant interaction effects of Trial*HA, $F(1, 210) = 10.43$, $p = .001$, $\eta^2 = .05$, Trial*HA**DRD4*, $F(1, 210) = 7.65$, $p = .006$, $\eta^2 = .04$, and Trial*HA**DRD4**education, $F(1, 210) = 7.61$, $p = .006$, $\eta^2 = .04$, on Accuracy and that of Trial**DRD4** HA *education on Time, $F(1, 210) = 10.14$, $p = .002$, $\eta^2 = .05$. Higher HA individuals were significantly more accurate in Trial 2 than in Trial 1 ($p = .001$). In this group, the accuracy increased by 15%, while in the lower HA group it did so by 5% only. This anxiety effect was dependent on the *DRD4* genotype (fig. 2). *DRD4 SS* homozygotes showed a moderate increase in the accuracy (by 8–12%) from Trial 1 to Trial 2 regardless of HA level. Anxiety affected accuracy changes in the presence of the *DRD4 L* allele ($p = .013$). A marked increase in the accuracy (by 23%) was seen in higher HA carriers of the *L* allele; in the lower HA**DRD4 L* group accuracy remained constant (0%). Moreover, the high anxious carriers of the *DRD4 L* allele showed a trend toward lengthening of scanning time (by 18%), while the other groups tended to reduce it (Trial*HA**DRD4* interaction effect on Time, $F(1, 210) = 3.73$, $p = .055$, $\eta^2 = .02$).

Post hoc analysis of the four-way interaction effect (Trial*HA**DRD4**education) on Accuracy revealed a significant increase in the accuracy from Trial 1 to Trial 2 ($p = .0002$) in the group of higher HA carriers of the *DRD4 L* alleles with secondary education. These individuals differed from the others significantly or at a trend level on the number of words they identified during the first trial. As a whole, they showed the low initial accuracy and the shortest initial scanning time and then improved their performance by 52% by means of extending the scanning period by 70%. However, they did not approach the accuracy level of the most successful groups (Table 1). In contrast, in the group of individuals with the same genotype and education level but lower anxiety both the accuracy and time decreased (by 13% and 23% respectively). It should be noted that in the post hoc analysis differences between groups on time changes did not reach statistical significance.

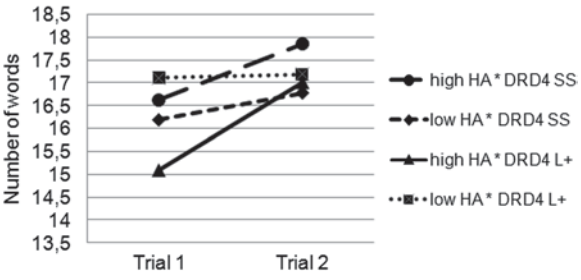

Figure 2. Dynamics of performance accuracy (Munsterberg's test) as a function of *DRD4 VNTR* genotype and TCI Harm Avoidance. HA – Harm Avoidance. *DRD4 SS* – genotypes with two short alleles (2–5 repeats), *DRD4 L+* - genotypes with at least one long allele (6–9 repeats). Trial 1 – results for the first sheet, Trial 2- results for the second sheet under instruction to perform the task as quickly and accurate as possible.

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Table 1. *Means (SD) of top-down attention measures as a function of DRD4 genotype, TCI Harm Avoidance and education*

Harm Avoidance	Lower HA				Higher HA			
DRD4 genotypes	*SS*		*L+*		*SS*		*L+*	
Education	Sec	High	Sec	High	Sec	High	Sec	High
n	25	59	10	30	18	51	7	18
Accuracy, Trial 1	14.8 (*3.5*)	17.0 (*4.6*)	17.5 (*6.0*)	17.4 (*4.8*)	15.2 (*3.3*)	16.7 (*3.9*)	12.0 (*4.4*)	17.2 (*4.5*)
Time, Trial 1	104 (*57*)	120 (*70*)	118 (*47*)	116 (*61*)	119 (*78*)	109 (*58*)	84 (*51*)	105 (*49*)
Accuracy, Trial 2	16.1 (*4.0*)	17.2 (*3.8*)	14.9 (*4.8*)	17.4 (*3.3*)	16.1 (*2.3*)	18.0 (3.1)	16.1 (1.7)	18.4 (3.7)
Time, Trial 2	106 (*64*)	94 (*46*)	88 (*37*)	107 (*46*)	91 (*39*)	96 (*45*)	117 (*64*)	89 (*42*)
Time changes, %	13 (*78*)	–8 (*52*)	–23 (*23*)	6 (*44*)	–5 (*48*)	1 (*45*)	70 (*109*)	–2 (*49*)
Accuracy changes, %	12 (*30*)	6 (*29*)	–13 (*24*)	5 (*24*)	10 (*24*)	12 (*28*)	52 (*59*)	11 (*23*)

Note: Sec – secondary education, High – higher education, *S – DRD4* alleles with 2–5 repeats, *L – DRD4* alleles with 6–9 repeats; negative values mean a decrease in accuracy or time; accuracy and time changes from the first trial to the second one were initially calculated for each individual as follows: Δaccuracy =(accuracy 2– accuracy 1)/ accuracy 1 *100% and Δtime= (time 2– time 1)/ time 1 *100%, and then were averaged for each group.

Influence of genotypes and anxiety on bottom-up attention

The logistic regression analysis revealed a significant effect of HA, measured as a continuous variable, on bottom-up attention, β = –0.07 (*SE* = 0.03), *Wald* (1) = 4.13, p = .042, while controlling for effects of age, sex and education. A higher HA was related to an increased likelihood of letter identification. A similar trend took place when HA was entered in the regression model as a dichotomous variable, β = 0.31 (*SE* = 0.18), *Wald* (1) = 3.07, p = .080. The lower HA group was divided approximately equally on those who identified at least one color letter and those who did not identified any letter (49 and 51%). In the higher HA group, percentage of those who identified at least one color letter was higher (63%). Controlling for age and education we did not reveal significant effects of genotypes or genotype*anxiety interactions on bottom-up attention.

Discussion

The main results of the present investigation can be summarized as follows. Trait anxiety, measured with the TCI Harm Avoidance scale, impacted both top-down and bottom-up attention. A higher HA level was related to the more prominent response to instruction to perform the task as accurate as possible. In addition, higher anxiety was linked to a trend toward more profound processing of irrelevant stimuli. The *DRD4* gene modified the HA effect solely on the top-down attention. The anxiety effect was largest in carriers of the *DRD4* long allele. In this group, higher HA was associated with a marked increase in performance accuracy from the first trial to the second one, while in case of lower anxiety accuracy remained practically constant. Furthermore, this effect was dependent on the education level with the largest HA effect on the accuracy increment taking place in the group of the *DRD4* long allele carriers with secondary education. According to the widely accepted interpretation (e.g., Ansari & Derakshan, 2011), accuracy reflects performance effectiveness, while time to complete the task may represent an indirect indicator of efficiency. Thus, our findings are in line with ACT statements (Eysenck et al., 2007), suggesting that under certain conditions high trait anxiety: 1) causes more profound processing of irrelevant stimuli increasing the influence of stimulus-driven attention system and 2) promotes the investment of additional resources to performance effectiveness.

It should be stressed that although the *DRD4**anxiety interaction effects were significant solely for accuracy, the whole pattern of results suggests that this interaction may influence changes in accuracy-speed tradeoff caused by motivation to perform the task as quickly and accurate as possible. Carriers of the *DRD4* long allele with higher anxiety demonstrated not only an accuracy increment but also lengthening of the scanning period, whereas those with lower anxiety showed an accuracy decrease and shortening of the scanning period. It has been previously suggested that when motivated people react by increasing the amount of effort or resources they expend to perform the task; these efforts may be translated into accuracy or speed. In most cases, one has to find balance between speed and accuracy to maximize reward outcomes, unless circumstances put absolute importance on the one of these response parameters (Gold & Shadlen, 2002).

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The default setting seems to be that people become faster without sacrificing accuracy (Bijleveld, Custers, & Aarts, 2010). This pattern of changes indeed took place in most of the groups in our investigation. However, our findings suggest that speed–accuracy tradeoffs are dependent on interactions of a number of factors including education level, HA and *DRD4* genotypes. Education level presumably reflects amount of cognitive reserve, i.e. internal (neuronal) processing resources, that an individual can invest in performance to improve its effectiveness (Stern, 2002). Secondary education level thus may indicate limited cognitive reserve. So in less educated people, a response to motivation might manifest itself behaviorally in the form of changes of searching time. Higher anxiety led to an increase in accuracy at the expense of a longer scanning (efficiency) in our study. Such a relationship has been previously interpreted as a sign that high anxiety leads to enhanced motivation to be more accurate and to invest additional resources to task performance (Ansari & Derakshan, 2011; Richards, French, Keogh, & Carter, 2000).

Two hypotheses may represent the framework for considering mechanisms whereby the interaction of the *DRD4* long allele and trait anxiety influences attention. The first one postulates that the gene is associated with extraversion, novelty seeking, and impulsivity in such a way that the *DRD4 L* allele leads to faster and less accurate reactions. Within this framework our results suggest that the long allele effects resulting in impulsive behavior and hyperactivity of behavioral activation system are evident only in low anxious individuals, while higher anxiety, an indicator of hyperactivity of behavioral inhibition system, counterbalances the long allele influence.

Alternatively, our findings may be considered in the framework of another hypothesis, according to which rather than predisposing to development of certain traits (novelty seeking, impulsivity) the *DRD4* long allele is associated with greater responsiveness to environment, thereby providing high developmental and behavioral plasticity (Belsky et al., 2009; Rende, 2012). This hypothesis has emerged from investigations of *DRD4* interactions with exogenous environmental factors, but it can apparently be extended to endogenous environment including trait anxiety. Previously Schmidt, Fox, Perez-Edgar, and Hamer (2009) investigated whether the interaction of *DRD4* with such endogenous environmental factor as frontal brain EEG asymmetry predicted child temperament. They found that the EEG asymmetry influenced temperament only in the presence of the *DRD4* long allele. Among the long allele carriers, the right frontal asymmetry presumably reflecting vulnerability to negative affect predicted poorer ability to focus and sustain attention as well as lower soothability scores. Thus, the results of Schmidt et al. (2009) indicate that the long allele compared to the short one is more sensitive to brain characteristics underlying differences in emotionality, and this is in line with our findings.

The interactions between HA, *DRD4* and education revealed in the present study may account for contradictory data concerning detrimental effects of high anxiety and the *DRD4* long allele on attention, which were obtained when anxiety and the gene were investigated separately. That is, some authors reported that in healthy individuals and in patients with attention deficit hyperactivity disorder, the *DRD4 7R* allele was associated with less accurate and faster reactions while others found the opposite pattern (Congdon, Lesch, & Canli, 2008; Kebir, Tabbane, Sengupta, & Joober, 2009; Kramer et al., 2009; Szekely et al., 2011). Data on speed-accuracy tradeoffs in individuals with high trait anxiety are also inconsistent. There is evidence that trait anxiety does not impact accuracy or enhances it, but slows reaction time down, suggesting the negative effect of anxiety on performance efficiency (Coombes, Higgins, Gamble, Cauraugh, & Janelle, 2009; Sadeh & Bredemeier, 2011). In contrast, others have found that individuals with high neuroticism (an anxiety-related trait) compared to those with low neuroticism are characterized by lower performance effectiveness preferring speed to accuracy (Flehmig, Steinborn, Westhoff, & Langner, 2010).

As mentioned above, our findings are consistent with the ACT hypothesis that anxiety favors bottom-up attention enhancing processing of irrelevant distractors (Eysenck et al. 2007; Sadeh & Bredemeier, 2011). However, the *DRD4* and *COMT* genes seem not to modify this influence. It is possible that the lack of dopaminergic genes effect on the balance between top-down and bottom-up attention in the present study is accounted for by simplicity of the task used or distractor characteristics which do not imply intense control of central executive component on interference. It is also possible that bottom-up attention is modified mostly by genes affecting other neurotransmission systems. For instance, cholinergic genes were shown to be associated with such domains of visual attention as orienting and spatial scaling without influencing working memory, whereas for genes modulating dopaminergic neurotransmission the opposite pattern of results was obtained (Greenwood, Lin, Sundararajan, Fryxell, & Parasuraman, 2009; Parasuraman, Greenwood, Kumar, & Fossella, 2005). It is important to note that in the present study the enhanced processing of colored letter did not result from longer scanning; on the contrary, it was correlated with a shorter searching period.

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At present, a great diversity of data concerning nature and power of *COMT Val158Met* polymorphism effects on cognition exists. This diversity may be accounted for by variation in baseline levels of prefrontal dopamine, sex dimorphism and COMT impact on both executive functions and emotion regulation. In particular, some authors related the *Met* allele with enhanced emotional reactivity and anxiety (Eley et al., 2003; Enoch, Xu, Ferro, Harris, & Goldman, 2003; Yeh et al., 2009). On this basis, it was suggested that the *COMT* polymorphism could partly explain individual differences in anxiety effects on cognitive processes implicated in working memory and decision-making (Goldman, Oroszi, & Ducci, 2005; Parasuraman & Jiang, 2012; Posner & Rothbart, 2009). However, like several other researchers, (Baekken, Skorpen, Stordal, Zwart, & Hagen, 2008; Barnett, Scoriels, & Munafo, 2008; Wray et al., 2008), we did not reveal associations between *COMT* and either anxiety-related traits or cognitive variables and did not find effects of *COMT**anxiety interaction on attention. This negative result may reflect a true lack of *COMT* effects on relations between anxiety and attention. Alternatively, behavioral level of analysis may be insufficient for recovering a role of *COMT* in task performance. Existing data (Dennis et al., 2010) suggest that influence of *COMT* on cognitive processes and its relation to anxiety manifest themselves at the level of brain activity and are not observable at the behavioral level.

Given high probability of type 1 and type 2 errors in association studies, present positive and negative results should be interpreted with caution. Further, large values of standard deviations of the accuracy and time measures deserve consideration as they point to a high variability in magnitude and directions of the dynamics within groups. This variability suggests that beside anxiety, education and *DRD4*, many other factors may influence speed-accuracy tradeoffs.

In sum, the findings are in accordance with some ACT statements regarding anxiety influence on top-down and bottom-up attention. In addition, they suggest that individual differences in trait anxiety effects on top-down attention are related to the *DRD4* genotypes and education level.

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