Impaired Executive Control Is Associated with a Variation in the Promoter Region of the Tryptophan Hydroxylase 2 Gene

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Abstract

■ Current models of attention describe attention not as a homogenous entity but as a set of neural networks whose measurement yields a set of three endophenotypes—alerting, orienting, and executive control. Previous findings revealed different neuroanatomical regions for these subsystems, and data from twin studies indicate differences in their heritability. The present study investigated the molecular genetic basis of attention in a sample of 100 healthy subjects. Attention performance was assessed with the attention network test that distinguishes alerting, orienting, and executive control (conflict) using a simple reaction time paradigm with different cues and congruent and incongruent flankers. Two gene loci on candidate genes for cognitive functioning, the functional catechol-*O*-methyltransferase (*COMT*) VAL158MET and the tryptophan hydroxylase 2 (*TPH2*) −703 G/T promoter polymorphism, were tested for possible associations with attention. *COMT* is involved in the catabolism of dopamine, and *TPH* is the rate-limiting enzyme for serotonin synthesis. Results showed no effect of the *COMT* polymorphism on attention performance. However, the TT genotype of *TPH2* −703 G/T was significantly associated with more errors (a possible indicator of impaired impulse control; $p = .001$) and with decreased performance in executive control ($p = .001$). This single-nucleotide polymorphism on the *TPH2* gene explained more than 10% of the variance in both indicators of attention stressing the role of the serotonergic system for cognitive functions. ■

INTRODUCTION

Intelligence is one of the most heritable psychological phenotypes known, and because of its importance for academic achievement and job performance (Jensen, 1998), the search for its biological basis is one of the greatest scientific challenges. Twin and adoption studies have demonstrated that about 70% of the variance in intelligence is determined by genes (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990); however, the search for specific candidate genes of intelligence has so far been rather unsuccessful (Reuter, Roth, Hove, & Hennig, 2006). One of the reasons for this is the complexity of the phenotype. Therefore, newer strategies prefer analyzing so-called endophenotypes of intelligence, which are distinct subcomponents of general cognitive ability, like memory, attention, vigilance, or executive control (Posthuma, Mulder, Boomsma, & De Geus, 2002; te Nijenhuis & van der Flier, 2002; Bowden, Carstairs, & Shores, 1999). These endophenotypes are less complex than general cognitive ability and, therefore, presumably determined by a smaller amount of genes (Reuter et al., 2005). Various genetic association studies have produced contradicting results, which can be accounted for by stratification effects, small sample sizes, or different phenotype definitions, yet with respect to cognitive functioning a line of evidence exists pointing unequivocally to the hypothesis that the functional VAL158MET polymorphism of the catechol-*O*-methyltransferase (*COMT*, an enzyme that degrades monoamines such as dopamine in the synaptic cleft) gene is a promising candidate gene (for a review, see Goldberg & Weinberger, 2004). A single-nucleotide polymorphism (SNP), a G→A transition in codon 158 of the *COMT* gene located at the q11 band of human chromosome 22, results in a three- to fourfold difference in *COMT* enzyme activity by coding for the synthesis of the amino acid methionine (MET; lower enzyme activity) instead of valine (VAL). Heterozygotes (VAL/MET genotype) have intermediate levels of *COMT* activity (Lachman et al., 1996). Other dopaminergic candidate genes have less successfully been tested for associations with cognitive functioning (e.g., Perry et al., 1997).

There is evidence that the serotonergic (5-HT) system is also involved in cognitive functioning; however the rationale for the implication of the 5-HT system in cognitive functions is less understood, and support from the literature is scarcer than for dopamine. Cuccaro, Wright, Abramson, Marsteller, and Valentine (1993) reported a

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significantly negative correlation between whole-blood 5-HT and cognitive–intellectual abilities in a sample of autistic patients and their first-degree relatives. By means of tryptophan depletion, an elegant method to investigate the involvement of 5-HT in brain functions, impairment in cognitive functioning could be demonstrated in both animal and healthy human subjects studies (Evers et al., 2005; Mazer et al., 1997). Further evidence emerges from clinical studies showing the beneficial effects of substances increasing central 5-HT activity. For example, Poyurovsky et al. (2003) showed in a double-blind placebo controlled study in a sample of schizophrenic patients that the 5-HT2a antagonist mianserin improved performance in neurocognitive tasks. In the same line, Harvey (2003) reported that the combined dopamine and serotonin receptor antagonist ziprasidone significantly improves multiple cognitive domains such as attention/vigilance, episodic memory, executive function, and visuomotor speed in schizophrenic patients. Results indicate that the preponderance of 5-HT2a antagonism over dopamine D2 blockade exerted by atypical antipsychotics may contribute to their cognitive-enhancing effects. All these findings underpin the role of the 5-HT system in cognitive functioning, although there is abundant evidence for a more salient role of the dopaminergic system. It is also possible that some of the 5-HT effects on cognitive functioning are mediated via an indirect pathway by influencing the activity of the dopaminergic system. It is known that the 5-HT system exerts an inhibitory effect on dopamine release (e.g., Porras et al., 2002).

The tryptophan hydroxylase (*TPH*) gene is a promising candidate gene for cognitive functioning because it is the rate-limiting enzyme of 5-HT synthesis. In numerous independent studies the *TPH1* gene has been reported to be associated with aggression, suicidal behavior, nicotine addiction, and other psychopathologies (e.g., Hennig, Reuter, Netter, Burk, & Landt, 2005; Reuter & Hennig, 2005a; Nielsen et al., 1998). However, these positive findings have been criticized as the *TPH1* gene is primarily expressed in the periphery and polymorphisms of the *TPH1* gene that showed positive associations with the phenotypes under investigation were located in intron 7. Alternative mechanisms making gene expression from an intronic sequence possible (splicing and exon skipping) have been ruled out (Shaltiel, Shamir, Agam, & Belmaker, 2005). Therefore, positive association studies with *TPH1* seem to result from linkage disequilibrium of the intronic SNPs with other functional as yet unidentified gene variations. The role of the *TPH1* gene for central nervous processes has recently experienced a renaissance because of an animal model demonstrating *TPH1* gene involvement in 5-HT synthesis during a late developmental stage of the brain (Nakamura et al., 2006). The previously published association between creativity and the A779C polymorphism of the *TPH1* gene, therefore, seems to provide serious evidence underlining the involvement of the 5-HT system in higher cognitive functions (Reuter, Roth, Holve, & Hennig, 2006).

Moreover, Walther et al. (2003) identified a second *TPH* isoform—referred to as *TPH2*—in mice, that is predominantly expressed in the brain stem, whereas the classical *TPH* gene—now labeled *TPH1*—is expressed in the gut, pineal gland, spleen, and thymus. The authors also identified a human *TPH2* ortholog on human chromosome 12p21.1. SNPs in the *TPH2* gene have now been detected, and first studies have demonstrated associations between *TPH2* gene variations and depression, ADHD, autism, and suicide (Coon et al., 2005; Walitza et al., 2005; Zhou et al., 2005; Zill et al., 2004). Moreover, functional studies emphasize the impact of the *TPH2* −703 G/T SNP on amygdala responses to emotional stimuli (Canli, Congdon, Gutknecht, Constable, & Lesch, 2005). Recent findings from two independent research units show that the TT genotype is associated with low anxiety and high extraversion (Reuter, Kuepper, & Hennig, in press; Gutknecht et al., in press), which is an indicator of low impulse control. Moreover, in another ongoing study of our own group, the prevalence of the TT genotype is significantly higher in drug addicted subjects than in controls. Because a lack of impulse control is associated with a higher risk for drug addiction, the TT genotype of the −703 G/T SNP is likely to be related to worse performance in cognitive tasks measuring prefrontal executive control.

The development of valid and reliable paradigms is the essential prerequisite for the investigation of the biological basis of endophenotypes of cognitive ability. Fan, McCandliss, Sommer, Raz, and Posner (2002) developed an attention network test (ANT) designed to evaluate the processing efficiency of the three attentional networks involved in the three subcomponents of attention proposed by Posner and Dehaene (1994), namely, alerting, orienting, and executive control. *Alerting* is defined as achieving and maintaining an alert state; *orienting* is the selection of information from sensory input; and *executive control* is defined as resolving conflict among responses. The functional efficiency of these three attentional networks is assessed by reaction time (RT) differences between conditions presenting alerting cues, spatial cues, flankers, or no cues at all. Functional imaging studies identified the neuroanatomical correlates of these three attentional networks. Frontal and parietal regions of the right hemisphere are engaged in controlling the alerting system; the superior parietal lobe is related to orienting, and the anterior cingulate; and the lateral prefrontal cortex are associated with executive control (for an overview, see Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan et al., 2002). In a twin study, the heritability of the executive control network could be demonstrated, whereas there was only some evidence for the heritability of alerting and no hint for a genetic impact on

orienting (Fan, Wu, Fossella, & Posner, 2001). First candidate genes for the attentional subsystems were identified. The *VNTR* polymorphism in exon III of the *DRD4* gene and a haplotype containing two genetic variants on the *MAO-A* gene showed an association with executive attention. The explained variance was 3.9% and 2.0%, respectively (Fossella et al., 2002). These results indicate once more that even endophenotypes of general cognitive ability are polygenically inherited. There were no significant differences among the three different genotypes of the *COMT* gene in any of the network scores. However, in another study using a slightly modified version of the ANT, an association between the *COMT* gene and performance could be demonstrated. The number of the MET alleles was positively related to performance in the attentional control task and negatively related to the activity in the cingulate as measured by functional magnetic resonance imaging (Blasi et al., 2005).

Therefore, the aim of the present study was to search for possible associations between attention performance as measured by the ANT and two further genetic variants, the −703 G/T SNP in the promoter region of the *TH2* gene (rs4570625) and the functional *COMT* VAL158MET (rs4680) polymorphism that has previously been shown to be related to executive control as measured by the Wisconsin Card Sorting Test (e.g., Malhotra et al., 2002). It has to be pointed out that cognitive functions such as attention and their biological basis are of substantial research interest and are not only considered as subcomponents of intelligence.

METHODS

Attention Network Test

In all trials, an arrow pointing to the left or the right direction is presented to the subject, who has to press a left or right button as fast as possible according to the direction of the arrow. The arrow is either located below or above a fixation cross. In some trials, cues announce when or where (and when) the arrow will appear. The reduction of RT due to the time cue is used to quantify the performance of the alerting network; the reduction of RT due to the spatial cue is used to quantify the performance of the orienting network. To assess executive control, the arrow is flanked in some trials by two further arrows on each side pointing either in the same or in the opposite direction conveying congruent and incongruent information, respectively. The increase in RT caused by the incongruent versus congruent flankers is used to quantify the efficiency of executive control networks to process the conflicting information (higher RT differences indicate poorer performance). In addition, the total RT and the total number of errors are global indicators of performance level.

One trial of the ANT consists of five events: (1) A fixation cross is presented for a variable duration (400–1600 msec); (2) an asterisk appears for 100 msec as warning cue indicating either where the target arrow will appear (spatial cue, above or below the fixation cross), or only when it will appear (center cue, replacing the fixation cross, or double cue, above and below the fixation cross); in the ''no-cue'' condition, the fixation cross is presented; (3) a fixation period of 400 msec follows; (4) the target arrow appears either alone or flanked by arrows pointing in the same or opposite direction (congruent and incongruent flankers); now, the subject has 1700 msec to respond by pressing the appropriate button to indicate the direction; (5) after the response, the fixation cross is shown until the trial ends after 4000 msec.

After a practice block consisting of 24 trials with feedback of the RT, 3 blocks of 96 trials follow, separated by short breaks. In each block, all 48 trial types are presented two times: 4 (cue types: no, spatial, center, double) × 3 (flanker: no, congruent, incongruent) × 2 (positions: above, below) × 2 (directions: left, right); in total, 72 trials per cue type, 96 trials per flanker condition.

Subjects

Out of a pool of $n = 440$ healthy white subjects of German origin who were members of the Giessen Gene Brain Behavior Project data bank and a priori genotyped with respect to the −703 G/T SNP in the promoter region of the *TH2* gene and the VAL158MET SNP in exon 3 of the *COMT* gene, $n = 100$ subjects ($n = 14$ men; $n = 86$ women; age: $M = 22.60$ years, $SD = 4.71$) were tested with the ANT. All participants were university students, guaranteeing a rather homogeneous sample with respect to intelligence and age. The control of intelligence as a possible confounding variable is important as it has been demonstrated that RT is negatively correlated with IQ (e.g., Der & Deary, 2003).

The genotype frequencies in the total sample ($n = 440$) were as follows: *COMT* VAL158MET: VAL/VAL, $n = 106$; VAL/MET, $n = 227$; MET/MET, $n = 107$ [test for Hardy–Weinberg equilibrium: $\chi^2(1) = 0.45$, *ns*]; *TPH2* −703 G/T: TT, $n = 17$; GT, $n = 160$; GG, $n = 263$ [test for Hardy–Weinberg equilibrium: $\chi^2(1) = 1.48$, *ns*]. The first proportion of subjects participating in the experimental part of the study ($n = 84$) was recruited via e-mail advertisement (admission was randomly assigned); a second part was deliberately invited according to their genotype to enhance the proportion of the rare TT carriers ($n = 8$); a third part ($n = 8$) was also deliberately invited according to their genotype to enhance the number of subjects to 100 and to assure that the overall distribution of genotypes was in Hardy–Weinberg equilibrium: *TPH2* −703 G/T: TT, $n = 11$; GT, $n = 37$; GG, $n = 52$ [test for Hardy–Weinberg equilibrium: $\chi^2(1) = 1.22$, *ns*]. Also, the genotype frequencies for the VAL158MET SNP were in Hardy–Weinberg equilibrium: VAL/VAL, $n = 30$; VAL/MET, $n = 46$; MET/MET, $n = 24$ [test for Hardy–Weinberg

equilibrium: $\chi^2(1) = 0.59$, *ns*]. The strategy of experimental testing after a priori genetic screening has two major advantages: First, rare genotypes can be tested with adequate power; second, the representativeness of the population is warranted.

Genetic Analyses

DNA was extracted from buccal cells to avoid a selective exclusion of subjects with blood and injection phobia. 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 *TPH2* −703 G/T polymorphism and the *COMT* VAL158MET polymorphism was performed by real-time PCR using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics). By means of the melting curve analyses, SNPs can be detected without conducting gel electrophoresis or ensuing sequencing after amplification. The primers and hybridization probes (TIB MOLBIOL, Berlin, Germany) and the PCR protocol for *COMT* were reported elsewhere (Reuter, Schmitz, Corr, & Hennig, 2006; Reuter & Hennig, 2005b); with respect to *TPH2* −703 G/T, the method is as follows:

forward primer: 5′-TCCATATAACTCTGCATAGAGGCA-3′;
reverse primer: 5′-GATATCCATTGCCTCAAGCA-3′;
anchor hybridization probe: 5′-LCRed640-CATGCAAATG-TGTGAGTGTATATATGTGTAATG-phosphate-3′;
sensor [G] hybridization probe: 5′-TCTGACTTGACATAT-TCTAATTTTG-fluorescein-3′.

The PCR run comprised 55 cycles of denaturation (95°C, 0 sec, ramp rate: 20°C/sec), annealing (61°C, 10 sec, ramp rate: 20°C/sec), acquisition of the fluorescence signal (40°C, 1 sec, ramp rate: 20°C/sec), and extension (72°C, 10 sec, ramp rate: 20°C/sec), which followed an incubation period of 10 min (95°C) to activate the FastStart Taq DNA Polymerase of the reaction mix (Light Cycler FastStart DNA Master Hybridization Probes; Roche Diagnostics). After amplification, a melting curve was generated by keeping the RT at 40°C for 2 min and then heating slowly to 75°C with a ramp rate of 0.2°C/sec. The fluorescence signal was plotted against temperature to yield the respective melting points (T_m) of the two alleles. The T_m for the T allele was 51.6°C, and for the G allele, 58.8°C.

RESULTS

There were no overall differences in RT in the ANT between men and women [$F(1,98) = 0.42$, $p = .516$]; therefore, sex was not considered as an additional factor in the ensuing analysis of variance models. Results of the genetic data showed a significant association between the −703 G/T SNP and the total numbers of errors in the ANT [$F(2,97) = 6.81$, $p = .002$, $\eta^2 = .123$] (see Figure 1 and Table 1) and between the −703 G/T SNP and the conflict score [$F(2,97) = 6.25$, $p = .003$, $\eta^2 = .114$] (see Figure 2 and Table 1). Post hoc Tukey tests showed that carriers of the TT genotype made significantly more errors and also showed significantly greater conflict behavior than carriers of the GT or GG genotypes, whereas the later two groups did not differ in any of the performance measures. Analyses on the allele level comparing subjects with at least one G allele (genotypes GT and GG) or without any G allele (genotype TT) resulted in even stronger effects: total number of errors: non-G allele (TT): $M = 15.46$, $SEM = 2.60$; G allele (GT and GG): $M = 5.72$, $SEM = 0.91$; $F(1,98) = 12.48$, $p = .001$, $\eta^2 = .113$); conflict behavior: non-G allele (TT): $M = 129.04$, $SEM = 9.95$; G allele (GT and GG): $M = 93.36$, $SEM = 3.50$; $F(1,98) = 11.44$, $p = .001$, $\eta^2 = .105$. The analysis based on the different flanker types revealed that the association between the −703 G/T polymorphism and the total error rate was caused by wrong responses to incongruent stimuli (see Table 1). The −703 G/T SNP was neither associated with alerting [$F(2,97) = 0.67$, $p = .514$] nor with orienting [$F(2,97) = 1.00$, $p = .373$] or with the total RT [$F(2,97) = 0.90$, $p = .410$].

The VAL158MET SNP of *COMT* showed neither an association with the total number of errors and the total RT nor with the three subcomponents of the ANT (see Table 1).

DISCUSSION

To investigate the biological basis of attention processes, variants of two candidate genes for cognitive functioning, *COMT* and *TPH2*, were tested for possible associa-

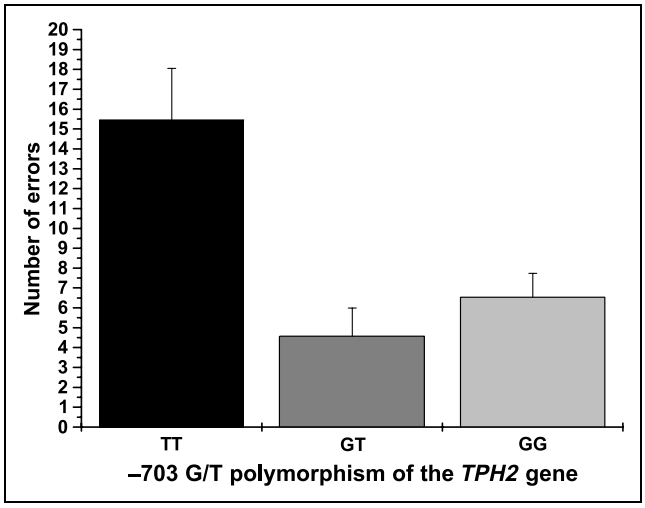

Figure 1. Association between the *TPH2* −703 G/T polymorphism and the total number of errors in the ANT.

Table 1. Association between the *COMT* VAL158MET, the *TPH2* −703 G/T Polymorphisms and Performance in the ANT: Descriptive Statistics, *M* (*SEM*), and Analysis of Variance Results

	COMT VAL158MET					*TPH2 −703 G/T*					
				Genotype					*Genotype*		*G allele*	
	VAL/VAL	*VAL/MET*	*MET/MET*	*F(2,97)*	*p Value*	*TT*	*GT*	*GG*	*F(2,97)*	*p Value*	*F(1,98)*	*p Value*
Mean RT, msec	534.58 (9.62)	519.42 (8.37)	521.76 (11.48)	0.72	.487	545.36 (19.22)	523.84 (8.37)	521.05 (7.71)	0.90	.410	1.76	.187
Errors: total	8.03 (2.63)	6.30 (0.86)	5.61 (0.95)	0.53	.591	15.45 (6.79)	4.57 (0.75)	6.54 (0.72)	6.81	**.002**	12.48	**.001**
Errors: neutral	0.73 (0.14)	0.98 (0.19)	1.09 (0.28)	0.65	.522	0.82 (0.30)	0.78 (0.17)	1.12 (0.19)	0.89	.414	0.17	.683
Errors: incongruent	7.10 (2.61)	4.89 (0.74)	4.00 (0.74)	0.94	.393	14.36 (6.74)	3.57 (0.67)	4.88 (0.58)	7.62	**.001**	14.75	**.0002**
Errors: congruent	0.20 (0.07)	0.43 (0.09)	0.52 (0.15)	2.23	.113	0.27 (0.14)	0.22 (0.07)	0.54 (0.10)	3.51	**.034**	0.47	.496
Errors: incongruent–congruent	6.90 (2.61)	4.46 (0.72)	3.48 (0.71)	1.16	.317	14.09 (6.74)	3.35 (0.66)	4.35 (0.57)	7.77	**.001**	15.32	**.0002**
Alerting	45.74 (4.87)	43.35 (2.53)	45.27 (5.14)	0.12	.885	48.47 (6.83)	41.30 (3.86)	45.84 (2.87)	0.67	.514	0.42	.521
Orienting	57.83 (4.92)	57.89 (3.20)	57.33 (4.25)	0.01	.995	60.64 (6.81)	53.11 (3.84)	59.68 (3.20)	1.00	.373	0.25	.620
Conflict	96.10 (7.87)	95.01 (4.22)	103.28 (7.34)	0.45	.639	129.04 (15.91)	97.62 (5.14)	90.33 (4.01)	6.25	**.003**	11.44	**.001**

Alerting effect = RT no cue – RT center cue; Orienting effect = RT center cue – RT spatial cue; Conflict effect = RT incongruent – RT congruent.
p values in **boldface** are statistically significant.

Figure 2. Association between the *TPH2* −703 G/T polymorphism and executive control (conflict) performance in the ANT (RT conflict = $RT_{incongruent} - RT_{congruent}$).

tions with the ANT. The ANT is a paradigm designed to decompose the three subcomponents of attention, namely, alerting, orienting, and executive control (conflict). The strategy to divide attention into smaller entities leads to a definition of even smaller endophenotypes of cognitive functioning, which facilitates the identification of functional candidate genes. A strategy of testing after a priori genotyping was applied to obtain appropriate cell frequencies even for the homozygous mutant of the −703 G/T polymorphism of the *TPH2* gene, which has a genotype frequency of less than 4%. Results revealed no association between *COMT* VAL158-MET and indicators of attention performance. However, there was a substantial association between the *TPH2* −703 G/T SNP and the total number of errors and executive control functioning. Carriers homozygous for the T allele performed significantly worse than subjects with at least one G allele. The fact that the reported association was limited to one subcomponent of attention supports functional imaging studies and previous findings from quantitative and molecular genetics. Functional imaging studies have demonstrated that the three subcomponents of attention as proposed by Posner and Petersen (1990) have a different neuronal basis (for a review, see Fan et al., 2002). Moreover, a twin study has demonstrated convincing evidence of heritability solely for the executive attention network that mediates stimulus and response conflict (Fan et al., 2001). It is, therefore, not surprising that the first study investigating the molecular genetic basis of the attentional networks found significant associations with the executive attention network only (Fossella et al., 2002). Our results support the hypothesis of distinct attentional networks and confirm previous findings that suggested heritability exclusively for the executive attention subcomponent. In line with Fossella et al. (2002), we could not detect an

association between the functional VAL158MET polymorphism of the *COMT* gene and attention performance. It is remarkable that not even executive control showed an association with *COMT* in the present study and in Fossella et al.'s (2002) study; although studies using the WCST, another paradigm measuring prefrontal executive functioning, showed robust effects of the *COMT* gene (e.g., Bilder et al., 2002; Malhotra et al., 2002). Obviously, executive control as defined by the ANT and the WCST are characterized by different task demands involving at least in part different neuronal correlates. Executive control as measured by the ANT conflict scores is a basal cognitive function characterized by the capacity to ignore distracting flankers when performing a simple reaction task. On the contrary, the WCST is a complex cognitive task where a rule has to be learned and applied across trials until conflicting information demands a switch of the previous learned strategy.

Another reason for the negative results with respect to the *COMT* gene could be the use of a homogenous sample with respect to intelligence. This strategy leads to a reduction in variance and therefore could suppress smaller gene effects. However, although the homogenous intelligence scores lead to conservative testing we detected a strong effect with respect to the *TPH2* gene. A shortcoming of our study was that because the subjects of the Giessen Gene Brain Behavior Project were a priori genotyped and no further post hoc genotyping was conducted, we could not test if the positive findings of Fossella et al.'s (2002) study with respect to the *DRD4* and the *MAO-A* gene could be replicated.

Another disadvantage of the present study is that the moderate sample size and the low proportion of men made it impossible to test for sex effects.

The reported effect size of the −703 G/T SNP with more than 11% explained variance in conflict behavior stresses the importance of the 5-HT system for the executive attention network and, therefore, for cognitive functioning. In subjects homozygous for the T allele in comparison to subjects with at least one G allele, the difference in RTs between the incongruent and the congruent condition was almost twice as high. The additional strong influence of the *TPH2* gene on the total error rate—more than 12% of explained variance—indicates the relevance of the 5-HT system for impulse control processes. It is striking that carriers of the TT genotype made nearly three times as many errors than carriers of at least one G allele. Higher number of errors may be caused by higher impulsiveness. There is a large amount of literature demonstrating the importance of the 5-HT system for impulsivity, impulse control disorders, and impulse control (for a review, see Lesch & Merschdorf, 2000). This assumption and our results are supported by another study reporting an association between the *TPH2* gene and response inhibition, a marker for impulsivity (Stoltenberg et al., 2006). Using a stop-signal computer task, an association between a genetic variant in intron 8 of the neuronal *TPH2* gene (rs1386483) and the stop-RT was found. The SNP investigated by us (rs4570625) and the one by Stoltenberg et al. (2006) are likely to be in linkage disequilibrium. This is because of the rs4570625 SNP and another SNP in intron 8 of the *TPH2* gene (rs1473473), only about 8000 bp in distance of the rs1386483, marking the borders of a haplotype block in a white sample (Zhou et al., 2005). Because the intronic SNP investigated by Stoltenberg et al. is unlikely to be functional, it is very likely that the association to impulse control is caused by the −703 G/T SNP (rs4570625), which showed an association to executive control in the present study.

Although the present results indicate a strong association to impaired executive control in carriers of the TT genotype of the −703 G/T SNP of the human neuronal *TPH2* gene, further studies have to (a) replicate this finding in independent samples, (b) demonstrate that a variation in rs4570625 is indeed associated with altered rates of 5-HT synthesis (indicator of functionality of this promoter SNP), and (c) demonstrate the relevance of the −703 G/T SNP for impulse control by investigating further phenotypes related to impulse control and by demonstrating the linkage between rs4570625 and rs1386483.

Furthermore, the version of the ANT adapted for functional magnetic resonance imaging studies (Fan et al., 2005) could be employed to elucidate as to how the change in serotonin synthesis in carriers of the TT genotype of the *TPH2* polymorphism influences brain functioning in a way that executive control is impaired. The approach of combining molecular genetics with brain imaging and behavioral testing has already been successfully used (Fan, Fossella, Sommer, Wu, & Posner, 2003) and holds great promise for the advancement of an integrative cognitive neuroscience.

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