Genetic Variation of Serotonin Function and Cognitive Control

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Abstract

■ Although it is widely accepted that serotonin plays a pivotal role in the modulation of anxiety- and depression-related personality traits as well as in the pathogenesis of anxiety disorders and depression, the role of serotonin in cognition is less clear. In the present study, we investigated the involvement of serotonin in cognitive behaviors by examining the impact of genetic variation in key regulators of serotonergic neurotransmission on behavioral measures in a cognitive control task. Eighty-five healthy participants performed a cued continuous performance task (the AX Continuous Performance Task [AX-CPT]) and were genotyped for polymorphisms in the transcriptional control regions of the tryptophan hydroxylase 2 gene (TPH2 G-703T; rs4570625) and the serotonin transporter gene (5-HTTLPR). The core result was that individuals lacking the rare TPH2 T allele were not faster than T allele carriers, but committed fewer errors and were less variable in responding. These findings parallel those of a recent study where an enhancement of executive control in individuals without the rare TPH2 T/T genotype was observed. Together with recent evidence that individuals without the T allele exhibit higher scores in anxiety- and depression-related personality traits, our results underscore the role of the TPH2 G-703T polymorphism in the modulation of behavior and raise the intriguing possibility that genetic variants associated with higher negative emotionality may have beneficial effects on some cognitive functions. ■

INTRODUCTION

Serotonin plays a pivotal role in the modulation of emotionality, and serotonergic dysfunction is a major vulnerability factor contributing to the pathogenesis of affective and anxiety disorders (Lesch, 2002; Nemeroff & Owens, 2002). However, given the serotonergic modulation of prefrontal brain areas implicated in higher cognitive functions (Goldman-Rakic, 1999), it is intriguing that the role of serotonin in cognition has only recently begun to attract more attention (see, e.g., Canli et al., 2006; Canli, Omura, et al., 2005; Robbins, 2005; Buhot, 1997).

This impression is paralleled by the fact that research into the behavioral role of genetic variation of serotonergic function primarily focuses on emotional rather than on cognitive traits. Two intensely studied genes of the serotonergic pathway are the genes encoding tryptophan hydroxylase isoform 2 (TPH2) and the serotonin transporter. Although so far, there is no evidence for functional variants in the TPH2 gene, TPH2 variation has repeatedly been associated with affective disorders (e.g., Harvey et al., 2004; Zill et al., 2004) and with amygdala reactivity to emotional stimuli (Brown et al., 2005; Canli, Congdon, Gutknecht, Constable, & Lesch, 2005). Moreover, two recent reports (Gutknecht et al., 2007; Reuter, Küpper, & Hennig, 2007) implicate TPH2 variation in the modulation of measures of negative emotionality such as *harm avoidance* or *neuroticism*. Reuter, Küpper, et al. (2007) showed that a presumably functional variant within the transcriptional control region of the gene, TPH2 G-703T (rs4570625), was associated with the temperament trait harm avoidance, with individuals without the rare −703 T/T genotype exhibiting higher scores in harm avoidance. Interestingly, in another study from this group (Reuter, Ott, Vaitl, & Hennig, 2007), this polymorphism was also associated with specific measures of executive control as assessed with the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2001). Individuals without the T/T genotype showed enhanced executive control or, more specifically, better conflict resolution between alternative responses. Further evidence that TPH2 variation may play a role in cognition comes from studies that have implicated TPH2 variants in the pathophysiology of attention deficit/hyperactivity disorder (ADHD; e.g., Sheehan et al., 2005; Walitza et al., 2005) or obsessive–compulsive disorder (OCD; Mössner et al., 2006), two disorders with prominent features of dysfunctional executive control.

With regard to the serotonin transporter gene, the short (s) variant of a repeat length polymorphism in the transcriptional control region of the gene (5-HTTLPR)

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results in lower transcriptional efficiency and, hence, in lower serotonin transporter function (Lesch et al., 1996). A considerable body of evidence has linked the s allele to negative emotionality (Lesch et al., 1996; for meta-analyses, see Munafò, Clark, & Flint, 2005; Schinka, Busch, & Robichaux-Keene, 2004; Sen, Burmeister, & Ghosh, 2004) and to stronger amygdala activation in response to fearful faces (e.g., Heinz et al., 2005; Hariri et al., 2002). However, more diverse 5-HTTLPR-associated functional and structural differences observed by Canli, Omura, et al. (2005) suggest a broader role of 5-HTTLPR in brain function, including cognitive and motor processes. However, there are only few studies that examined the role of 5-HTTLPR in cognition in more detail. Among those studies, two event-related potential (ERP) studies by Fallgatter and coworkers deserve attention because they suggest enhanced responsiveness of prefrontal cortical areas in 5-HTTLPR s allele carriers. In the first study (Fallgatter, Jatzke, Bartsch, Hamelbeck, & Lesch, 1999), s allele carriers showed stronger anteriorization of the so-called NoGo-P3, an ERP proposed to reflect mechanisms of inhibitory response control in the anterior cingulate cortex (ACC). In the second study (Fallgatter et al., 2004), s allele carriers showed an enhanced error-related negativity, an ERP assumed to be generated by ACC-mediated processes of performance monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Furthermore, the ACC receives not only high catecholaminergic but also serotonergic input (Paus, 2001). Taken together, these findings suggest that genetically driven variation in serotonin function influences ACC-mediated processes of conflict monitoring subserving cognitive control.

A behavioral task often used to assess executive functions such as conflict monitoring processes is the AX Continuous Performance Task (AX-CPT; Servan-Schreiber, Cohen, & Steingard, 1996), a task similar to that used in Fallgatter et al. (1999). Participants are required to perform a target response whenever the cue letter A is followed by the probe letter X (AX trials) and to perform a nontarget response if the cue A is followed by another letter (AY trials), or if the probe X is preceded by another letter (BX trials), or if both cue and probe are not-A and not-X, respectively (BY trials). The task was designed to maximize response conflict, as AX target responses are the predominate response (70% of the trials), and hence, nontarget trials of the AY and BX type induce response conflict. More precisely, the difficulty on AY trials is that the cue A triggers the expectation of the probe X and thus, the wrong (target) response. Conversely, on BX trials, the probe X might trigger the wrong (target) response although the cue B already unequivocally determines the nontarget response. Performance on these trials can thus be taken as a measure of cue maintenance and flexible updating in working memory (see also Dreisbach, 2006).

Based on the evidence outlined above, the present study focused on the potential impact of genetic variation of serotonergic function on cognitive control as assessed by AX-CPT hit rates and mean reaction times (RTs). In addition, another RT measure was examined, namely, RT variability, that is, variability of RTs from trial to trial as expressed in intraindividual RT standard deviations. RT variability can be conceived of as an index of the efficiency of executive control processes and has been shown to be increased in frontal lobe damage (Murtha, Cismaru, Waechter, & Chertkow, 2002) and ADHD (e.g., Scheres, Oosterlaan, & Sergeant, 2001; Leth-Steensen, Elbaz, & Douglas, 2000). Although so far, individual differences in RT variability have been linked especially to variation in norepinephrine function (e.g., Frank, Santamaria, O'Reilly, & Willcutt, 2007; Aston-Jones & Cohen, 2005), the serotonergic modulation of prefrontal areas (Goldman-Rakic, 1999) might also implicate serotonin to be one of the neurotransmitters involved in the modulation of RT variability. Interestingly, RT variability in choice RT tasks has recently been demonstrated to be elevated in individuals scoring high on the personality dimension neuroticism leading to the hypothesis of neuroticism as ''mental noise'' (Robinson & Tamir, 2005). More specifically, these authors assume that individuals scoring high on neuroticism tend to worry about their ability to cope with future events and consequently may try to overcome expected information-processing deficits by cognitive control even in tasks where automatic processing is more adequate. This hypothesis raises the possibility that possible effects of 5-HTTLPR and the TPH2 G-703T polymorphism on cognitive behaviors might be mediated by these polymorphisms' influence on neuroticism or related measures of negative emotionality (e.g., Reuter, Küpper, et al., 2007; Lesch et al., 1996).

Taken together, we expected that potential alterations in serotonergic function in carriers of the 5-HTTLPR s allele and the TPH2 −703 T allele should be reflected in hit rates, mean RT and RT variability. Moreover, we examined whether possible genetic effects on these cognitive measures might be mediated by neuroticism.

METHODS

Participants

Participants were 85 right-handed university students of Central European descent (16 men; age, mean 21.5 ± 3.3 years, range 18–34 years) who confirmed that they were free of relevant health problems, had never received psychopharmacological treatment, and did not abuse drugs. Participants gave written informed consent and received monetary compensation or course credit. The revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992) was used to assess neuroticism. Six participants did not return the NEO-PI-R; hence, only 78 participants were available for analyses on neuroticism. The study was carried out in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of the German Psychological Association.

Tasks and Procedure

The AX-CPT was either the first or the last of three behavioral paradigms, with the order being counterbalanced across participants. Participants were continuously presented a cue for 300 msec followed by a probe 1550 msec after cue onset. The probe remained visible until a button press was made, with a 2000-msec feedback for erroneous responses only. The next cue was presented 500 msec after the response or the feedback, respectively. The cues were either an A or one of 10 other letters (B cues: B, D, E, F, G, M, P, S, U, Z); the probes were either an X or again one of the 10 other letters (Y probes). A target response was required if an A was followed by an X (AX, 70% of the trials). A nontarget response was required in all other occasions, that is, AY, BX, or BY (10% each). The responses were made by pressing either a right or a left button on the keyboard, with the assignment of targets and nontargets to right and left keys being counterbalanced across participants. After a short training phase, three blocks of 200 trials each were presented and reactions were recorded using Presentation 8.0 (Neurobehavioral Systems, Albany, CA).

Genotyping

Buccal samples were obtained and DNA was extracted using the BuccalAmp system (Epicentre Technologies, Madison, WI). Genotypes were determined as described earlier for 5-HTTLPR (Lesch et al., 1996) and TPH2 G-703T (Walitza et al., 2005). Allele frequencies of 5-HTTLPR were 65% for the l allele and 35% for the s allele; genotype frequencies were 12% for s/s ($n = 10$), 47% for l/s ($n = 40$), and 41% for l/l ($n = 35$). Allele frequencies of TPH2 G-703T were 72% for the G allele and 28% for the T allele; the genotype frequencies were 49% for G/G ($n = 42$), 45% for G/T ($n = 38$), and 6% for T/T ($n = 5$). Both genotypes were in Hardy–Weinberg equilibrium (chi-square tests with $df = 1$; 5-HTTLPR: $\chi^2 = 0.08$, $p = .780$; TPH2 G-703T: $\chi^2 = 0.90$, $p = .342$). Due to the low frequency of the TPH2 T/T genotype and in accordance with previous studies (Brown et al., 2005; Canli, Congdon, et al., 2005), carriers of one or two copies of the T allele (T+, $n = 43$) were grouped together and contrasted to T allele noncarriers (T−, $n = 42$) in the statistical analyses.

Statistical Analyses

As there were generally low error rates (mean 1.5%) and percentages of slow responses, that is, responses with RT > 1000 (mean 1.4%), only correct trials with RT < 1000 msec were considered for statistical analyses. Because Kolmogorov–Smirnov tests indicated that hit rates were not normally distributed ($p \leq .002$), nonparametric tests were used to examine task main effects (Friedman test for dependent variables) and possible genotypic differences in hit rates (Kruskal–Wallis test for k independent groups for 5-HTTLPR; Mann–Whitney U test for two independent groups for TPH2 G-703T). Genotypic effects on mean RTs were examined using repeated measures analysis of variance (ANOVA) with condition (AX, AY, BX, and BY) as within-subjects factor, and TPH2 (T−, T+) and 5-HTTLPR (s/s, l/s, and l/l) as between-subjects factors. Furthermore, the following covariates were entered: age, sex, the order of the AX-CPT in the sequence of the three paradigms (order: first or last), the hand for the target response (go-hand: left or right), and duration of sleep in the night before the test session. No covariate was significantly associated with genotypes (nonparametric tests, $p \geq .151$). RT variability, that is, the standard deviation of individual RTs, was highly correlated with mean RTs (ranging from $r = .65$ in the AY condition to $r = .77$ in the BX condition). Therefore, we adopted the approach by Robinson and Tamir (2005) and residualized RT variability for mean RT using linear regression separately for each condition to control RT variability for mean RTs. The standardized residuals were then entered into a repeated measures ANOVA using the same model as that for mean RT. Further details on the statistical analyses are given in the Results section.

RESULTS

Hit Rates

Table 1 gives the mean hit rates in the four AX-CPT conditions, stratified for 5-HTTLPR and TPH2 G-703T genotype. There was a significant task main effect (Friedman test, $p < .001$) with lowest hit rates in the AY condition. There were no differences in hit rates between 5-HTTLPR genotype groups (Kruskal–Wallis tests, all $p \geq .230$). However, noncarriers of the TPH2 T allele showed significantly higher hit rates than T allele carriers in the AX condition (Mann–Whitney U test, $p = .006$) and in the average hit rate across all conditions ($p = .042$; other $p \geq .098$).

Mean RT

Detailed statistics of the repeated measures ANOVA for mean RTs (mRT) are provided in Table 2. For reasons of readability, only p values and the explained variance η^2 of task main effects and genotype-specific effects will be given in the text.

There was a condition main effect ($p = .028$, $\eta^2 = 0.05$) with the expected pattern of mRTs in the four conditions emerging, that is, highest mRT in the AY condition (see Figure 1A–D). A covariate effect emerged for age (see Table 2). With regard to genotypic effects, there were no condition-specific effects of 5-HTTLPR and TPH2 genotypes (all $p \geq .656$, $\eta^2 \leq 0.02$; see Figure 1A-D). Furthermore, neither 5-HTTLPR nor the TPH2 polymorphism had a main effect on the average mRT across condition (both

Table 1. Mean Hit Rates and Standard Errors of Means in Percent

Genotype	*n*	*AX*	*AY*	*BX*	*BY*	*Average*
Total sample	85	99.4 (0.1)	94.3 (1.0)	97.5 (0.7)	99.6 (0.2)	97.7 (0.4)
5-HTTLPR						
s/s	10	99.4 (0.3)	94.1 (2.4)	98.5 (1.6)	99.5 (0.4)	97.9 (0.9)
l/s	40	99.4 (0.1)	94.3 (1.1)	97.0 (0.7)	99.5 (0.2)	97.6 (0.4)
l/l	35	99.4 (0.2)	94.6 (1.2)	96.8 (0.8)	99.9 (0.2)	97.7 (0.4)
TPH2 G-703T						
T−	42	99.7 (0.2)	94.4 (1.6)	98.8 (1.0)	99.9 (0.3)	98.2 (0.6)
T+	43	99.1 (0.2)	94.2 (1.2)	96.2 (0.8)	99.4 (0.2)	97.2 (0.4)

Table 2. Results of Repeated Measures ANOVAs for Mean RT (mRT) and RT Variability (sdRT)

	mRT				*sdRT*			
Source of Variation	*F*	*df*	*p*	η^2	*F*	*df*	*p*	η^2
Within-subjects Effects								
Condition	3.74*	1.9	.028*	0.05*	1.61	2.7	.193	0.02
Condition × Age[c]	4.85*	1.9	.010[1,*]	0.06*	0.99	2.7	.394	0.01
Condition × Sex[c]	1.29	1.9	.279	0.02	0.46	2.7	.690	0.01
Condition × Sleep duration[c]	1.96	1.9	.147	0.03	2.80*	2.7	.048[2,*]	0.04*
Condition × Paradigm order[c]	0.91	1.9	.401	0.01	0.37	2.7	.751	0.01
Condition × Hand go-response[c]	0.73	1.9	.479	0.01	0.64	2.7	.573	0.01
Condition × TPH2	0.27	1.9	.753	<0.01	0.66	2.7	.559	0.01
Condition × 5-HTTLPR	0.60	3.9	.656	0.02	2.32*	5.3	.041*	0.06*
Condition × 5-HTTLPR × TPH2	0.46	3.9	.757	0.01	1.06	5.3	.388	0.03
Error		142.8				196.3		
Between-subjects Effects								
Age[c]	8.23*	1	.005[1,*]	0.10*	0.01	1	.923	<0.01
Sex[c]	0.36	1	.551	0.01	2.56	1	.114	0.03
Sleep duration[c]	1.71	1	.195	0.02	0.13	1	.716	<0.01
Paradigm order[c]	0.30	1	.585	<0.0	5.63*	1	.020[3,*]	0.07*
Hand for go-response[c]	0.10	1	.756	<0.01	1.84	1	.179	0.02
TPH2	1.01	1	.317	0.01	5.90*	1	.018*	0.07*
5-HTTLPR	1.09	2	.341	0.03	2.19	2	.119	0.06
5-HTTLPR × TPH2	3.17*	2	.048*	0.08*	0.40	2	.669	0.01
Error		74				74		

[c]Items marked by a superscript c are covariates. Description of covariate effects: [1]Younger participants exhibited faster mRTs especially in the nontarget conditions; [2]longer duration of sleep was associated with higher sdRT in the AY and lower sdRT in the BX condition; [3]sdRT was lower when the AX-CPT was the first paradigm to be performed.

*$p < .05$.

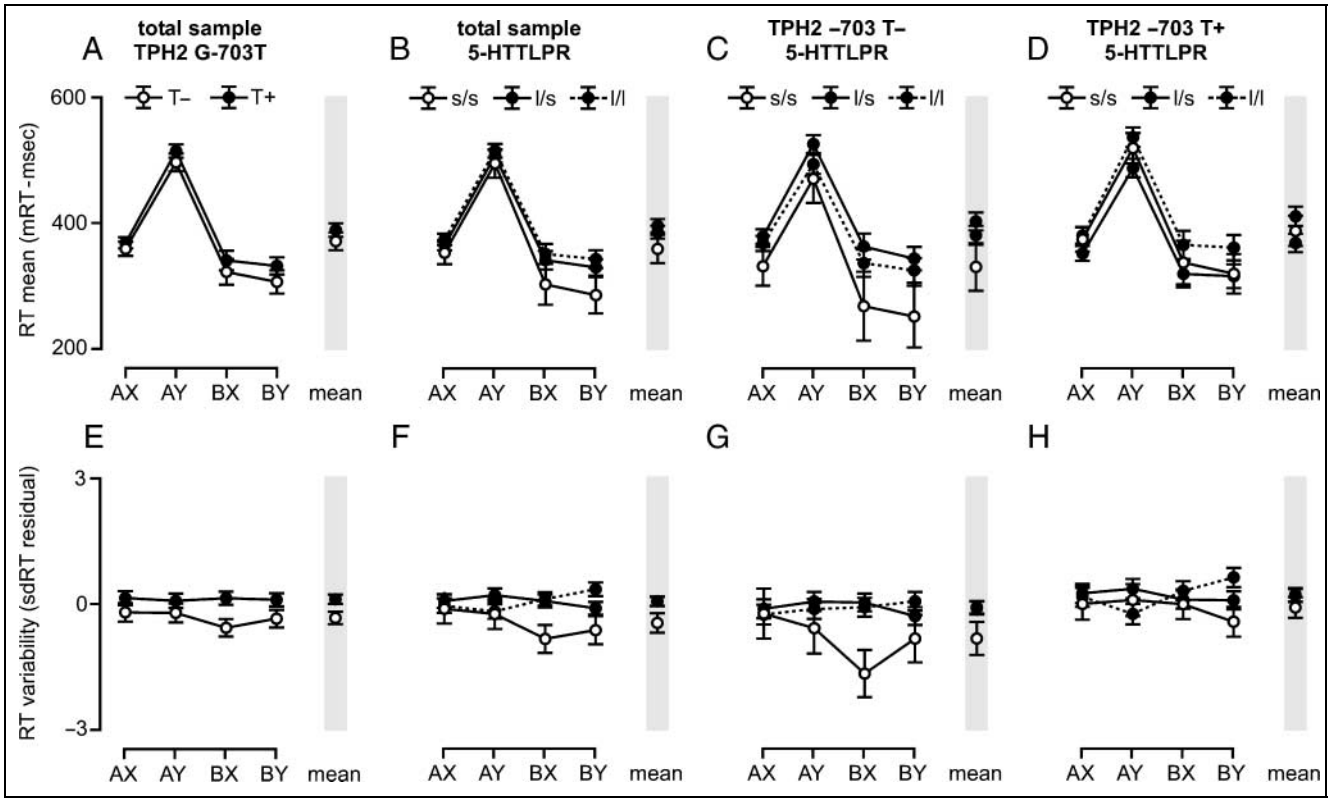

Figure 1. Mean RT (mRT, A–D) and RT variability (sdRT, E–H) in the four conditions of the AX-CPT. Gray-shaded columns: mean mRT/sdRT across conditions. Error bars reflect standard errors of means. (A, E) mRT/sdRT of TPH2 G-703T genotype groups. T− = T allele noncarriers (n = 42); T+ = T allele carriers (n = 43). (B, F) mRT/sdRT of 5-HTTLPR genotype groups (s/s: n = 10, l/s: n = 40, l/l: n = 35). (C, G) mRT/sdRT of 5-HTTLPR genotype groups among TPH2 −703 T allele noncarriers (s/s: n = 3, l/s: n = 21, l/l: n = 18). (D, H) mRT/sdRT of 5-HTTLPR genotype groups (s/s: n = 7, l/s: n = 19, l/l: n = 17) among TPH2 −703 T allele carriers.

$p \geq .317$, $\eta^2 \leq 0.03$). However, there was a significant 5-HTTLPR × TPH2 G-703T interaction effect on the average mRT ($p = .048$, $\eta^2 = 0.08$), descriptively indicating that 5-HTTLPR s/s individuals showed lower mRT only in the absence of the TPH2 T allele (see Figure 1C and D; note, however, that this group comprised only three individuals).

RT Variability

As mentioned in the Methods section, RT variability (sdRT) was residualized for mRT separately for condition, using linear regression that resulted in an equalization of condition means. Therefore, in the repeated measures ANOVA of sdRT (for detailed statistics, see Table 2), the condition main effect ($p = .193$, $\eta^2 = 0.02$) could not be interpreted. Covariate effects emerged for paradigm order and for sleep duration. With regard to genotype-specific effects, the Condition × TPH2 G-703T and the Condition × 5-HTTLPR × TPH2 G-703T interactions were not significant (both $p \geq .388$, $\eta^2 \leq 0.03$; see Figure 1E, G, and H, respectively). However, there was a significant interaction effect of Condition × 5-HTTLPR ($p = .041$, $\eta^2 = 0.06$): compared to 5-HTTLPR l/l and s/l genotypes, the s/s genotype group exhibited lower RT variability in the BX and BY conditions (see Figure 1F). In addition, there was a significant TPH2 G-703T main effect on the average sdRT across conditions ($p = .018$, $\eta^2 = 0.07$), with noncarriers of the TPH2 −703 T allele exhibiting lower average sdRT across conditions (see Figure 1E). There was no main effect of 5-HTTLPR and no interaction of the polymorphisms on average sdRT (both $p \geq .119$, $\eta^2 \leq 0.06$).

Impact of Hit Rates

Despite the generally very low number of errors in the total sample, the possibility remains that the above results are biased by so-called post-error slowing, that is, higher RTs after an error has been committed, which evidently results in higher mean RTs and RT variability when more errors are committed. Indeed, evidence for post-error slowing was provided by post hoc comparisons of RTs for hits following hits versus RTs for hits following errors in a subsample of 41 participants who had committed enough errors (i.e., ≥4 errors; data available upon request). Therefore, the higher sdRT of TPH2 −703 T allele carriers as compared to noncarriers may be explained by post-error slowing because T allele carriers also showed lower hit rates (i.e., made more

errors, see above). To address this issue, we excluded hit trials following erroneous responses from the calculation of mRT and sdRT. When repeating the respective analyses with these values, all results remained unchanged (data available upon request).

The Role of Neuroticism

As outlined in the Introduction, both 5-HTTLPR and the TPH2 G-703T polymorphism have been associated with neuroticism or related measures or negative emotionality (e.g., Reuter, Küpper, et al., 2007; Lesch et al., 1996). Given that high scores in neuroticism indeed reflect mental noise and are related to higher RT variability (Robinson & Tamir, 2005), the associations between sdRT and the two polymorphisms might be mediated by their influence on neuroticism. We addressed this issue by analyzing the impact of neuroticism scores in the 78 participants for whom NEO-PI-R data were available.

First, possible associations between 5-HTTLPR and TPH2 G-703T and NEO neuroticism were assessed by means of univariate ANOVA. Not surprisingly given the small sample size, there were no significant main or interaction effects of the polymorphisms on neuroticism, although the main effect of the TPH2 polymorphism pointed in the expected direction (neuroticism means ± *SEM*: T−: 100.6 ± 4.8 vs. T+: 89.5 ± 3.6) and approached significance, $F(1,79) = 3.46$, $p = .067$, $\eta^2 = 0.05$ (other $p \geq .468$, $\eta^2 \leq 0.02$).

When carrying out the repeated measures ANOVA for sdRT in this subsample (first without consideration of neuroticism), we observed comparable effects as in the total sample with a TPH2 main effect on average sdRT, $F(1,67) = 5.88$, $p = .018$, $\eta^2 = 0.08$, and a Condition × 5-HTTLPR interaction, $F(5.4,182.2) = 2.58$, $p = .024$, $\eta^2 = 0.07$. When entering neuroticism as covariate into the ANOVA model, the genotypic effects remained essentially unchanged for the Condition × 5-HTTLPR interaction, $F(5.6,184.7) = 2.40$, $p = .033$, $\eta^2 = 0.07$, or became even stronger for the TPH2 main effect on the average sdRT, $F(1,66) = 7.93$, $p = .006$, $\eta^2 = 0.11$. Neuroticism showed no interaction with condition, $F(2.7,180.0) = 0.40$, $p = .735$, $\eta^2 = 0.01$, and had no significant effect on average sdRT, although a tendency in the expected direction emerged, that is, a positive correlation between sdRT and neuroticism, $F(1,66) = 2.88$, $p = .094$, $\eta^2 = 0.04$. However, when dropping the polymorphisms from the model, this tendency vanished, $F(1,71) = 0.86$, $p = .357$, $\eta^2 = 0.01$. That is, neuroticism alone did not account for much of the variance in sdRT and had no substantial impact on the genotypic effects.

DISCUSSION

Taken together, the data presented here provide further evidence for a role of serotonin in cognition by showing that variation in genes of the serotonergic signaling pathway influences behavioral measures of cognitive control in a working memory task. Specifically, our data show higher hit rates and lower RT variability in the absence of the TPH2 −703 T allele, whereas there are no mean RT differences between the TPH2 genotypes. This means that although individuals without the T allele are not faster, they are less variable in responding and commit fewer errors than T allele carriers. These findings parallel and extend those of Reuter, Ott, et al. (2007), who found that individuals without the T/T genotype showed enhanced executive control as determined using the ANT (Fan et al., 2001). Although it has to be noted that we did not *exactly* replicate this finding because we aggregated the rare T/T genotype and the G/T genotype, this aggregation is in accordance with a number of earlier studies on the TPH2 G-703T polymorphism (e.g., Brown et al., 2005; Canli, Congdon, et al., 2005). Nevertheless, future studies should try to examine in more detail the possibly unique features of the T/T genotype by employing larger samples.

With regard to 5-HTTLPR, the results are less conclusive. The significant interaction of the TPH2 polymorphism and 5-HTTLPR on mean RT cannot be interpreted because the T− × s/s group consisted of only three individuals. The s/s genotype group consisted of only 10 individuals, and hence the significant condition-specific effect of this polymorphism on RT variability must be interpreted with caution. Nevertheless, this Condition × Genotype interaction deserves attention. This effect was due to reduced RT variability of the s/s genotype group in the BX and BY conditions, that is, conditions where the cue B already determines the response to which probe ever. This suggests that especially individuals with the 5-HTTLPR s/s genotype are able to use this information to prepare the upcoming (nontarget) response and may point to a higher efficiency of cognitive control processes in s/s genotype carriers. In our view, this tentative finding warrants further examination of the role of 5-HTTLPR in cognition.

More specifically, future studies should address in more detail the possible impact of 5-HTTLPR on ACC-mediated processes of cognitive control, as our data only partly show a 5-HTTLPR genotype effect in conditions reflecting processes of conflict monitoring or response inhibition (i.e., significant effects for BX, but not for AY trials). This issue is even more important for the TPH2 polymorphism. Whereas Reuter, Ott, et al. (2007) clearly demonstrated an effect of this polymorphism on executive control in the ANT, the present result of overall reduced error rates and RT variability, but a lack of significant condition-specific effects, might also be explained by referring to nonspecific, for example, motivational or arousal-related effects of this polymorphism on performance. Furthermore, it would be of interest to examine why the 5-HTTLPR genotype did not affect performance in the AX-CPT in exactly the same way the

TPH2 polymorphism did. It may be speculated that the putatively mainly developmental effects of 5-HTTLPR (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004) have a somewhat different impact on certain behaviors than the rather sustained effects of TPH2 variation on 5-HT availability.

Regarding a mediation of the observed effects by neuroticism and its possible influence on RT variability, our analyses show that the genotypic effects on RT variability are not altered when controlling for neuroticism, and moreover, they only provide very limited evidence for an association of neuroticism with RT variability. However, it has to be noted that these results do not disqualify the appealing hypothesis of neuroticism as mental noise. As it was not our intention to test this hypothesis, our setting differed in several aspects from the setting used by Robinson and Tamir (2005). The most important aspect may be that they used choice RT tasks that did not require to maintain and to update task sets or to deal with response conflict to a large extent; that is, they used tasks that rather require automatic processing than a high degree of executive control. As the authors propose, individuals high on neuroticism tend to worry about their ability to cope with future events and consequently try to overcome expected information-processing deficits by cognitive control. Therefore, they may exhibit performance instability in tasks where automatic processing is appropriate, but may not show instability in tasks requiring cognitive control.

Although the present analyses could not show a substantial impact of neuroticism on RT variability, it is intriguing that the TPH2 T allele noncarriers who exhibited less RT variability and committed less errors also showed tendentially higher neuroticism scores even in this relatively small sample. Although the effect slightly missed significance, it accounted for 5% of the variation in neuroticism, which is comparably high for associations between a polymorphism and self-report measures of personality traits. Furthermore, it is to some extent in line with the results of Reuter, Küpper, et al. (2007) who found that individuals without the T/T genotype exhibited higher scores in negative emotionality as assessed with the temperament scale harm avoidance. Taken together with the finding of Reuter, Ott, et al. (2007) that individuals without the T/T genotype showed enhanced executive control in the ANT, the available evidence raises the intriguing possibility that a genetic variant associated with higher negative emotionality may have beneficial effects on some cognitive control functions. Our results for 5-HTTLPR reinforce this notion as they point to enhanced cognitive control in individuals with the s/s genotype that is assumed to be associated with high negative emotionality (e.g., Lesch et al., 1996).

This converging evidence on an association of genetic variation along the serotonergic signaling pathway with both higher negative emotionality and enhanced cognitive control may at first glance seem counterintuitive. However, we want to emphasize that the evidence concerning an effect of genetic variation in serotonin function on both higher negative emotionality and improved cognitive control functions does not necessarily imply that negative emotionality is *directly* related to cognitive functions. Such a direct relation is neither supported by our results nor should it be expected given the current evidence. Rather, the genetic polymorphisms examined here may influence certain brain structures and circuits that are involved in both emotional and cognitive–behavioral regulation, but which may have a different impact in one situation (being confronted with emotional stimuli) than in another (being challenged by a demanding cognitive task). As an example, the amygdala has originally been investigated with regard to its role in emotion, but its connections with the prefrontal cortex make it likely that it also affects cortical regions implicated in cognitive control or working memory. Indeed, a recent imaging study by Schaefer et al. (2006) showed that in a 3-back working memory task, higher event-related amygdala activity was associated with faster RTs without affecting accuracy, whereas in a 1-back task, amygdala activity was associated with slower RTs. This correlation was not influenced by mood state or temperament variables.

This finding also supports the above-mentioned notion that a possible relation between higher negative emotionality and worse cognitive performance might extend only to simple tasks that can be processed automatically, whereas in tasks requiring controlled processing, negative emotionality might have beneficial effects. Such effects related to task-demands may also explain why we observed lower RT variability in a TPH2 G-703T genotype that has previously been associated with higher negative emotionality, whereas Robinson and Tamir (2005), using less demanding tasks, found negative emotionality to be correlated with elevated RT variability. Further evidence supporting the notion of task-demand-specific effects also comes from human studies employing acute tryptophan depletion (ATD), a simple method to induce a transient decrease in serotonergic neurotransmission. ATD has mood-lowering effects on some individuals, especially if they have a history of depression (Reilly, McTavish, & Young, 1997). Concerning cognitive effects of ATD, it has been reported that it impairs memory consolidation but improves focused attention (Riedel, Klaassen, & Schmitt, 2002) and Stroop performance (Evers, van der Veen, Jolles, Deutz, & Schmitt, 2006), that is, tasks that demand effortful control for effective performance.

Among the limitations of the present study, the possible impact of the participants' sex deserves attention. The imbalanced sex ratio may have impacted the results, and using sex as an independent factor would have been more informative than its usage as a covariate. However, given the small sample size, this was not possible. Moreover, possible sex-specific effects on cognition like the impact of the menstrual cycle (Hampson, 1990) could

not be controlled. The role of sex in cognition should therefore be considered in more detail in future studies.

It is evident that none of our results would survive a correction of the significance level for the multiple tests performed. However, with respect to the effects observed for the TPH2 G-703T polymorphism, they parallel those of a previous report (Reuter, Ott, et al., 2007), and hence, in our view, can add important details to the emerging evidence of a modulation of cognitive control functions by serotonergic neurotransmission in general and the TPH2 G-703T polymorphism in detail. The repeated observation that genetic variants associated with higher scores in anxiety- and depression-related personality traits may have beneficial effects on some cognitive functions may encourage further research into the exact nature of these functions, their interplay with emotional traits, and their underlying neurobiological mechanisms.

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