Variation in Key Genes of Serotonin and Norepinephrine Function Predicts Gamma-Band Activity during Goal-Directed Attention

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Recent evidence shows that genetic variations in key regulators of serotonergic (5-HT) signaling explain variance in executive tasks, which suggests modulatory actions of 5-HT on goal-directed selective attention as one possible underlying mechanism. To investigate this link, 130 volunteers were genotyped for the 5-HT transporter gene-linked polymorphic region (5-HTTLPR) and for a variation (TPH2-703 G/T) of the TPH2 gene coding for the rate-limiting enzyme of 5-HT synthesis in the brain. Additionally, a functional polymorphism of the norepinephrine transporter gene (NET-3081 A/T) was considered, which was recently found to predict attention and working memory processes in interaction with serotonergic genes. The flanker-based Attention Network Test was used to assess goal-directed attention and the efficiency of attentional networks. Event-related gamma-band activity served to indicate selective attention at the intermediate phenotype level. The main findings were that 5-HTTLPR s allele and TPH2 G-allele homozygotes showed increased induced gamma-band activity during target processing when combined with the NET A/A genotype compared with other genotype combinations, and that gamma activity mediates the genotype-specific effects on task performance. The results further support a modulatory role of 5-HT and NE function in the top-down attentional selection of motivationally relevant over competing or irrelevant sensory input.

Keywords: gamma band, oscillations, genetic variation, norepinephrine, selective attention, serotonin

Introduction

Converging evidence suggests that serotonergic (5-HT) neurotransmission is not only an important modulator of mood and emotion regulation and associated clinical syndromes such as depression and anxiety (e.g., Lucki 1998), but may also be critically involved in cognitive and executive control functions. This notion is supported by evidence on projections from the raphe nuclei, where central 5-HT is synthesized, to frontal brain areas, where 5-HT receptor and transporter sites are relatively abundant (see Arnsten and Goldman-Rakic 1984; Preece et al. 2004; Varnas et al. 2004). Furthermore, it was shown that a global reduction of 5-HT availability following acute tryptophan depletion results in adverse effects on learning and long-term memory (e.g., Park et al. 1994; Riedel et al. 1999; van der Veen et al. 2006). With regard to executive functions, the effects of 5-HT are less clear. For example, it was demonstrated that selective 5-HT depletions in the orbitofrontal cortex resulted in perseveration deficits in reversal learning tasks, which may point to inhibition impairments (for review, see Cools et al. 2008), whereas the 5-HT agonist "fenfluramine" was observed to reduce impulsive responding (see Clark et al. 2004). In contrast, there is evidence that lowering 5-HT improves focused/selective attention (for reviews, see Booij et al. 2003; Schmitt et al. 2006) and that stimulating 5-HT by reuptake inhibitors (e.g., "fluoxetine" and "citalopram") appears to impair vigilance (Schmitt et al. 2006). Findings on the 5-choice serial reaction time (RT) task in rats using neurochemical lesions and 5-HT agents lend support to the role of 5-HT in mediating different aspects of attentional control performance (for review, see Robbins 2002).

These specific effects of 5-HT on subprocesses of executive function may then also affect more global executive measures that are reflected in multicomponent tasks such as the Wisconsin Card Sorting test (WCST, Borg et al. 2009) or may contribute to the impact of 5-HT on long-term memory (e.g., Riedel et al. 1999; Roiser et al. 2007). Regulatory activity of receptor and transporter action or of metabolic mechanisms mediating 5-HT biosynthesis and degradation can be expected to moderate the influence of 5-HT on executive processing. Nevertheless, in this regard, relatively little is known about their exact role. Moreover, structural and functional interactions with dopamine and norepinephrine (NE) systems that are known to shape executive control processes need to be considered when estimating the impact of 5-HT on executive measures (e.g., Puumala and Sirvio 1998; Berridge and Waterhouse 2003).

Recently, functional genetic variations that provide "natural sources" of variance within particular constituents of the 5-HT circuitry have been associated with executive functioning. One of these variations is the 5-HT transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) in the promoter of the gene encoding the 5-HTT (SLC6A4), which is considered a key regulator of the 5-HT system mediating the reuptake of 5-HT from the synaptic cleft to presynaptic nerve terminals. The short (s)-allelic variant of this polymorphism has been associated with lower transcriptional efficiency and lower 5-HT transporter function relative to the long (l) allele (Lesch et al. 1996). There might be allele-specific developmental effects on brain morphology and function, too (Ansorge et al. 2004; Jedema et al. 2010). In seminal studies, the s allele has been linked to negative emotionality (Lesch et al. 1996) and to heightened amygdala activation in response to emotional stimuli (Hariri et al. 2002). Recent meta-analytic data support the role of adverse life events as moderating factor between s allele and affective disorders (Karg et al. 2011), and converging evidence suggests a general tendency of increased processing of motivationally relevant cues in s-allele carriers that may also lead to cognitive improvements (Homberg and Lesch 2011).
The first evidence for a possible role of 5-HTTLPR in executive processing was provided by Fallgatter et al. (1999), who reported stronger anteriorization of the so-called NoGo-P3 event-related potential (ERP) in s-allele carriers by using a Go/NoGo task. Typically, such type of cognitive control tasks requires to handle competing response alternatives and thus enhance the ability to inhibit distracting or irrelevant events and to focus on goal-relevant stimuli, which is mediated by lateral prefrontal cortex (PFC) and anterior cingulate cortices. Superior Go/NoGo performance as indicated by lower response variability on response-conflict trials in a Continuous Performance task (Strobel et al. 2007) and by less omission errors to target stimuli (Roiser et al. 2007) suggests s/s carriers to be more focused on goal-relevant information than other genotypes (see also Enge, Fleischhauer, Lesch, Strobel 2011). A similar pattern was found for the WCST incorporating a range of executive measures and considered to tap cognitive flexibility (Borg et al. 2009). Further, Anderson et al. (2012) observed s-allele carriers to exhibit superior storage capacity in visual working memory, and we previously found s/s carriers to show improved attentional selection of target stimuli during the n-back working memory task (Enge, Fleischhauer, Lesch, Reif et al. 2011). Moreover, we observed interactions with a functional NE transporter polymorphism suggesting interplay of NE and 5-HT in shaping such goal-directed behavior (see also Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005).

A further key regulator of the 5-HT system is the rate-limiting enzyme of 5-HT biosynthesis named tryptophan hydroxylase (TPH). The gene that codes for the brain-specific isoform of TPH, called TPH2 (Walther and Bader 2003; Gutknecht et al. 2007), shows a common single-nucleotide polymorphism (SNP) in its regulatory promoter region (TPH2 -703 G/T; rs4570625). There is evidence that the G allele of this gene variation is linked to reduced mRNA levels that result in lower 5-HT concentration compared with the rare T allele (Lin et al. 2007; but see Scheuch et al. 2007; Chen et al. 2008). Functional significance of TPH2 -703 G/T is indicated by genomic imaging studies (e.g., Canli et al. 2005), and recent data suggest TPH2 -703 G/T to be implicated in cognitive control processes: Reuter et al. (2007) found an association of TPH2 -703 G/T with the executive control network of the RT-based Attention Network Test (ANT, Fan et al. 2002). Carriers of the T/T genotype exhibited less conflict resolution and made considerable more erroneous responses than those with at least one G allele. Given the relevance of 5-HT for impulsive behavior (e.g., Lesch and Merschdorf 2000), Reuter et al. (2007) concluded that TPH2 -703 G/T may impact on impulse control circuits. In a similar vein, Strobel et al. (2007) reported carriers of the rare T allele to show overall stronger anteriorization and higher RT variability indicating impaired executive control while performing the AX Continuous Performance task that evokes focused attention and inhibitory control. Moreover, Osinsky et al. (2009) observed response deficits in subjects homozygous for the T allele compared with G/T and G/G carriers using the Stroop task, a complex executive control measure stressing top-down selective attention, goal maintenance, and response inhibition.

Taken together, based on the available evidence, 5-HTTLPR and TPH2 -703 G/T were considered as candidates to mediate goal-directed behavior. Specifically, carriers homozygous for the s allele of 5-HTTLPR and the G allele of TPH2 -703 G/T showed benefits in executive function tasks. This may result from enhanced attentional processing of motivationally relevant stimuli relative to irrelevant sensory input suggesting genotype-dependent variation in the control of selective attention (i.e., the neural amplification of goal-relevant information in sensory pathways). In addition, such increased attentional processing might be observed by the activity of specific attentional networks (Posner and Petersen 1990; Fan et al. 2002).

To this end, we used the ANT that requires responding to centrally located target arrows, which can be neutral, congruent, or incongruent, depending on the presence/absence and direction of flanking arrows. Hence, target response time and target accuracy measures would provide initial information about the top-down control of selective attention on goal-relevant stimuli of varying difficulty. Moreover, the ANT allows conclusions on the efficiency of attentional networks (i.e., orienting, alerting, and executive control, Posner and Petersen 1990; Fan et al. 2002), which can be assessed by how target RT is influenced by alerting cues, spatial cues, and flankers. To obtain information whether 5-HTTLPR and TPH2 -703 G/T are associated with specific network activity might be interesting because genotype-dependent performance differences on selective attention may also be promoted by how individuals handle conflict (“executive control network” of ANT) or/and by the degree of attentional sensitivity to incoming stimuli which would refer to sustained attention or vigilance (“alerting network” of ANT).

Finally, given the long path between distal genotype and overt behavior, we further applied an “intermediate phenotype” approach that has been proven to be useful in identifying gene effects (Gottesman and Gould 2003). Here, we concentrated on event-related desynchronization/synchronization (ERD/ERS, Makeig 1993; Pfurtscheller and Lopes da Silva 1999) of neuronal oscillation in gamma-band activity (30–100 Hz) in the electroencephalogram (EEG) to tap the decrease or increase in rhythmic activity of task-specific neural assemblies relative to baseline. Such stimulus-related gamma-band activity typically consists of an early so-called evoked gamma-band response that is phase locked to stimulus onset as well as an induced gamma-band part that is not strictly phase locked, that is, jitters in latency from trial to trial. Evoked gamma-band responses have frequently been observed at a frequency of about 40 Hz with a peak latency before 150 ms; induced gamma occurs later in time (after 250 ms) and often oscillate at higher frequencies such as around 70 Hz in the visual domain (see Herrmann et al. 2004; Hoogenboom et al. 2006). Findings in animals and humans suggest that gamma-band oscillations play a fundamental role in attention and (working) memory-related processes indicating whether a sensory stimulus is processed effectively: In particular, gamma-band oscillatory activity has been tightly associated with top-down attentional selection (see Jensen et al. 2007; Womelsdorf and Fries 2007), which facilitates effective processing as it enables to selectively amplify the most relevant sensory input, while inhibiting distracting or irrelevant events (e.g., Desimone and Duncan 1995). Gamma-band synchronization in local neurons of a frontoparietal attention network including connections to visual and oculomotor structures that convey the relevant features of the attended stimuli (for review, see Noudoost et al. 2010) has been found to functionally result in improved behavioral outcomes such as lower...
response latencies, higher accuracy levels, and successful memory formation, as evidenced in animals and humans (for reviews, see Jensen et al. 2007; Womelsdorf and Fries 2007; Fries 2009).

Taken together, we examined genotype-dependent performance outcomes and gamma-band ERD/ERS in response to target stimuli of varying difficulty (neutral, congruent, and incongruent) and with regard to specific attentional networks (orienting, alerting, and conflict). We expected individuals homozygous for the 5-HTTLPR s allele and for the TPH2 -703 G/T G allele to be associated with improved performance and increased target-related gamma-band synchronization indicating enhanced top-down selective attention to goal-relevant information. In expectation of gene x gene interactions, we further considered a functional gene variation of the NE transporter (NET -3081 A/T) that has been found to explain variance in executive function and dysfunction, especially in ADHD (Kim et al. 2006; Hahn et al. 2009). Most interestingly, interactions of NET -3081 A/T and 5-HTTLPR on both target accuracy and P3 ERP latency in the n-back task suggest benefits for homozygous carriers of the A allele (NET -3081 A/T) and the s allele (5-HTTLPR) compared with other genotype combinations (Enge, Fleischhauer, Lesch, Reif et al. 2011). To our knowledge, this is the first study on the role of genetic variation in key regulators of 5-HT- and NE-related function in relation to oscillatory brain activity during executive processing.

Materials and Methods

Participants
Participants were 130 student volunteers of middle European descent (62 men, age mean ± SD 23 ± 5.6 years, range 18–33 years) who gave written informed consent prior to testing. They received either monetary compensation or course credit upon study completion. All subjects had normal or corrected-to-normal vision and were right handed according to the Edinburgh Handedness Inventory (Oldfield 1971). Prior to the study, volunteers were screened for exclusion criteria. All participants examined in the present study reported to have no history of neurologic/psychiatric diseases, substance abuse, or dependence, to have never received psychopharmacological treatment, and to have no current health problems. Possible confounding factors, such as age, sex, and negative emotionality, sleep duration, smoking status, as well as caffeine and alcohol consumption were assessed. The study was conducted in accordance with the Declaration of Helsinki (revised version) and followed the ethical standards of the German Psychological Association.

Genotyping
Buccal samples were obtained, and DNA was extracted using the Buccalamp system (Epigenics Technologies, Madison, WI). 5-HTTLPR was genotyped by polymerase chain reaction amplification according to a previously published protocol (Lesch et al. 1996). Recently, a functional SNP was detected within the 5-HTTLPR 1 allele with an A to G substitution (rs25531) of minor allele frequency (>9%), designated L4 and L5 (Nakamura et al. 2000). The L4 variant has been associated with high levels of in vitro 5-HT mRNA expression; the L5 variant, however, is considered to be functionally comparable with the low expressing s allele. The SNP was genotyped using the protocol described by Wendland et al. (2006). Homozygous s allele, L4/L4, and s/L5 cases were collapsed (e.g., Hu et al. 2006) and reclassified as s/s genotype (n = 50; 23%). Both heterozygous s/LA and L4/L5 cases were reclassified as s/L1 genotype (n = 54; 42%). Carriers with 2 copies of the L4 allele are referred to as L1/L1 genotype (n = 46; 35%).

Genotypes of TPH2 -703 G/T (rs4570625) were determined as described earlier (Walitza et al. 2005). Genotype frequencies of TPH2-703 G/T were 64% for G/G (n = 83), 29% for G/T (n = 38), and 7% for T/T (n = 9). Because of the low frequency of the T/T genotype and in accordance with previous studies (e.g., Canli et al. 2005; Chen et al. 2008) subjects with 1 or 2 copies of the T allele (T+, n = 47) were grouped together and contrasted to homozygous G/G carriers. Further, a functional A to T SNP (rs28586840) in the promoter of the NE transporter gene (NET, SLC6A2) at position -3081 upstream of the translational start site was genotyped according to the protocol of Kim et al. (2006), with the minor T allele of this polymorphism exhibiting decreased transcriptional activity and reduced promoter function relative to the A allele. Genotype frequencies were 48% for A/A (n = 62), 40% for A/T (n = 52), and 12% for T/T (n = 16). Because of the low frequency of the rare T/T genotype and based on findings that the A/T and T/T genotypes are overrepresented in ADHD cases (Kim et al. 2006), where executive control is impaired (Willcutt et al. 2005), carriers with at least one T allele were collapsed (T+, n = 68) and compared with A/A carriers. Genotypes of all polymorphisms were in Hardy–Weinberg equilibrium (all P > 0.20). The TPH2 -703 G/T and the NET -3081 A/T are in the following referred to as TPH2 and NET, respectively.

Task and Procedure
Participants were seated in a dimly lit, acoustically shielded room about 65 cm in front of a computer screen and the electrode cap was attached. Responses on ANT targets were collected by 2 input buttons of a keypad. The target stimulus consisted of a horizontal black line with a leftward- or rightward-pointing arrowhead. It was presented at the central position and was surrounded by 2 flanking arrows on either side pointing to the same direction (congruent condition), to the opposite direction (incongruent condition), or by flankers that only contained lines (neutral condition). After the presentation of a fixation cross of variable duration (400–1600 ms) and a warning cue (100 ms) followed by an invariant fixation period (400 ms), targets and flankers were presented simultaneously in 1 of 2 locations, either 1.06° above or below the fixation cross. Targets and flankers immediately disappeared after the participants’ response or after 1700 ms in case no response occurred and a variable fixation period followed. The entire trial duration was 4000 ms. The ANT consisted of 4 warning cue conditions: “no cue” condition in which only the fixation was presented, the “center cue” condition where an asterisk at the fixation location appeared, the “double-cue” condition where asterisks were presented at the 2 possible target locations, and the “spatial cue” condition in which a cue was presented at the valid position of the appearing target. For the alerting effect, the mean RT of the double cue conditions was subtracted from the mean RT of the no-cue conditions. For the conflict monitoring effect, the mean RT of the spatial cue conditions was subtracted from the mean RT of the center cues. The conflict effect of the executive control network was calculated by the mean RT of all incongruent flanker conditions minus the mean RT of all congruent conditions. The ANT contained 1 practice block of 24 trials. Experimental conditions were run in 3 blocks of 96 trials each all in all resulting in 288 trials, that is, 96 trials per target condition (congruent, incongruent, and neutral) or 72 trials per cue condition (no, center, double, and spatial). The order of the cue and target conditions was randomized. Participants were requested to respond as fast and accurately as possible (see also Fan et al. 2002).

EEG Recordings
EEG, vertical electrooculogram, and horizontal electrooculogram were continuously recorded from 32 Ag/AgCl electrodes, attached to an electrode cap, and positioned according to the enhanced 10–20 system. AFz was used as ground, and all electrodes were referenced to linked mastoids; impedances were kept <5 kΩ. The sampling rate was 500 Hz, and the data were hardware filtered using a bandpass of 0.1–100 Hz. Continuous EEGs were epoched offline from ~2048 to 2048 ms after stimulus onset. Epochs were submitted to an extended informax independent component analysis (ICA) to remove muscle activity, electrical noise artifacts, and ocular artifacts such as eye
blinks, eye movements, and saccadic activity (Jung et al. 2000; Keren et al. 2010) using EEGLAB (Delorme and Makeig 2004). In addition, ICA-corrected epochs with values that exceeded a threshold of ±100 mV were rejected before further processing. This resulted in a mean percentage of rejected trials per condition of 1.5 (SD = 2.1).

The data were then submitted to a time–frequency analysis to estimate signal power of brain oscillations in the gamma-band frequency range using a Morlet based wavelet that provides an adequate balance between time and frequency resolution and that has been suggested and detailed elsewhere (Tallon-Baudry et al. 1997; Tallon-Baudry and Bertrand 1999). A resolution factor of $m = f/\sigma_f$ of 7 was used and the signal was convolved from 30 to 100 Hz in 1-Hz steps. Single trials were wavelet filtered and the resulting absolute values were averaged to gain total gamma-band activity including those that is phase locked and nonphase locked to the stimulus reflecting the evoked and induced fraction of the gamma response. Using the approach described in Pfurtscheller and Lopes da Silva (1999), power changes were calculated relative to a preceding reference or baseline period (−1.1 to −0.6 s) to obtain an individual and condition-specific measure of ERD/ERS that is defined as the percentage of gamma-band power decrease or increase, respectively.

As expected from the literature, visual inspection of the grand average time–frequency representation revealed 2 marked local gamma-band increases (see Supplementary Material for a figure of averaged gamma-band ERD/ERS): An early gamma increase (~100–250 ms after target onset) occurred between 40 and 60 Hz demonstrating evoked gamma-band activity, which is considered as phase locked to stimulus onset. The second gamma peak (~400–700 ms after target onset) was between 70 and 80 Hz and marks the induced fraction of gamma (see Tallon-Baudry and Bertrand 1999; Herrmann et al. 2004; Hoogenboom et al. 2006). An ANOVA including the within-subjects factors “frequancy band” (30–100 Hz; in 10 Hz clusters) and “time window” (0–1600 ms after stimulus onset; in 100 ms epochs) confirmed visual inspection by a highly significant frequency band × time window interaction, $F_{9,11970} = 26.75$, $P < 0.001$, $\eta^2_p = 0.17$, $\varepsilon = 0.10$, and by significant simple comparisons between the different frequency bands in the time windows, as outlined above (all $P < 0.05$).

Data Analysis

First, analyses were performed to ensure that the ANT task characteristics as proposed by Fan et al. (2002) can be replicated, then genotype-specific main and interaction effects of 5-HTTLPR, TPH2, and NET on behavioral performance data were examined. A 5-way mixed-model ANOVA was conducted separately for error rate (in percent) and mean RT (normalized via log-transformation) as dependent variables including the within-subjects factors “target condition” (neutral, congruent, and incongruent targets) and “cue type” (no, double, center, and spatial cue) and the between-subjects factors 5-HTTLPR, TPH2, and NET. Additionally, univariate ANOVAs were conducted to examine genotype-dependent differences in the efficiency of the “alerting”, “orienting”, and “conflict” networks. Each network effect was calculated as RT difference score between 2 cue conditions (alerting: no cue condition minus double-cue condition; orienting: center cue minus spatial cue) or target conditions (conflict: incongruent targets minus congruent targets) divided by the mean RT (see Fan et al. 2002).

Second, considering gamma-band oscillatory activity (ERD/ERS), a 6-way mixed-model ANOVA was conducted for genotype-specific effects on “evoked” gamma-band activity (40–60 Hz) as well as on “induced” gamma-band activity (70–80 Hz). The ANOVAs included the within-subjects factors “target condition” (neutral, congruent, and incongruent target), “position” (Fz, Cz, and Pz), and “time window” (0–1600 ms after stimulus onset; in 100 ms epochs) and the between-subjects factors 5-HTTLPR, TPH2, and NET. Moreover, the specific effects on gamma-band activity difference scores referring to the alerting, orienting, and conflict networks were examined. Similar to the RT-based network calculations (see above), differences in gamma-band activity on target stimuli dependent on alerting cues, spatial cues, and target types were calculated. These network difference scores were entered in a 5-way mixed-model ANOVA with “position” (Fz, Cz, and Pz), and “time window” (0–1600 ms after stimulus onset; in 100 ms epochs) as within- and 5-HTTLPR, TPH2, and NET as between-subjects factors.

Third, mediation analyses were applied to estimate possible indirect effects of genetic variations on the behavioral outcome mediated by induced gamma ERS using an SPSS macro of Hayes (2012) that allows the implementation of a bootstrapping method. The indirect (mediated) effects were estimated by the computation of bias-corrected bootstrap confidence intervals based on multiple resamples of the dataset. This procedure overcomes problems of non-normal distribution of indirect effects and thus is more powerful than the frequently used Sobel test and the causal steps approach suggested by Baron and Kenny (1986) especially in samples of $N < 500$ (see Preacher et al. 2007). As recommended by Zhao et al. (2010), we focused on the mean value of the indirect effect $(a \times b)$ with $a$ referring to the effect of the independent variable “genotype” on the mediator “gamma” and $b$ indicating the effect of gamma on the dependent variable “ANT performance” controlling for genotype. If the 95% bootstrap confidence interval (based on 5000 resamples) does not include zero, the null hypothesis of no mediation effect can be rejected at an alpha level of 0.05 (Preacher et al. 2007).

Age and sex were considered as covariates when significantly related to within- or between-subjects factors of the ANOVA models. Other potential confounds such as negative emotionality, sleep duration as well as nicotine, caffeine, and alcohol consumption during the past 24 h were not associated with variables used in the ANOVAs (all $P > 0.10$). Greenhouse–Geisser corrected degrees of freedom were applied, and original degrees of freedom, epsilon adjustment values, and corresponding $F$ values were reported where appropriate. Simple effects tests that were conducted on significant interactions are given in parentheses. The resulting $P$ values were also adjusted for multiple comparisons at the 5% level using the false discovery rate (FDR) procedure. FDR is defined as the expected proportion of falsely rejected hypotheses among the total number of null hypotheses rejected (Benjamini and Hochberg 1995). All analyses were performed by SPSS 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

Analyses of ANT Task Characteristics

First, it was determined whether the ANT task effects as proposed by Fan et al. (2002) could be replicated. For RT, the ANOVA showed a highly significant effect of target condition, $F_{2, 254} = 1075.15$, $P < 0.001$, $\eta^2_p = 0.90$, $\varepsilon = 0.62$. In accordance with the assumption made for the conflict network (see Fan et al. 2002), significantly larger RTs were observed for incongruent targets ($\log RT = 6.31–550$ ms) compared with congruent ($6.12–455$ ms) and neutral ones ($6.11–450$ ms; all $P < 0.001$). Moreover, the effect of Cue Type was highly significant, $F_{3, 351} = 672.41$, $P < 0.001$, $\eta^2_p = 0.85$, $\varepsilon = 0.68$: As expected for the alerting network, significantly larger RTs were found for the no cue ($6.25–520$ ms) compared with the double-cue condition ($6.19–490$ ms; $P < 0.001$). For the orienting network, larger RTs for the center cue ($6.20–495$ ms) than for the spatial-cue condition ($6.08–440$ ms; $P < 0.001$) were observed as expected.

Similar results were obtained for accuracy (error rate in percent). Highly significant effects for target condition, $F_{2, 254} = 101.34$, $P < 0.001$, $\eta^2_p = 0.46$, $\varepsilon = 0.54$, and Cue Type, $F_{3, 351} = 15.09$, $P < 0.001$, $\eta^2_p = 0.11$, $\varepsilon = 0.92$, were observed. For both conflict and orienting networks, error rate was larger for incongruent targets (6.3%) than for neutral (0.8%) or congruent ones (0.6%; all $P < 0.001$), and fewer errors were made when the target was preceded by a spatial cue (1.7%) than by a center cue (2.9%; $P < 0.001$).
The Role of 5-HTTLPR, TPH2, and NET in ANT Performance

The ANOVA on error rate as dependent variable showed a significant interaction of 5-HTTLPR × NET, \( F_{1,117} = 5.69, P = 0.004, \eta^2_p = 0.09 \). An interaction of 5-HTTLPR × NET × target condition, \( F_{4, 234} = 5.83, P = 0.003, \eta^2_p = 0.09, \varepsilon = 0.54 \), qualified this effect and demonstrated that genotypic differences mainly occurred in response to incongruent targets. As depicted in Figure 1A, for incongruent targets, 5-HTTLPR s/s carriers better performed when carrying the NET A/A genotype relative to the T allele \((P = 0.002, \eta^2_p = 0.08, \varepsilon = 0.62)\, that, however, only approached significance. Additionally, it suggests that the observed accuracy performance of 5-HTTLPR s/s carriers homozygous for the A allele of NET was not at the expense of RT. Moreover, as expected, the ANOVA on RT as criterion revealed a highly significant main effect of TPH2, \( F_{1,117} = 7.21, P = 0.008, \eta^2_p = 0.06 \), indicating overall faster RTs to targets for individuals carrying the G/G genotype as compared to T-allele carriers of TPH2 (see Fig. 1B).

No significant effects were observed for network efficiency of the alerting, orienting, and conflict networks (all \( P > 0.10 \)) suggesting that the genotypic impact on the target responses was relatively unaffected by cue condition or target type.

The Role of 5-HTTLPR, TPH2, and NET in Gamma-Band Activity

For evoked gamma-band activity (40–60 Hz), no genotype-related main or interaction effects were revealed (all \( P > 0.05 \)). In contrast, genotype-related effects on induced gamma-band activity (70–80 Hz) emerged as indicated by a highly significant effect of 5-HTTLPR × time window, \( F_{50, 1740} = 3.03, P = 0.008, \eta^2_p = 0.05, \varepsilon = 0.19 \), which was qualified by a 5-HTTLPR × NET × time window interaction, \( F_{50, 1740} = 2.53, P = 0.023, \eta^2_p = 0.04, \varepsilon = 0.19 \). As depicted in Figure 2A, individuals with the s/s genotype showed higher induced gamma-band synchronization (i.e., event-related gamma increase; ERS) in the time range of 300–700 ms after target onset than those with the l allele when carrying the A/A genotype of NET \((P = 0.0002–0.008, \eta^2_p = 0.09–0.11)\). These differences survived FDR correction for multiple comparisons (\( n = 16 \), FDR cutoff \( P \leq 0.008 \)). For the NET T allele, no significant difference between 5-HTTLPR genotypes occurred (all \( P > 0.30, \eta^2_p < 0.01 \)).

Similarly, an interaction of TPH2 × time window was observed, \( F_{15, 1740} = 3.63, P = 0.015, \eta^2_p = 0.03, \varepsilon = 0.19 \). The 3-way interaction of TPH2 × NET × time window that qualified the significant TPH2 × time window effect only approached statistical significance, \( F_{15, 1740} = 2.49, P = 0.064, \eta^2_p = 0.02, \varepsilon = 0.19 \). However, as expected from previous work (e.g., Kim et al. 2006; Strobel et al. 2007; Enge, Fleischhauer, Lesch, Reif et al. 2011), it suggests that NET moderates the differences between the TPH2 genotypes (see Fig. 2B), paralleling the results found for 5-HTTLPR. Indicated by simple comparisons, larger induced gamma-band activity between 300 and 700 ms was observed for the G/G than for the T-allelic group of TPH2 when combined with the A/A genotype of NET \((P = 0.004–0.058, \eta^2_p = 0.04–0.07)\), whereas no significant differences were found for the T-allele carriers of NET (all \( P > 0.30, \eta^2_p < 0.01 \)). Note that genotypic differences in the time range of 400–600 ms remained significant after FDR correction \((n = 16, \text{FDR cutoff } P \leq 0.006)\). Further, in line with previous results (see Womelsdorf and Fries 2007), gamma-band ERS was associated with performance benefits. Correlation analysis revealed that in the time range of 300–700 ms, increased induced gamma resulted in lower mean RT \((r = -0.31, P < 0.001, \text{range between } r = -0.16 \text{ and } r = -0.40)\).

Regarding genotypic effects on gamma-band network efficacy, a significant main effect of 5-HTTLPR was observed for the conflict network (gamma-band activity incongruent targets minus congruent targets), \( F_{2, 18} = 3.51, P = 0.033, \eta^2_p = 0.06 \). S-allele carriers exhibited small positive conflict difference scores \((s/s = 0.60, s/l = 0.80)\), indicating somewhat larger gamma-band activity for incongruent than for congruent targets whereas l/l carriers showed large negative scores \((-2.87)\) indicating higher gamma-band activity on congruent than on incongruent trials \((s/s \text{ vs. } l/l: P = 0.045; s/l \text{ vs. } l/l: P = 0.016)\). As indicated by correlation analysis, individuals that showed more positive gamma-band difference scores in the conflict network showed significantly lower error rates on incongruent trials \((r = -0.18, P = 0.046)\). For alerting and orienting, no effects occurred (all \( P > 0.10 \)).

Mediation of Genotypic Effects on ANT Performance by Induced Gamma Oscillations

Next, based on the ANOVA results, it was examined whether the observed differences between genotype groups in RT and error performance were mediated by gamma-band activity. First, it was investigated whether the moderated effect of 5-HTTLPR (independent variable) by NET (moderator) on error rate to incongruent targets (dependent variable) is mediated by induced gamma-band ERS (mediator). Because a moderation of NET was only observed for 5-HTTLPR s/s genotype carriers, whereas for s/l and l/l carriers, no differences occurred (see Fig. 1A), s/s carriers (=1) were contrasted to l/l carriers (=0). Similar coding was used for NET \((0 = \text{ T allele, } 1 = \text{ A/A genotype})\). As there was also a moderating effect of NET on the relationship between 5-HTTLPR and gamma-band activity, conditional indirect effects (i.e., indirect effects depending on the value of the moderator NET) were estimated (see Supplementary Fig. 2A). The interaction between 5-HTTLPR and NET on induced gamma-band ERS reached significance \((a = 20.61, P = 0.015)\) whereas the effect of gamma-band ERS on error rate, controlling for 5-HTTLPR and NET was statistically not different from zero \((b = 0.02, P = 0.483)\). The 95% bootstrap confidence interval (CI) for the product of \((a \times b = 0.375)\) that quantifies the indirect effect ranged from \(-0.72 \text{ to } 2.03\). Because the confidence interval includes zero, the moderation of 5-HTTLPR by NET on error rate is not significantly mediated by gamma-band activity. Neither did the conditional indirect effects (depending on the value of the moderator NET) reach statistical significance at \( \alpha = 0.05 \).

Based on the interaction of 5-HTTLPR × NET × target condition on RT, a similar mediation analysis was run. In contrast to error rate, induced gamma-band ERS was predictive for RT
(b = −0.01, P = 0.021) and the estimate of the indirect effect reached significance as indicated by a 95% CI excluding zero (a × b = −0.025, 95% bootstrap CI = −0.065 to −0.004) suggesting that the moderated effect of 5-HTTLPR × NET on RT is mediated by induced gamma-band activity. Moreover, the model provides evidence for a conditional indirect effect:
so, for NET A/A carriers, the bootstrapping procedure revealed a significant mediation ($a \times b_{A/A} = -0.022$, 95% bootstrap CI = $-0.056$ to $-0.004$), whereas for NET T-allele carriers, the indirect effect did not reach statistical significance ($a \times b_T = 0.003$, 95% bootstrap CI = $-0.005$ to $-0.018$). That is, the interaction of 5-HTTLPR × NET on RT is mediated by induced gamma ERS for NET A/A but not for T-allele carriers.

Moreover, it was examined whether the TPH2 main effect on mean RT was mediated by induced gamma ERS. Because TPH2 also interacted with NET in predicting gamma, we again conducted a moderated mediation analysis estimating conditional indirect effects depending on the value of NET (see Supplementary Fig. 2B). In fact, bootstrapping procedure yielded a significant indirect effect for the NET A/A genotype ($a \times b_{A/A} = -0.011$, 95% bootstrap CI = $-0.027$ to $-0.001$), but not for the NET T allele ($a \times b_T = -0.002$, 95% bootstrap CI = $-0.014$ to $-0.005$). Similar to the results of 5-HTTLPR this indicates that the effect of TPH2 on RT was mediated by induced gamma-band activity for NET A/A carriers only.

Discussion
In this study, we intended to further a mechanistic understanding of the role of 5-HT in executive functioning by examining the impact of genetic variation in key regulators of 5-HT signaling on top-down selective attention. Based on the known interplay of 5-HT and NE circuitries in visual top-down attention, and in line with our previous findings, we also expected 5-HT × NE interactions. Response speed and accuracy in the flanker-based ANT were used to tap genotype-dependent differences in focusing attention to goal-relevant stimuli. Further, oscillatory gamma-band activity was used to assess top-down attentional selection and network activity at the intermediate phenotype level.

Genetic Effects on ANT Performance
For the serotonin transporter variation (5-HTTLPR), carriers of the s/s genotype were expected to outperform other genotypes especially when combined with the common A/A genotype of the NE transporter variation (NET), as suggested by recent results (Enge, Fleischhauer, Lesch, Reif et al. 2011; see also Kim et al. 2006). Accordingly, an interaction of these gene variations indeed demonstrated that carriers possessing both of these genotypes exhibited lowest error rates on incongruent targets, whereas as expected, the opposite pattern was found for 5-HTTLPR s/s carriers with the NET T allele. Further analysis revealed that these effects were not at the expense of increased target RT. For the tryptophan hydroxylase polymorphism (TPH2) that putatively impacts on the function of the rate-limiting enzyme of 5-HT biosynthesis in the brain, we expected improved performance in individuals homozygous for the G allele, relative to T-allele carriers. In fact, we found a highly significant main effect of TPH2 indicating faster responses on targets in G/G carriers. Again, these lower response latencies were not at the cost of reduced accuracy.

For 5-HTTLPR, the observed role in ANT performance concur with findings suggesting the s allele to be associated with enhanced executive functioning: Cognitive flexibility in reversal learning tasks that require goal-directed responding depending on changes in the motivational value of stimuli has been shown to be enhanced in animals that functionally resemble human s-allele carriers (Finger et al. 2007; Brigman et al. 2010; Jedema et al. 2010). Similarly, human s/s carriers performed better on indices of the Wisconsin Card Sorting Test (Borg et al. 2009), and in Go/NoGo tasks that challenge the ability to inhibit distracting events, but to flexibly focus attention to goal-relevant information, s/s carriers made less omission errors (Roiser et al. 2007) and showed condition-specific lower RT variability (Strobel et al. 2007). Beneficial effects on RT measures have also been reported for other executive tasks such as the speed-related cued-reinforcement reaction time paradigm (Roiser et al. 2006) and the n-back working memory task (Enge, Fleischhauer, Lesch, Reif et al. 2011). Importantly, the latter study revealed similar interactions between 5-HTTLPR and NET on target response accuracy. In line with the present results, s/s carriers improved when possessing the A/A genotype of NET, but not when they carried the T-allelic type. The T allele, in turn, was found to downregulate NET promoter activity, and to be over-represented in ADHD cases were selective attention deficits belong to the core symptoms (e.g., Kim et al. 2006; Hahn et al. 2009).

For TPH2 703 G/T, our results support the few available studies showing that the G allele of this variant is associated with improved executive performance: Using the ANT, Reuter et al. (2007) found that G-allele carriers were better able to selectively focus on targets in presence of interfering events as they showed markedly higher response accuracy than T/T carriers. Similarly, Strobel et al. (2007) found individuals lacking the T allele to show overall higher accuracy and lower RT variability when selecting targets from competing response alternatives using the AX Continuous Performance task. These effects may be mediated by the role of TPH2 in impulse control (Canli et al. 2005; Waider et al. 2011) or impulsivity (Reuter et al. 2008).

Genetic Effects on Event-Related Gamma-Band Synchronization
Besides the interactions of 5-HTTLPR and NET on incongruent targets, there were no direct effects of 5-HTTLPR at the behavioral level. Given the relatively small effects of genetic variants, these and possible other effects at the performance level could have been detected in a larger sample. However, given our sample size, they are more likely to be detected by using intermediate phenotypes (Gottesman and Gould 2003; Meyer-Lindenberg and Weinberger 2006). As outlined in the Introduction section, we focused on the modulation of neuronal oscillations in the gamma-band frequency range as recent research has shown that increased gamma-band oscillations are related to top-down selective visual attention via a frontoparietally modulated enhancement of signal efficacy in neuronal assemblies encoding features of the attended stimuli (Desimone and Duncan 1995; Corbetta and Shulman 2002; Noudoost et al. 2010; Baluch and Itti 2011). Furthermore, increased gamma-band oscillations have been shown to be functionally linked to improved behavioral outcomes such as higher accuracy levels and faster behavioral responses (Jensen et al. 2007; Womelsdorf and Fries 2007; Fries 2009). Thus, we expected genotype-dependent differences of 5-HTTLPR and TPH2 on top-down attention to be reflected in target-specific gamma-band activity. This is clearly supported by our data as we observed increased event-related induced gamma-band activity...
synchronization in the timeframe between 300 and 700 ms after target onset for 5-HTTLPR s-allele homozygotes when additionally the A/A genotype of NET was present. For TPH2, a similar but less pronounced interaction with NET occurred that approached significance but was in line with our expectation on the role of TPH2 in attentional processing and of NET as potential moderator (e.g., Kim et al. 2006; Strobel et al. 2007; Enge, Fleischhauer, Lesch, Reif et al. 2011). Again, the NET A/A genotype produced significant differences between the TPH2 G/G and T+ genotype with larger gamma-band activity for G/G carriers. This suggests the A/A genotype to facilitate attentional selection especially when combined with certain 5-HT-relevant genotypes and may relate to the role of NE in amplifying target-related neural signals (Aston-Jones and Cohen 2005). The fact that similar 5-HT × NET interactions were found for behavioral accuracy and P3b event-related potential latency indicating processing efficiency (Enge, Fleischhauer, Lesch, Reif et al. 2011; see also Polich 2007) supports this notion. Moreover, it has to be noted that among the sequence of significant P values in the time-frequency domain most of the comparisons have survived correction for multiple comparisons by FDR. Alternatively, broader time windows (i.e., epochs) would have reduced the number of comparisons but would have been less appropriate to reflect the nature of the relationship of genotype and gamma oscillations over the time course. Overall, the effect pattern suggests a very low probability of being a false positive.

Furthermore, although no direct associations between the examined gene variants and ANT network efficiency were detected at the behavioral level, 5-HTTLPR showed to be associated with the executive control (conflict) network at the endophenotypic level: The induced gamma-band increase in s/s carriers in the more difficult incongruent compared with the congruent flanker condition may mirror the increased activity of target-specific neural populations that can improve target processing and may prevent the interfering incongruent flankers from gaining control over behavior. In support of this, more positive gamma-band conflict network scores were associated with lower error rates to incongruent trials.

Mediation of Genotypic Effects on ANT Performance by Induced Gamma Oscillations

As 5-HTTLPR and TPH2 predicted both behavioral performance and induced gamma-band activity, we also investigated whether the observed genotype-dependent differences in RT and error rate were mediated by gamma. Using the bootstrapping procedure (see Preacher et al. 2007), the results indeed showed that the effects of 5-HTTLPR and TPH2, respectively, on RT were mediated by induced gamma oscillations and that this mediation effect was moderated by NET (conditional indirect effect). Significant indirect effects via gamma-band activity were found for NET A/A but not for T-allele carriers, which mirrors the moderating effect of NET on the relationship between 5-HTTLPR/TPH2 and gamma-band activity as revealed by the ANOVA results. Considering that complex mediation models require large samples of 500–1000 subjects to detect typically small effect sizes of common genetic variants (see Preacher et al. 2007; Hyde et al. 2011), the real magnitude of mediating effects might have been underestimated. Thus, the observed indirect effects can be regarded as strong evidence for the validity of gamma oscillations as intermediate phenotype mediating the pathway between distal genotype and behavioral performance and underscore the role of 5-HT and NE modulation in goal-directed attention.

An Integration of 5-HT and NE Effects in Goal-Directed Selective Attention

In view of the available evidence, we propose a tentative framework that may integrate many of the 5-HTTLPR and TPH2 findings on executive control within the broader context of top-down controlled attentional selection processes that underlie the ability to guide the selection of goal-relevant stimuli over competing or irrelevant input (Desimone and Duncan 1995; Lavie et al. 2004; Aron 2007).

It is known that top-down selective attention involves amplifying visual input by increasing firing rates and synchronization of neuronal populations throughout the visual cortex. This, in turn, increases signal-to-noise ratio improving processing in cell clusters coding features of the attended object (e.g., Kastner and Ungerleider 2000; Womelsdorf and Fries 2007; Noudoost et al. 2010). The activity in visual areas that is thought to be modulated by a frontoparietal attention network that encompasses corticocortical feedback projections between prefrontal regions and visual areas in the extrastriate cortex, including neurons in the frontal eye field, in the lateral PFC, in the lateral intraparietal area, in the middle temporal area, and in area V4 (for reviews, see Corbetta and Shulman 2002; Gazzaley et al. 2007; Noudoost et al. 2010; Baluch and Itti 2011). Furthermore, the frontal sources of this network are suggested to be involved in the maintenance of processing priorities between relevant and irrelevant stimuli that serve to flexibly guide behavior according to current goals (e.g., de Fockert et al. 2001; Lavie et al. 2004).

Several lines of evidence suggest a modulatory effect of 5-HT on the top-down attentional selection of visual information. Animal studies using local infusions of 5-HT system-selective neurotoxins or the administration of 5-HT system targeting pharmacologic compounds demonstrated attention-related performance effects on target accuracy, response latency, and impulsive responding, as outlined above (for review, see Robbins 2002; Cools et al. 2008). Similar results have been obtained for executive control tasks in humans that largely depend on the ability to focus on task-relevant information but to ignore or inhibit interfering aspects of the visual environment (Booij et al. 2003; Schmitt et al. 2006; Enge, Fleischhauer, Lesch, Reif et al. 2011; Homberg and Lesch 2011). Likewise, NE has been shown to be involved in the modulation of selective attention (Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005): Neurons in the LC have been observed to selectively respond to salient visual stimuli (e.g., Grant et al. 1988) and to show large phasic bursts in the presence of target-relevant signals, but to be less responsive when nontargets appear (Aston-Jones et al. 1994), which is suggested to optimize performance (for review, see Aston-Jones and Cohen 2005). Moreover, evidence from structural and neurohistological analyses suggests interplay of 5-HT and NE in visual processing and prefrontal cortical functioning. There are ascending projections from locus coeruleus (LC) and raphe nuclei to prefrontal areas and descending prefrontal cortical projections to the LC/raphe region (e.g., Arnsten and Goldman-Rakic 1984). Dense NE/5-HT innervation of cortical and subcortical visual areas (e.g., Morrison and Foote...
further suggests a functional and structural interplay of both neuromodulatory systems in visual attention.

Taken together, 5-HT and NE-modulated augmentation of goal-relevant stimuli can be assumed to play a crucial and interactive role in top-down controlled attentional selection.

However, beyond the evidence that 5-HT may impact the frontoparietal attention circuits thereby influencing visual selective attention, the precise mechanism by which 5-HT exerts this influence is complicated by the fact that 5-HT has multiple functions in mediating executive performance (e.g., Robbins 2002; Schmitt et al. 2006). For example, given its role in impulse control (e.g., Lesch and Merschdorf 2000; Cools et al. 2008), on a functional level, it might be possible that the impact of 5-HT on goal-directed attention might actually reflect a 5-HT-mediated goal-state-dependent inhibition of irrelevant stimuli that, in turn, can enhance attentional selection of relevant inputs by reducing distractibility. Together with NE-modulated augmentation of task-relevant stimuli (e.g., Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005) such inhibitory effects of 5-HT may have also contributed to the observed effects on top-down controlled attentional selection.

Within this context, the 5-HTTLPR s allele—previously linked to anxiety- and depression-related traits and an increased risk for affective disorders (Lesch et al. 1996; Hariri et al. 2002; Homberg and Lesch 2011), especially in interaction with environmental adversity (e.g., Karg et al. 2011)—might be viewed as a plasticity gene that improves attentional selection of several types of motivationally relevant signals (e.g., Belsky et al. 2009; Fox et al. 2011). This may explain both, the enhanced selective attention to negative events leading to increased vulnerability for affective disorders under adverse environmental conditions (e.g., MacLeod et al. 2002; Osinsky et al. 2008), and, in the cognitive domain, the improved processing of goal-relevant stimuli.

Conclusion and Future Research
Together with previous research suggesting specific genotypes of 5-HTTLPR and TPH2 to be associated with improved executive functions, the results of the present study might be integrated within a framework suggesting these gene variations to modulate top-down controlled attentional selection processes that underlie the ability to guide the selection of goal-relevant stimuli over competing or irrelevant input.

The main finding was that carriers homozygous for the s allele (5-HTTLPR) and for the G allele (TPH2 -703 G/T) showed increased target-related induced gamma-band synchronization when combined with the A/A genotype of the (NE) transporter variation (NET -3081 A/T). Further evidence comes from mediation analyses showing that performance effects of 5-HTTLPR and TPH2 were significantly mediated by induced gamma oscillations in NET A/A carriers only. Overall, these results were interpreted to indicate the interplay of 5-HT and NE signaling on visual selective attention, including the role of NE action in amplifying target-relevant stimuli. In this context, the A/A genotype of NET has been recently implicated to lower the risk for ADHD and to improve executive performance, especially by interactions with 5-HTTLPR, as outlined above. Because the 5-HTTLPR and TPH2-related impact on induced gamma oscillations and behavioral outcomes was driven by NET our results point to the importance of gene × gene interactions in explaining phenotypic variance (e.g., Meyer-Lindenberg and Weinberger 2006). Not considering interactions in turn may explain ambiguous results on single genetic variants. Accordingly, based on the interplay of neuromodulatory systems future research should pay more attention on genetic interactions, but may also focus on the role of possible gene × environmental effects in executive processing. Besides, it would be interesting whether the vulnerability for depression in s/s carriers of 5-HTTLPR under adverse environmental conditions is modulated by NET.

Further, attention-induced gamma-band oscillation has been shown to be vital to integrate the features of attended objects into coherent representations, which appears to be essential for short-term and long-term memory encoding (e.g., Jensen et al. 2007; Womelsdorf and Fries 2007). Because 5-HT modulation has been found to impact on long-term memory and learning (e.g., Park et al. 1994; Booij et al. 2003), it might be interesting to know whether the relationship of 5-HT and memory could be mediated by the influence of 5-HT on focused attention. Interestingly, initial results suggest 5-HTTLPR to contribute to differences in long-term memory, with s/s carriers showing improved episodic memory (Roiser et al. 2007).

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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