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The tricks of the trait: Neural implementation of personality varies with genotype-dependent serotonin levels

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ABSTRACT

Gray's Reinforcement Sensitivity Theory (RST) has developed into one of the most prominent personality theories of the last decades. The RST postulates a Behavioral Inhibition System (BIS) modulating the reaction to stimuli indicating aversive events. A number of psychiatric disorders including depression, anxiety disorders, and psychosomatic illnesses have been associated with extreme BIS responsiveness. In recent years, neuroimaging studies have implicated the amygdala-septo-hippocampal circuit as an important neural substrate of the BIS. However, the neurogenetic basis of the regulation of this behaviorally and clinically essential system remains unclear. Investigating the effects of two functional genetic polymorphisms (tryptophan hydroxylase-2, G-703T, and serotonin transporter, serotonin transporter gene-linked polymorphic region) in 89 human participants, we find significantly different patterns of associations between BIS scores and amygdala–hippocampus connectivity during loss anticipation for genotype groups regarding both polymorphisms. Specifically, the correlation between amygdala–hippocampus connectivity and Gray's trait anxiety scores is positive in individuals homozygous for the *TPH2* G-allele, while carriers of at least one T-allele show a negative association. Likewise, individuals homozygous for the 5-HTTLPR L_A variant display a positive association while carriers of the S/L_G allele show a trend towards a negative association. Thus, we show converging evidence of different neural implementation of the BIS depending on genotype-dependent levels of serotonin. We provide evidence suggesting that genotype-dependent serotonin levels and thus putative changes in the efficiency of serotonergic neurotransmission might not only alter brain activation levels directly, but also more fundamentally impact the neural implementation of personality traits. We outline the direct clinical implications arising from this finding and discuss the complex interplay of neural responses, genes and personality traits in this context.

Introduction

Developed as a theory of personality which is firmly rooted in neurobiology, Gray's Reinforcement Sensitivity Theory (RST; Gray, 1982) has grown to strongly influence basic as well as clinical research in a large number of disciplines including psychiatry, psychology, pharmacology, animal research, and neuroscience (for a comprehensive review, see Corr, 2008). The RST postulates behavior to be mediated by the activity of three motivational systems: the Fight–Flight System, the Behavioral Approach System, and the Behavioral Inhibition System (BIS). The latter is triggered by signals of punishment or non-reward, which then leads to an inhibition of motor activity as well as increased levels of arousal and attention (for a partially revised version of the theory, see Gray and McNaughton, 2000). Defined to reflect trait sensitivity to punishment, Gray's trait anxiety (Gray, 1991) determines the extent to which aversive stimuli activate the BIS. Increased trait anxiety (heightened BIS responsiveness) has been linked to emotional states of anxiety, subjectively experienced as worry and rumination, and a sense of possible danger. Also, a number of psychiatric disorders including depression, anxiety disorders, and psychosomatic illnesses have been associated with extreme BIS responsiveness (Corr, 2008).

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Based on theoretical considerations and evidence from pharmacological studies (for a review see McNaughton et al., 2007), the septo-hippocampal system (SHS) is considered the neural substrate of the BIS. More recently, structural and functional neuroimaging studies in humans corroborated this view, while also implicating the amygdala as a vital component of the BIS in humans (Barros-Loscertales et al., 2006; Hahn et al., 2010b). In combination with other neural structures, such as the medial prefrontal cortex and the perigenual cingulate cortex (Heinz et al., 2005; Pezawas et al., 2005), the amygdala-SHS circuit may play a pivotal role for dysfunctional neural processing and altered serotonergic (5-HT) neurotransmission underlying psychiatric disorders, such as depression, anxiety disorders, and psychosomatic illnesses. Despite direct evidence showing that genetic variants affecting 5-HT neurotransmission by modulating synaptic 5-HT levels impact the BIS (Whisman et al., 2011) and the vast amount of research relating the BIS to these psychiatric disorders associated with 5-HT neurotransmission, the neurogenetic basis of the BIS as a behaviorally and clinically essential system in humans remains unclear.

In the present study, we thus seek to explore potential effects of differential genotype-dependent 5-HT levels on amygdala-SHS dynamics as they relate to Gray's BIS. To this end, we assess the effects of polymorphisms modulating the gene expression of two key regulators of 5-HT levels: a) brain-specific 5-HT synthesizing enzyme tryptophan hydroxylase-2 (*TPH2*; G-703T; rs4570625) and b) serotonin transporter (5-HTTLPR; serotonin transporter gene-linked polymorphic region; and linked rs25531) genotype. Specifically, we hypothesize that differences in *TPH2* and 5-HTTLPR/rs25531 genotype modulate amygdala-SHS dynamics previously associated with Gray's trait anxiety. Thereby, we attempt to shed light on the neurochemical and genetic basis of Gray's BIS as it relates to numerous psychopathologies.

Materials and methods

Participants

Ninety-six healthy subjects participated in the present study. Data from forty-six participants has been used previously in another study (Hahn et al., 2010b). Seven subjects had to be excluded from further analyses due to excessive head motion (translation larger than 2 mm and/or rotation larger than 2° in any direction). Thus, data of eighty-nine subjects (forty-nine females) between 18 and 51 years (mean = 27.8, SD = 7.5) were analyzed. All were recruited from the local community through advertisements. The participants 1. had no first-degree relative with a neurologic or psychiatric disorder, 2. had no history of dependence on illicit drugs and alcohol, 3. were currently not taking any psychotropic medication, and 4. reported no sensorimotor deficits or other neurological disorders. In order to exclude participants suffering from psychiatric disorders in general and anxiety disorders in particular, we interviewed all subjects using the structured clinical interview (SCID; Wittchen et al., 1997) screening questionnaire for DSM-IV.

Written informed consent was obtained after detailed explanation of the study protocol. The study was approved by the Ethics Committee of the University of Würzburg, and all procedures involved were in accordance with the latest version of the Declaration of Helsinki.

Genotyping and stratification

Genomic DNA was extracted from whole blood samples according to a standard desalting protocol. Genotyping procedures were performed as previously described using polymerase chain reaction (PCR) and gel electrophoresis. Genotyping of the *TPH2* G-703T single nucleotide polymorphism (SNP) within the transcriptional control region of the *TPH2* gene was done as published in Canli et al. (2005a). Based on findings showing that *TPH2* expression is decreased in carriers of the G-allele (Lin et al., 2007) and in accordance with several previous studies investigating its functional impact (e.g. Canli et al., 2008), we defined two groups: a) subjects homozygous for the *TPH2* G-allele (n = 62) and b) carriers of at least one T-allele (n = 27).

Genotyping of the 43-bp insertion/deletion polymorphism in the regulatory region of the serotonin transporter gene (5-HTTLPR; Lesch et al., 1996; Wendland et al., 2006) has previously been described. We additionally performed genotyping of an A/G SNP (rs25531) present within and in linkage disequilibrium with the 5-HTTLPR. *5-HTT* expression profiles have been shown to be comparable between short (S)-allele carriers and carriers of the long (L) 5-HTTLPR allele containing the G-allele of rs25531 (L_G). Based on this data we grouped our sample into a) carriers of at least one short allele (S) or at least one L_G-allele (n = 54; S + L_G) and b) subjects homozygous for the 5-HTTLPR L variant also carrying the A-allele of rs25531 (n = 35; L_A/L_A).

There were no significant genotype-dependent differences for age (*TPH2*: $t_{(87)} = 1.31$; $p = 0.20$; 5-HTTLPR/rs25531: $t_{(87)} = .76$; $p = 0.45$) or gender (*TPH2*: $X^2_{(1)} = .28$; $p = 0.65$; 5-HTTLPR/rs25531: $X^2_{(1)} = 2.65$; $p = 0.11$). *TPH2* and *5-HTT* variation was not significantly associated (Phi = −.115; p = .33).

The definition of genotype grouping was based on the (simplistic) model of the regulation of 5-HT levels by its synaptic reuptake (5-HTT) and synthesis (TPH2), which both impact 5-HT levels (and putative long-term developmental effects for 5-HT neurotransmission). We thus aimed to compare individuals with the largest assumed differences in 5-HT levels based on both *TPH2* as well as *5-HTT* genotype:

a) the low-5-HT level group: comprising *TPH2* G-allele homozygotes and 5-HTTLPR L_A-allele homozygotes (n = 18) and b) the high-5-HT level group: comprising *TPH2* T-allele carriers who also carry at least one 5-HTTLPR S or L_G-allele (n = 16). There were no significant genotype-dependent differences for age ($t_{(32)} = 1.28$; $p = 0.21$) or gender ($X^2_{(1)} = .39$; $p = 0.73$).

All polymorphisms were in Hardy–Weinberg equilibrium (TPH2: $CHI^2 = .92$; $p = .34$; 5-HTTLPR: $CHI^2 = .01$; $p = .92$). Please also note that *TPH2* and *5-HTT* variation was not significantly associated (Phi = −.115; p = .33), as expected given their localization on different chromosomes.

Task description and procedures

We conducted a modified version of the Monetary Incentive Delay (MID) Task developed by Knutson et al. (2001) consisting of 60 trials, each of 10 s duration which has been used previously (all details can be found in Hahn et al., 2010b). During each trial, participants saw one of three different cue shapes (presentation time 2000 ms each) followed by a fixation cross as they waited a variable interval (2250–2750 ms). Thereafter, they responded with a button press to a white target square which appeared for a variable length of time depending on the subject's performance. Specifically, the mean reaction time obtained from the ten practice trials was used as the initial target duration. It was increased by 30 ms if the subject failed to respond fast enough on more than one out of the last three consecutive trials. Likewise, it was decreased by 30 ms if the subject succeeded on more than two out of the last three consecutive trials. With this, we sought to ensure that participants lost on an average of 33% of the trials, thereby yielding a proportion of hits and misses comparable to that reported by Knutson et al. (2001). Additionally, target duration was set as to never decrease below 100 ms and never exceed 1000 ms. Feedback screens (2000 ms), which followed the disappearance of the target, informed participants of whether they had reacted in time during that trial and indicated their total in Euros at that point.

Initially, participants started with an amount of 10 Euros of which they were instructed to lose as little as possible. Cues signaled the possibility of losing 0.05 € (n = 20; a square with one horizontal line) or 1.00 € (n = 20; a square with three horizontal lines). The third cue (n = 20; a triangle) indicated that no money could be lost

during this trial. The three trial types were randomly ordered within the experiment. The length of the inter-trial interval was randomly jittered in steps of 83 ms between 83 and 2000 ms.

MRI acquisition and analyses

Imaging was performed using a 1.5 T Siemens Magnetom Avanto TIM-system MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 12 channel head coil. In a single session, twenty-four 4-mm-thick, interleaved axial slices (in-plane resolution: 3.28 × 3.28 mm) oriented at the AC–PC transverse plane were acquired with 1 mm interslice gap, using a T2*-sensitive single-shot EPI sequence with following the parameters: repetition time (TR; 2000 ms), echo time (TE; 40 ms), flip angle (90°), matrix (64 × 64), field of view (FOV; 210 × 210 mm^2), and number of volumes (310). The first six volumes were discarded to account for magnetization saturation effects. Stimuli were presented via MRI-compatible goggles (VisuaStim; Magnetic Resonance Technologies, Northridge, CA) using Presentation (Neurobehavioral Systems; http://www.neurobs.com).

Data were preprocessed using SPM5 (Wellcome Department of Cognitive Neurology, UK, implemented in Matlab 7.0, Math Works, Natick, MA): Slice-time correction was applied and images were realigned to the first functional volume. The mean image of the scans was computed and used as the source image for spatial normalization of the data to MNI space using the SPM5 template. Data were not spatially smoothed. The time series in each voxel were high pass-filtered to 1/128 Hz to remove low-frequency noise, corrected for temporal auto-correlation using an autoregressive model with a lag of 1, and mean corrected.

We focus all further analyses on the amygdala and the hippocampus. Both regions of interest (ROIs) were defined using voxel masks from a publication-based probabilistic MNI atlas (http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html) at a probability threshold of 0.5 (Fox and Lancaster, 2002).

Functional connectivity was calculated for each individual in accordance with previous work (Hahn et al., 2010b) as the correlation of the mean amygdala beta series obtained using Rissman's methods (Rissman et al., 2004) with each voxel in the hippocampus, yielding single-subject z-maps. These connectivity maps formed the basis for all second-level analyses (for a detailed description of all analyses, see Hahn et al., 2010b). In accordance with previous work showing the 1 € loss anticipation condition to be the most reliable (Hahn et al., 2010b), only this contrast is considered for the purpose of this study.

For all further analyses, we entered centered psychometric scores, centered genotype data, and their interaction term as regressors in a General Linear Model. In order to analyze the interaction of genotype and psychometric scores, the interaction-term was tested for significance. In the correlation analyses done for descriptive purposes, psychometric data were correlated with (connectivity-) data over those voxel clusters, which were significantly activated in the respective analysis. Likewise, cluster correlation coefficients and p-values are reported.

Correction for multiple comparisons within each ROI was realized using a Monte Carlo simulation approach running AlphaSim (B.D. Ward; provided with AFNI software) with a single voxel p-value of 0.05. The spatial intercorrelations between the voxels as modeled by the FWHM of a Gaussian kernel were calculated using the 3dFWHMx AFNI software routine. With this procedure, ROI-specific cluster-sizes corresponding to a corrected threshold of $p < 0.05$ were determined. The ROI-specific cluster-sizes calculated with AlphaSim were applied in all further image-analyses ensuring a corrected α-level of 5% (respective z- and t-statistics of the peak voxel are provided in parentheses).

Psychometric testing

All participants completed the German version of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001). The SPSRQ is a 48-item self-report measure of Gray's trait *sensitivity to punishment* (SP) and *sensitivity to reward* (SR) dimensions. The scales are particularly designed to measure Gray's concepts by linking SR to the Behavioral Activation System (BAS) and SP to the Behavioral Inhibition System (BIS). The two scales show retest reliabilities of 0.87 and 0.89 for the reward and the punishment scale, respectively, and good construct validity has also been shown (Sava and Sperneac, 2006).

Results

Behavioral data

Participants attained a mean score of 8.06 (SD = 4.43) and 9.22 (SD = 3.79) on the SP- and the SR-scales, respectively. As expected, the two scales were not significantly correlated ($r = -0.15$; $p = 0.16$). Furthermore, significant genotype-dependent differences could neither be found for SP (*TPH2*: $t_{(87)} = .08$; $p = 0.94$; 5-HTTLPR/rs25531: $t_{(87)} = .20$; $p = 0.85$; high- vs. low-5-HT level group: $t_{(32)} = .79$; $p = 0.44$) nor for SR (*TPH2*: $t_{(87)} = .25$; $p = 0.81$; 5-HTTLPR/rs25531: $t_{(87)} = .41$; $p = 0.69$; high- vs. low-5-HT level group: $t_{(32)} = .92$; $p = 0.36$).

During the MID-task, participants failed to respond in time on an average of 35% (SD = 2.0) of the trials. Thus, the proportion of hits and misses is roughly equal to the 66% for which we aimed following Knutson et al. (2001). Also, the number of loss-trials did not differ significantly between the genetic groups ($t_{(87)} = .64$; $p = 0.52$).

Functional neuroimaging data

As expected, significant responses during loss anticipation were observed in the bilateral amygdala ($z = 5.65$; $p < 0.05$) and hippocampus ($z = 5.81$; $p < 0.05$). In accordance with our previous work (Hahn et al., 2010b), SP-scores were not correlated with responses during loss anticipation in either the amygdala or the hippocampus and no correlations with SR-scores could be found. Additionally, no significant effects of genotype on the responses during loss anticipation were observed.

Functional connectivity data

Significantly positive bilateral amygdala–hippocampus connectivity was found during loss anticipation ($t_{(88)} = 26.09$; $p < 0.05$). In addition, connectivity during loss anticipation was positively associated with SP-scores ($z = 3.32$; $p < 0.05$; right hemisphere). Replicating our previous findings in a larger sample, none of the measures displayed a significant correlation with SR-scores.

Effect of TPH2 genotype on the association between Gray's trait anxiety and functional connectivity

We revealed a significant interaction of the investigated *TPH2* genotype and Gray's trait anxiety scores affecting left amygdala–hippocampus-connectivity ($z = 2.93$; $p < .05$, corrected), indicating that the correlation between amygdala–hippocampus connectivity and Gray's trait anxiety scores is moderated by differences in genotype-dependent 5-HT neurotransmission efficiency.

More specifically, the correlation between amygdala–hippocampus connectivity and Gray's trait anxiety scores as described above turned out to be positive in individuals homozygous for the *TPH2* G-allele ($r = .42$; $p < .001$), while carriers of at least one T-allele showed a negative association ($r = -.42$; $p = .03$; Fig. 1).

Effect of 5-HTT genotype on the association between Gray's trait anxiety and functional connectivity

A pattern of results similar to the one observed for *TPH2* genotype was also apparent for the *5-HTT* genotype ($z = 2.91$; $p < .05$)

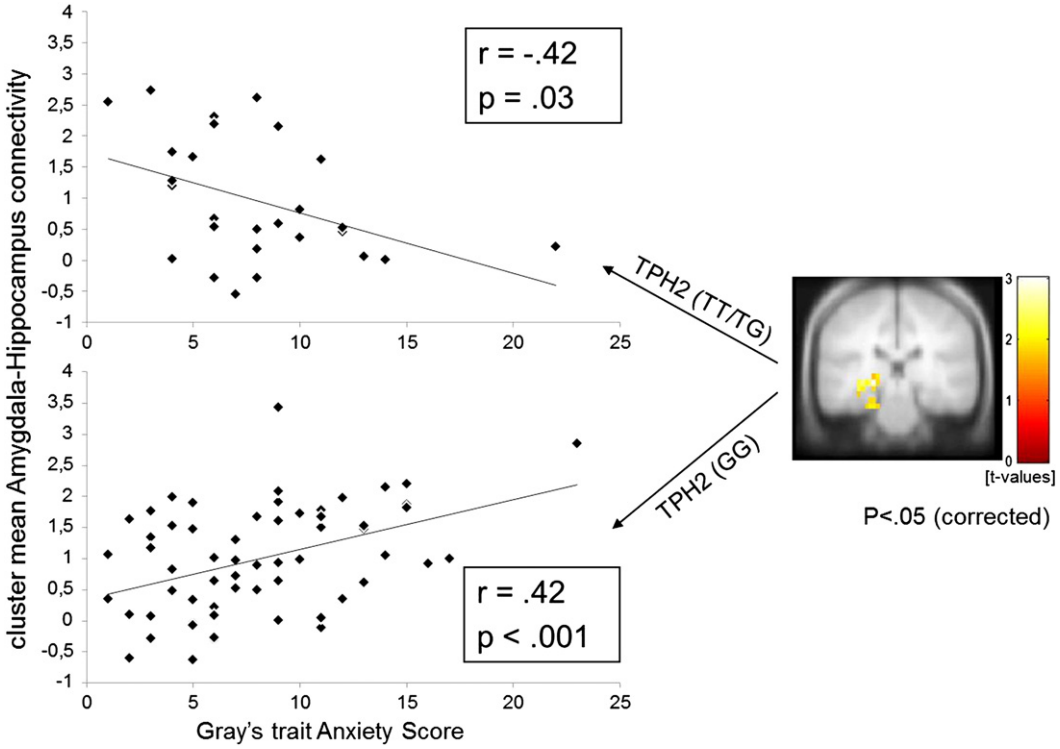

Fig. 1. Effect of *TPH2* genotype on the association between Gray's trait anxiety and functional amygdala–hippocampus connectivity ($p < .05$, corrected; right panel). Scatter plots (left panel) display the association between Gray's trait anxiety scores and amygdala–hippocampus connectivity (averaged over significant clusters) for each genetic group.

with individuals homozygous for the 5-HTTLPR L variant displaying a positive association ($r = .63$; $p < .001$) and carriers of the S allele showing a trend towards a negative association ($r = -.26$; $p = .06$) with Gray's trait anxiety scores in the right hemisphere (Fig. 2).

Effect of low versus high 5-HT levels on the association between Gray's trait anxiety and functional connectivity

Comparing the low- versus high-5-HT level groups revealed the effects described for *TPH2* and *5-HTT* genotypes separately in an even

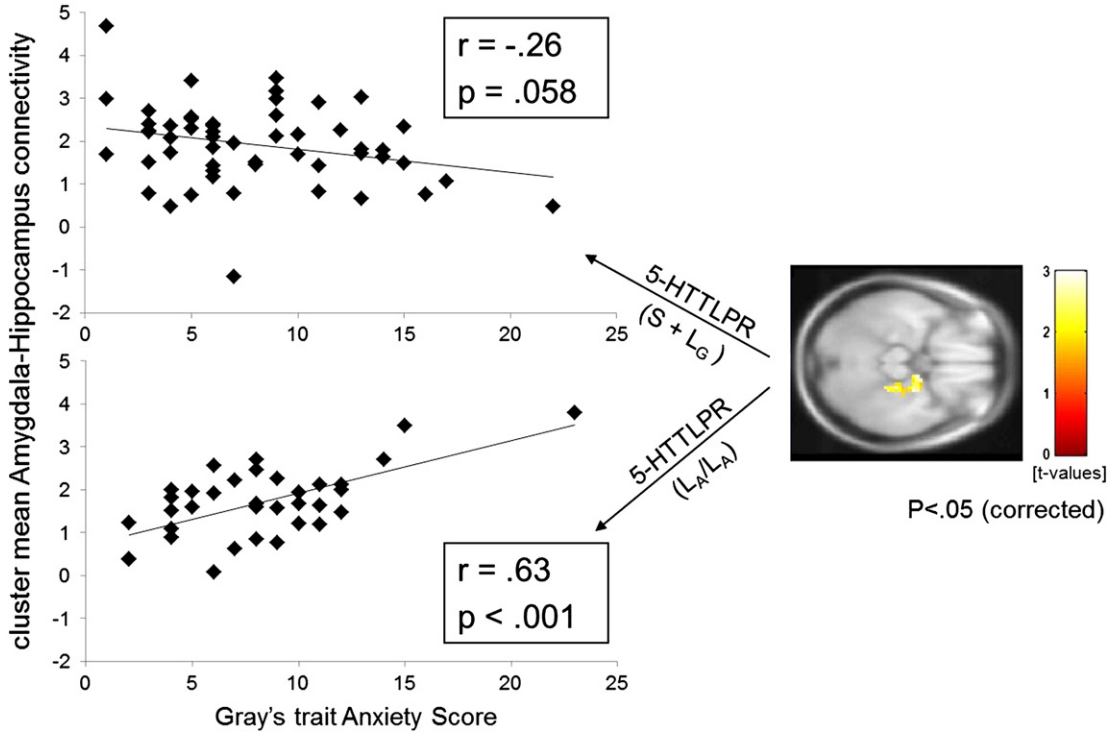

Fig. 2. Effect of *5-HTT* genotype on the association between Gray's trait anxiety and functional amygdala–hippocampus connectivity ($p < .05$, corrected; right panel). Scatter plots (left panel) display the association between Gray's trait anxiety scores and amygdala–hippocampus connectivity (averaged over significant clusters) for each genetic group.

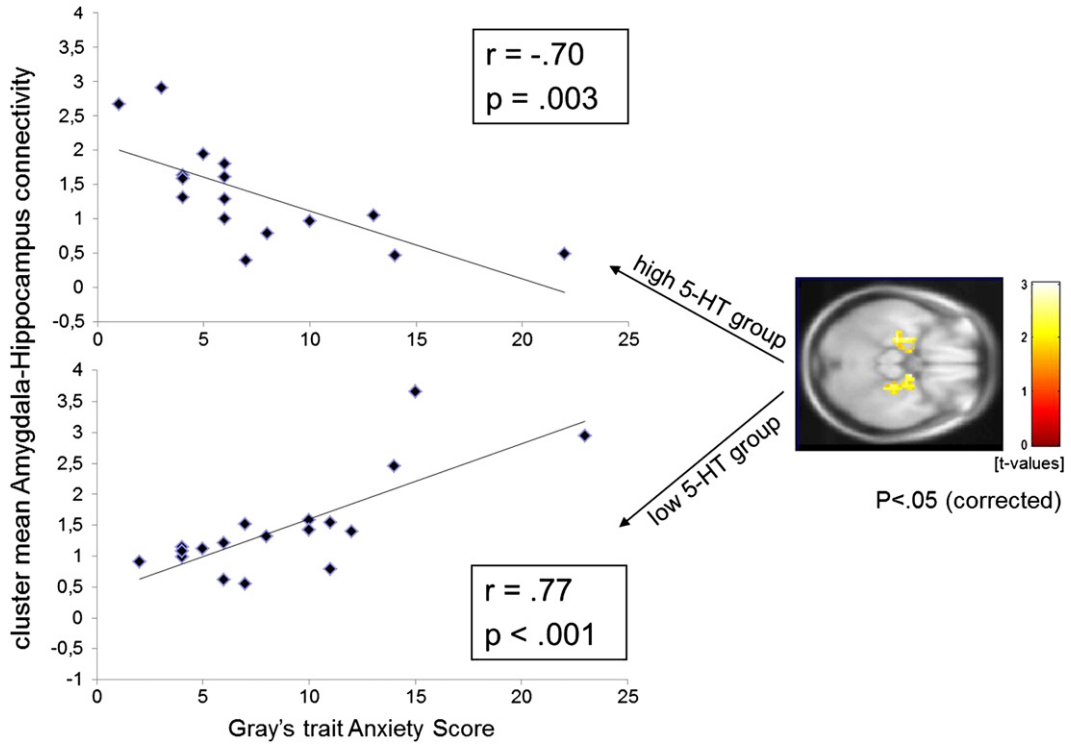

Fig. 3. Effect of low versus high 5-HT efficiency on the association between Gray's trait anxiety and functional amygdala–hippocampus connectivity ($p < .05$, corrected; right panel). Scatter plots (left panel) display the association between Gray's trait anxiety scores and amygdala–hippocampus connectivity (averaged over significant clusters) for the low versus the high 5-HT efficiency group.

more pronounced manner: an extended, bilateral pattern of combined-genotype group by trait–score interaction was present ($z = 3.51$; $p < .05$, corrected). Specifically, the correlation between amygdala–hippocampus connectivity during loss anticipation and Gray's trait anxiety scores was positive in the low-5-HT group ($r = .77$; $p < .001$), while it was negative in the high-5-HT group ($r = -.70$; $p = .003$; Fig. 3).

Discussion

In the present study, we replicated – in a larger sample – findings showing that functional connectivity between the amygdala and the hippocampus is associated with Gray's trait anxiety (Hahn et al., 2010b). Most importantly, however, we showed that this correlation between amygdala–hippocampus connectivity and Gray's trait anxiety scores is moderated by differences in genotype-dependent 5-HT levels. The association between Gray's trait anxiety and the neural dynamics of the amygdala-septo-hippocampal circuit is thus dependent on *TPH2* and *5-HTT* genotypes. Specifically, the correlation between amygdala–hippocampus connectivity and Gray's anxiety is positive in individuals homozygous for the *TPH2* G-allele or the 5-HTTLPR/rs25531 L_A variant, while carriers of the *TPH2* T-allele or of the S/L_G-allele showed a negative association. Our findings were validated by the fact that the independent subgroups of *TPH2* and *5-HTT* genotypes (with comparable theoretical impact on 5-HT levels and 5-HT neurotransmission, respectively) showed highly similar moderator effects. The different associations between Gray's trait anxiety and amygdala–hippocampus connectivity for the low- and the high-5-HT level group support this view even beyond the effect of a single genetic polymorphism, stressing the relevance of genotype-dependent 5-HT levels in general and their functional consequences for 5-HT neurotransmission.

From these findings, the more general issue of how different neural implementations might arise is of interest. Do they emerge as a result of neural adaptive changes, i.e. in response to the environment, or does for instance genotype impact neural plasticity during development which would imply a gene-by-environment interaction? In this context, support for the generalizability of our findings to other personality traits comes from two studies investigating Gray's Behavioral Approach System (BAS): Recently, Passamonti et al. (2012) showed that tryptophan depletion which reduces 5-HT availability impacts the relationship between BAS-drive scores and the functional connectivity between the amygdala and the ventral anterior cingulate cortex (vACC) during the presentation of angry faces. Interestingly, low 5-HT level subjects (L_A/L_A or G/G-allele carriers in our study) showed a positive correlation between BAS-drive scores and amygdala–vACC whereas subjects with no tryptophan depletion showed a negative correlation (S/L_G carriers in our study). While our study investigated genetic influences on 5-HT neurotransmission, the BIS and a functional paradigm of loss anticipation, the findings of Passamonti et al. indirectly support our results in that the trait x amygdala-connectivity interaction is positive in a low 5-HT state whereas it is negative in a (relatively) high 5-HT level state.

Moreover, findings suggest that dopamine transporter (DAT, *SLC6A3*) genotype moderates the association between ventral striatal reactivity and Gray's trait reward sensitivity (Hahn et al., 2011). Specifically, homozygous carriers of the *DAT* 10-repeat allele exhibited a strong positive correlation between reward sensitivity and reward-related ventral striatal activity whereas this relationship was absent in the *DAT* 9-repeat allele carriers. In this context, the possibility is discussed that this effect might arise from *DAT*-dependent differences in dopamine availability during development affecting synaptic plasticity within the ventral striatum. As a neuromodulator, 5-HT plays an important role for the development of serotonergic and other neurons, prior to its function as a neurotransmitter (for a review see Daubert and Condron, 2010). Genotype-dependent 5-HT function might thereby impact gray matter volumes and neural function of these regions in the mature brain (Canli et al., 2005b; Frodl et al., 2008). Complementing

studies showing a genotype-dependent impact of 5-HT on neuroanatomy and activation of single brain regions, the functional connectivity between key brain areas, i.e. the neurobiological substrate of both of Gray's personality traits (BIS/BAS), might be different depending on serotonergic and dopaminergic genes, respectively.

Also, it is highly interesting that these different implementations do not lead to genotype-dependent changes in personality: In our sample, no significant genotype-dependent differences regarding Gray's trait anxiety could be found (*TPH2*: $t_{(87)} = .08$; $p = 0.94$; 5-HTTLPR/rs25531: $t_{(87)} = .20$; $p = 0.85$; high- vs. low-5-HT level group: $t_{(32)} = .79$; $p = 0.44$). Thus, different neural implementations may occur without behaviorally measureable consequences. This, again, underlines the importance of current endophenotype approaches based on neuroimaging (Gottesman and Gould, 2003).

It is important to note, that the present study investigated genotypes, which may modulate 5-HT levels. However, long-term developmental effects have been suggested to underlie the functional impact of 5-HT levels on 5-HT neurotransmission, which complicates the direct translation of putative 5-HT levels into a measure of the effectiveness of 5-HT neurotransmission. For instance, while serotonin reuptake inhibitors (SSRIs) have been shown to produce an acute increase of 5-HT levels, the antidepressive/anxiolytic long-term effect may result from functional changes in the ratio of 5-HT auto- and heteroreceptors in the amygdala and the hippocampus (with a compensatory upregulation of 5-HT_{1A} heteroreceptors following SSRI therapy; Hahn et al., 2010a). Also, SSRIs may desensitize 5-HT_{1A} autoreceptors, increase 5-HT neurotransmission and thereby affect long-term psychopathological symptoms (El Mansari et al., 2005). Thus, 5-HT levels may represent an initial state, which may be adaptively altered via other (sub)cellular (compensatory) processes. Moreover, epigenetic mechanisms debated for stress and life-events moderating the risk for depression associated with the S/L_A allele may have to be considered (Karg et al., 2011). Genotype-dependent 5-HT levels can be directly translated into an index for the effectiveness of 5-HT neurotransmission, because other susceptibility factors (personality or psychopathology) and environmental processes may shape the triadic interplay between genotype, brain activation and personality investigated in the present study.

In addition to the relevance of endophenotypes for the understanding of the link between personality and neuronal dynamics, our findings enable us to make testable predictions regarding clinically relevant phenomena: As has been argued before (Hahn et al., 2010b), higher amygdala–hippocampus connectivity might reflect easier propagation of arousal-related amygdala activity to the hippocampus/septum which, in turn, might lead to higher BIS responsiveness. However, according to our findings, these dynamics might arise only in individuals with relatively low levels of 5-HT, as assumed for *5-HTT* L_A/L_A carriers and *TPH2* G-allele homozygotes, where we found the correlation between amygdala-hippocampus connectivity and Gray's trait anxiety to be positive. In this subgroup, overactive amygdala might thus be the primary source of heightened trait anxiety, which would render anxiety patients among these individuals likely to benefit from relaxation techniques – such as mindfulness – that directly target functional and structural states of the amygdala (Goldin and Gross, 2010; Holzel et al., 2010).

Alternatively, taking the more hippocampus-centered view proposed by Gray and McNaughton (2000), the key problem underlying enhanced anxiety could lie in suboptimal functioning of the hippocampus including reduced connectivity to the amygdala, potentially resulting in reduced extinction memory and reduced context-dependent top-down control over fear, again with the result of a hyperactive BIS. We suggest that this might be the mechanism underlying punishment sensitivity in individuals with relatively elevated 5-HT levels (*5-HTT* S/L_G carriers or *TPH2* T-allele carriers; McNaughton and Gray, 2000) for whom the correlation between the amygdala–hippocampus connectivity and Gray's trait anxiety is negative. Following this argument, highly anxious individuals in this subgroup might benefit most from cognitive interventions which support the modulating role of the hippocampus and other cortical structures in controlling anxiety, and less much from relaxation techniques targeted primarily at arousal reduction. While this line of argument is speculative as the causal direction of the amygdala–hippocampus interaction is unknown, it can nonetheless serve to illustrate the potential relevance of finding interactions between brain connectivity, genotype, and mental functioning with respect to theoretical models and the development of individualized treatment.

While the present study focused on amygdala–hippocampus interactions, functional amygdala-connectivity with the medial prefrontal cortex (Heinz et al., 2005) and the perigenual cingulate (Pezawas et al., 2005), respectively, is also impacted by the S-allele of 5-HTTLPR. Specifically, S-carriers showed relatively increased amygdala–medial prefrontal functional connectivity and amygdala connectivity to the perigenual cingulate was reduced relative to L/L-allele carriers. Importantly, 30% of the variance in amygdala–perigenual cingulate connectivity was explained by trait Harm Avoidance. While we investigated the triadic interplay of trait–connectivity–genotype, the present finding of S/L_G-carriers showing a negative association between amygdala–hippocampus connectivity and trait sensitivity to punishment may stem from a related process.

Generally, our findings underline the necessity to take into account the complex interplay between genetics, traits and neural measures. In particular, those studies showing an association between traits and neural activation need to carefully consider the possible impact of altered neurotransmission or neuroanatomy as a consequence of genotype differences. While such associations might be reliable, they may be selectively missing or reversed in subgroups of the samples as shown here. Therefore, investigating the interaction between all three pivotal players (trait, neural activity, and genes) can be viewed as a means to complement previous studies relating behavior, traits, and psychopathologies to neural activation.

In conclusion, our results provide a significant advance in understanding the link between personality and neural dynamics. We uncovered and formally tested the moderating effect of genotype-dependent 5-HT levels on the functional dynamics of the amygdala-septo-hippocampal circuit underlying Gray's trait anxiety. These findings may have implications for psychopathologies, such as depression and anxiety disorders which have been linked to the BIS and which are thought to, in part, arise from 5-HT dysfunction.

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Conflict of interest

The authors declare no conflict of interest.

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