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The functional 5-HT1A receptor polymorphism affects response inhibition processes in a context-dependent manner

Christian Beste[a,*], Katharina Domschke[b], Britta Radenz[b], Michael Falkenstein[c], Carsten Konrad[b,d]

[a] Institute for Cognitive Neuroscience, Department of Biopsychology, Ruhr-Universität Bochum, Universitätsstraße 150, D-44780 Bochum, Germany
[b] Department of Psychiatry and Psychotherapy, University of Münster, Germany
[c] IFADO – Leibniz Institute, Dortmund, Germany
[d] Department of Psychiatry and Psychotherapy, University of Marburg, Germany

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ABSTRACT

Cognitive control processes may depend on contextual information, sometimes improving performance, but impairing performance if expectancies about forthcoming events induce pre-potent responses. The neurobiological bases of these effects are not understood. Here, we examine context-dependent variations of response control processes using the AX-CPT task with respect to the relevance of the functional serotonin 1A receptor polymorphism (5-HT1A C(−1019)G) in a sample of healthy subjects ($N = 90$) by means of event-related potentials (ERPs).

The results show that, when context information is helpful to drive behavioural performance, carriers of the −1019G allele reveal compromised cognitive control. Yet, they show enhanced task performance when strong context representations would lead to declines in behavioural control. These findings are paralleled by modulations of the (Nogo)-P3 ERP-component. These results show for the first time that, even though the −1019G allele enhances the risk to develop anxiety disorders, it also confers an advantage to its carriers in terms of better cognitive control processes in conditions where contextual information compromises cognitive control. Effects of the 5-HT1A C(−1019)G polymorphism were further modulated by anxiety sensitivity. As the functional effect of the 5-HT1A C(−1019)G polymorphism has previously been shown to be rather specific for serotonergic 1A autoreceptors in the dorsal raphe nucleus (DRN), the results suggest that contextual modulations in cognitive control may be exerted by the DRN.

1. Introduction

Processes of cognitive control are known to be altered in psychiatric disorders, such as anxiety and obsessive-compulsive disorder (e.g. Morein-Zamir, Fineberg, Robbins, & Sahakian, 2010; Rubia et al., 2010; Völlm et al., 2010). Recent results suggest that subjects scoring high on measures of anxiety-related personality traits committed fewer false alarms in speeded response inhibition tasks, thus showing superior response inhibition performance and cognitive control (Baving, Rellum, Laucht, & Schmidt, 2004; Righi, Mecacci, & Viggiano, 2009; Sehlmeyer et al., 2010). In particular, Sehlmeyer et al. (2010) showed that anxious subjects maintain a higher level of cognitive control to prepare and to monitor the outcome of their actions, which is reflected in electrophysiological responses.

In the development of anxiety disorders, the −1019G allele of the functional serotonin 1A receptor polymorphism (5-HT1A C(−1019)G) (Huang et al., 2004) likely plays an important role (e.g. Domschke et al., 2006; Freitag et al., 2006; Rothe et al., 2004; Strobel et al., 2003; for review: Drago, Ronchi, & Serretti, 2008). Serotonin 1A receptors are strongly expressed in the anterior cingulate cortex (ACC) (Frey, Rosa-Neto, Lubarsky, & Diksic, 2008; Hensler, 2006), which is a crucial part of human anxiety circuitry and which is also of importance for response inhibition (e.g. de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Fallgatter, Bartsch, Zielasek, & Herrmann, 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Rushworth, Walton, Kennerley, & Bannerman, 2004). However, it has to be acknowledged that the functional effect of the 5-HT1A C(−1019)G polymorphism is specific for autoreceptors located in the dorsal raphe nucleus (DRN) (e.g. Czesak, Lemonde, Peterson, Rogaeva, & Albert, 2006; Parsey et al., 2006) and may only indirectly affect the above mentioned structures by their neocortical projections.

Based upon all this, it is likely that variations in serotonergic tone modulate response inhibition processes. Direct evidence is provided by a study showing that variations in the 5-HTTLPR polymorphism affect event-related potential (ERP) correlates of response inhibition (Fallgatter, Jatzke, Bartsch, Hamelbeck, & Lesch, 1999).

Yet, cognitive control processes such as response inhibition and selection also depend on how well contextual conditions are

* Corresponding author. Tel.: +49 234 322 4323; fax: +49 234 321 4377.
E-mail address: christian.beste@rub.de (C. Beste).

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represented and maintained in dorsolateral prefrontal networks and how this information can be used to guide response inhibition processes and cognitive control (Braver & Barch, 2002). "Context" is conceptualized as any task-relevant information that is internally represented, such that it may bias processing in the pathways responsible for task performance (Braver & Barch, 2002). In the AX-CPT task, contextual information is required to drive or inhibit responses to a target stimulus (e.g. Dias, Foxe, & Javitt, 2003; Edwards, Barch, & Braver, 2010; Javitt, Rabinowicz, Silipo, & Dias, 2007; Leung, McClure, Siever, Barch, & Harvey, 2007). Target trials occur when the cue 'A' is followed by the probe 'X', requiring a response by the subject. Opposed to this, on trials where the 'X' is preceded by another cue, the subjects are required to suppress the response on the 'X' (BX-trials) and to execute another response. Because response inhibition is only successful in BX-trials when the cue is correctly held online in working memory, BX-trials provide an index of the integrity of context representations and how these influence cognitive control (Braver & Barch, 2002). In AX-trials occuring with high frequency, robust context representations evoke robust response tendencies prior to the onset of the probe (Braver & Barch, 2002), leading to an increased probability of false alarms in cases where 'A' is not followed by an 'X' probe (i.e., AY-trials, where a non-target response, identical to BX-trials, has to be executed). Stable contextual representation therefore impairs performance on AY-trials. However, to the extent stable contextual representations impair performance of these AY trials, they increase performance on BX-trials (Braver & Barch, 2002). The performance increase on BX-trials, that is suppression of the response to an X, crucially depends on the maintenance of contextual information (i.e., B). Therefore, performances in AY and BX trials are modulated in opposing directions. An important feature of the AX-CPT paradigm is its ability to manipulate the stability of context representation by varying the cue-target interval (e.g. the interval between 'A' and 'Y'). In sum, the AX-CPT paradigm therefore allows an investigation of differential gene effects on the establishment of context information (short delay intervals) versus the maintenance of these representation (long delay intervals) (Braver & Barch, 2002). The dopaminergic system is known to be important for the maintenance of context information (long delay intervals) (Seamans & Yang, 2004). If the influence of the serotonergic system on the dopaminergic system (e.g. Remington, 2008) is only subtle, we hypothesize that (i) maintenance of information (i.e., performance in long delay intervals) may not be affected by the 5-HT1A C(−1019)G genotype. Previous findings suggest that anxious subjects maintain a higher level of cognitive control and response inhibition (Righi et al., 2009; Ruchsow et al., 2007; Sehlmeyer et al., 2010). Other findings indicate an association of the −1019G allele with anxiety disorders (Drago et al., 2008). We therefore further hypothesize that (ii) carriers of the −1019G allele show better performance in trials when a non-target response has to be executed: i.e. G allele carriers show lower rates of false alarms in AY trials than the CC genotype group. However, since AY and BX-trials reflect antagonistic processes (Braver & Barch, 2002; Edwards et al., 2010), we also hypothesize that performance on BX-trials is then relatively worse in −1019G allele carriers, compared to the CC genotype group. This would suggest that relatively elevated levels of serotonergic tone in the CC, compared to the CG and GG genotype groups (e.g. Albert & Lemonde, 2004; Lemonde et al., 2003), may stabilize context representations. Importantly, such a result would suggest that even though the −1019G allele confers a risk to develop neuropsychiatric disorders, it also confers an advantage to its carriers. Yet, this advantage is restricted to circumstances where stable context representations compromise cognitive control processes. In other cases, where a stability of context representations is beneficial for cognitive control (i.e. BX trials), the −1019G allele confers a downside to its carriers. As the 5-HT1A C(−1019)G polymorphism is associated with anxiety-related personality traits (e.g. Domschke et al., 2006; Fakra et al., 2009; Hettema et al., 2008), which is also associated with altered response inhibition performance, both factors may modulate contextual response–inhibition performance. The relative importance of these factors is estimated using regression analyses.

To objectify the neuronal processes underlying response control, event-related potentials (ERPs) are recorded, reflecting different sub-processes of response inhibition (Nogo-N2/Nogo-P3) (e.g. Band and van Boxtel, 1999; Beste, Saft, Andrich, Gold, & Falkenstein, 2008a; Beste, Willemssen, Saft, & Falkenstein, 2010; Falkenstein, 2006; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Roche, Garavan, Foxe, & O'Mara, 2005; Schmajuk, Liotti, Busse, & Woldorff, 2006). The measurement of ERPs is of crucial importance to determine which subprocesses of response inhibition are modulated by genotype variations. As the evaluation of a stimulus with respect to its context is most important in the AX-CPT paradigm, especially the Nogo-P3 may be affected by genotype variations, since the Nogo-P3 most likely reflects evaluative processes related to the outcome monitoring of inhibition processes (e.g. Band and van Boxtel, 1999; Beste et al., 2008a; Roche et al., 2005; Schmajuk et al., 2006). Concerning genotype modulations of delay-length effects, the 'contingent negative variation (CNV) is examined. The CNV likely reflects preparation for task-relevant processes (Brunia & van Boxtel, 2001; Dias et al., 2003; Walter et al., 1964) that occur within a period between a cue and a target response. Given that context representations are less stable in G allele carriers, the CNV should be reduced in G allele carriers, compared to the CC genotype group.

2. Materials and methods

2.1. Participants

A sample of $N = 90$ genetically unrelated subjects of Caucasian descent was recruited by newspaper announcements. Twenty-two subjects carried the CC genotype, 40 the CG and 28 the GG genotype. The methods for genotyping are given in the next subsection. Hardy-Weinberg criteria, as calculated by the online program DeFinetti (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM), were fulfilled for the distribution of 5-HT1A C(−1019)G genotypes ($p > .3$). The mean age of the subjects was 25.2 years (standard deviation ±5.2). Age did not differ between genotype groups ($F(2,89) = 0.5$; $p > .5$). The sample consisted of 32 males and 58 females. Sexes were comparably distributed across the different 5-HT1A C(−1019)G genotype groups according to the Kruskal–Wallis Test (*H*-Test) ($\chi^2 = 0.008$; df = 1; $p > .8$). As the 5-HT1A C(−1019)G polymorphism is also associated with anxiety (e.g. Fakra et al., 2009; Hettema et al., 2008), anxiety sensitivity (ASI) (McNally, 2002) was also examined. The mean ASI score was 19.9 (±11.02). A univariate ANOVA revealed a statistically significant difference between genotype groups ($F(2,89) = 3.79$ $p = .026$) (CC: 15.7 ± 10.4, CG: 23.9 ± 10.8, GG: 20.1 ± 12.8). Bonferroni-corrected post-hoc independent samples *t*-tests revealed that the ASI score was higher in the CG ($p = .03$) and GG genotype group ($p = .04$) compared to the CC genotype group. CG and GG groups did not differ significantly ($p > .4$). Volunteers were paid 8 Euros per hour as compensation. All subjects enrolled into the study underwent an extensive monitoring for psychiatric symptoms (mood/anxiety) that also included possible drug intake using telephone interviews and self-report measures. The study was approved by the ethics committee of the University of Münster. All subjects gave written informed consent.

2.2. Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from a 10 ml ethylendiamine-tetraacetate (EDTA) venous blood sample with the Qiagen FlexiGene DNA kit (Qiagen, Hilden, Germany). The 5-HT1A C(−1019)G (rs6295) polymorphism was genotyped by means of a polymerase chain reaction (PCR)-based restriction fragment length polymorphism assay. Primers were designed to amplify a 296 base pair (bp) DNA fragment containing the forward primer 122-F, 5′-AGTTTTGTTCTTCATTTCGAGAT-3′ and reverse mutagenic primer 122-R, 5′-GAAGAAGACCGAGTGTGTCT**A**C-3′. The mutagenic primer was constructed in order to introduce an artificial polymorphic restriction site. Using a Biometra T-Gradient thermocycler (Whatman, Göttingen, Germany) standard PCR was carried out in a total volume of 20 μl containing 60 ng of genomic DNA, 1× PCR buffer, 8 pmol of each primer, 8 mM deoxynucleotide triphosphates (dNTPs) and 0.4 units (U) of Taq polymerase (5Prime, Hamburg, Germany). After an initial step of denaturation at 94 °C for 5 min, 35 cycles were carried out consisting of 94 °C

for 30 s, 54 °C (annealing temperature) for 30 s, 72 °C for 60 s and a final extension step of 10 min at 72 °C. Subsequent digestion overnight for 16 h at 65 °C of an 8 μl sample of the PCR product was accomplished with 3 U of TaiI (Fermentas, St. Leon-Rot, Germany) in a total volume of 20 μl resulting in two patterns of fragments consisting of 203 + 57 + 36 bp for the G allele and 183 + 57 + 36 + 20 bp for the C allele. Digestion products were visualized by silver staining after separation on a 15% polyacrylamide gel in 1× TBE buffer (Tris–Borate, EDTA) at 220 V for 3 h. Genotypes were determined blind to phenotype and independently by two investigators with an agreement rate of 100%.

2.3. AX-CPT task

We used a classical AX-CPT paradigm (e.g. Edwards et al., 2010). As in typical AX-CPT tasks, participants were presented with cue-probe pairs, with the cue and the probe separated by fixed time intervals that are varied to increase demands on prefrontal networks. AX-trials, i.e. when the valid cue ('A') is followed by a valid probe ('X'), occur with 70% frequency and require a target response by the subject. In subjects with strong contextual representations, this high frequency of these trials induces an attentional expectancy (Edwards et al., 2010) and hence a strong tendency to respond even in the other non-target conditions (i.e., AY, BX and BY), which occur with 10% frequency each. In AY trials a valid cue ('A') is presented before an invalid probe (not X), in BX trials an invalid cue ('B') is followed by a valid probe (i.e. X) and in BY-trials both the cue and the probe are invalid. Participants were required to the press a response button with one thumb on target trials (AX-trials) and another response button with the other thumb on the non-target trials (i.e., a 'non-target response button). This button was identical for all non-target trials. The buttons to be pressed for target and non-target trials were counterbalanced across subjects, i.e., half of the subject used the left thumb for the target button and the other half of the subjects used the right thumb for the target button. In all trials the cue was presented for 250 ms and the probe was presented for 250 ms. The subjects were required to respond within 800 ms. Subjects exceeding 800 ms for their response received auditory feedback (1000 Hz tone) instructing the participants to respond faster. Responses outside this time interval were classified as 'omissions'. 'False alarms' were defined as wrong button presses. Responses before the target were also classified as 'error responses', but this never occurred. Two different cue-target intervals (CTI) were administered. In the short condition, the CTI was 1000 ms. In the long condition the CTI was 2000 ms. Trials with short and long CTI were presented in randomized sequence. In each of the two blocks a total of 300 trials were presented with 210 AX-trials and 30 AY, BX and BY-trials. The inter-trial interval (ITI) was 1600 ms, randomly jittered between 1500 and 1700 ms.

2.4. EEG data recording and analysis

During the task the EEG was recorded from 24 Ag-AgCl electrodes (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, left mastoid – M1, right mastoid – M2) against a reference electrode located at Cz at a sampling rate of 500 Hz applying a filter bandwidth 0–80 Hz to the EEG. Electrode impedances were kept below 5 kΩ. EEG was filtered off-line from 0.5 to 16 Hz. Eye movements were monitored and recorded by means of two lateral and four vertical EOG electrodes. These EOG electrodes were used to correct trials for ocular artifact by means of the Gratton–Coles-Algorithm (Gratton, Coles, & Donchin, 1983). Results of the ocular correction procedure were visually inspected. Artifact rejection procedures were applied twice: automatically, with an amplitude threshold of ±80 μV, and visually by rejecting all trials contaminated by technical artifacts. Before quantifying ERPs, the data was re-referenced to linked mastoids. The N2 and P3 amplitudes and latencies were evaluated in correct AX, BX, and AY trials only. The baseline was set at 200 ms pre-stimulus until stimulus presentation. The N2 was defined as the most negative peak occurring 200 till 300 ms after stimulus onset, and was measured relative to this baseline (e.g. Beste et al., 2011). The P3 was measured relative to the baseline. The P3 was defined as the most positive peak occurring 350–500 ms after stimulus onset (e.g. Beste et al., 2011). Amplitudes and peak latencies were measured for each subject separately. The amplitude of the CNV was quantified at electrodes Cz and Pz in the time interval −100 ms till target presentation (Wild-Wall & Falkenstein, 2010), relative to a pre-cue baseline (−200 ms till Cue presentation).

2.5. Statistical analyses

Behavioural and neurophysiological data were analyzed using mixed design ANOVAs. The ability to use context is assessed by investigating patterns of performance on the two most challenging trial types, AY and BX (e.g. Edwards et al., 2010). For the behavioural data, the error rates were analyzed using an ANOVA with the within-subject factors trial type (i.e. AX, AY, BX) and delay (short vs. long) and the between-subject factor genotype group (CC, CG, GG). The neurophysiological data of the N2 and P3 were analyzed in two separate ANOVAs using electrode (Fz, FCz) and trial type as within-subject factors and genotype group as between subject factor. For the CNV electrodes Cz and Pz were used and analyzed with the identical ANOVA design as outlined above. The degrees of freedom were adjusted using the Greenhouse–Geisser-Correction when appropriate. In addition, separate univariate ANOVAs of the post-hoc tests were calculated when necessary and Bonferroni-corrected where appropriate. All variables included in ANOVA analyses were normally distributed as indicated by the Kolmogorov–Smirnov Test (all $z < 1.1$; $p > .2$; one-tailed). As a measure of variability the standard error of the mean (SEM) together with the mean is given throughout. To validate the obtained effects, we used a cross-validation procedure where we divided participants in each genotype group randomly into two subgroups. Then, all ANOVAs were repeated using the randomly created subgroups as an additional between-subject factor (refer: Beste, Baune, Domschke, Falkenstein, & Konrad, 2010d).

3. Results

3.1. Behavioural data

When analyzing error rates, the ANOVA revealed a main effect of trial type ($F(2,178) = 79.71$; $p < .001$; $\eta = .47$). Post-hoc tests showed that the error rates were highest in the BX condition (8.5 ± 0.2) followed by the AY (7.4 ± 0.2) and AX condition (4.6 ± 0.2) (all conditions differed from each other $p < .001$). The main effect of delay revealed that error rates were higher in long delay condition (8.1 ± 0.1) than in the short delay condition (6.1 ± 0.2) ($F(1,89) = 180.65$; $p < .001$; $\eta = .64$). The main effect genotype was significant ($F(2,87) = 3.41$; $p = .037$; $\eta = .07$). Bonferroni corrected post-hoc tests revealed that the CC genotype group committed fewer errors (6.8 ± 0.2), than the CG genotype group (7.6 ± 0.2). No difference was evident, when comparing both of these groups with the GG genotype (7.3 ± 0.15) group (p's > .3) (Fig. 1).

There was a three-way interaction trial type × delay × genotype group ($F(4,178) = 19.87$; $p < .001$; $\eta = .31$). Univariate ANOVAs examining genotype group differences in the long delay condition for each trial type separately (i.e. AX, AY, BX) showed that the genotype groups did not differ from each other (all $F < 1.8$; $p > .2$). Opposed to this, there were genotype group differences in error rates in the short delay condition for the AY and BX condition. Post-hoc tests for the AY condition revealed that the CC genotype group commit-

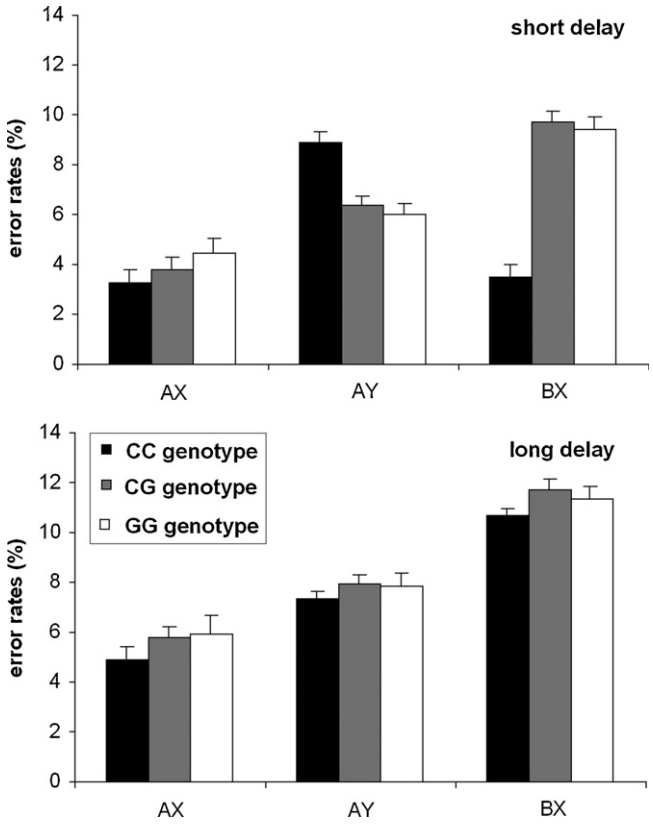

Fig. 1. Rates of response error for the different trial types (i.e., AX, AY, BX on the *x*-axis), for the different genotype groups (i.e., CC, CG, GG in different colours), and for short and long length of the delay interval (top and bottom part of the panel).

Table 1
Mean reaction times (RTs) and standard error of the mean (SEM) for the different trial types on short and long delay intervals for the different genotype groups.

Genotype group	Delay length	AX trials	AY trials	BX trials
CC	Short	334 (12)	343 (13)	344 (9)
	Long	330 (10)	334 (11)	336 (11)
CG	Short	348 (10)	353 (10)	333 (8)
	Long	341 (9)	348 (10)	335 (9)
GG	Short	341 (6)	330 (9)	335 (9)
	Long	330 (12)	360 (11)	331 (15)

ted more errors (8.9 ± 0.5) than the CG (6.3 ± 0.4) and GG (6.1 ± 0.5) genotype groups (each difference: $p = .001$). Opposed to this, no difference was evident between the CG and GG genotype groups ($p > .8$). For the BX condition the groups differed ($F(2,89) = 38.47$; $p < .001$; $\eta = .46$), but the pattern was reversed: the CC genotype group committed fewer errors (3.8 ± 0.6) than the CG (9.7 ± 0.4) and GG (9.2 ± 0.5) genotype groups ($p < .001$). The CG and GG genotype groups did not differ from each other, as indicated by post-hoc tests ($p > .5$).

Analyzing the response times (RTs) in a repeated measures of variance using the within subject factors trial type (i.e. AX, AY, BX) and delay (short vs. long) and the between subject factor genotype group (CC, CG, GG) did not reveal any significant effect (all $F < 1.7$; $p > .18$). The RTs in the different experimental conditions, for each genotype are given in Table 1.

The pattern of results is substantiated by the cross-validation analysis, where no effect of the cross-validation factor was found (all $F < .6$; $p > .3$).

3.2. Neurophysiological data

The ERPs on AX, AY and BX trials are shown in Fig. 2 separated for each genotype group and delay length.

N2-effects: For the N2-amplitudes only the main effect trial type was significant ($F(2,180) = 28.22$; $p < .001$; $\eta = .23$) showing that amplitudes were most negative in the BX ($-2.2\,\mu V \pm 0.2$) condition, followed by the AY ($-1.8 \pm 0.2\,\mu V$) and AX condition ($-0.4 \pm 0.3\,\mu V$) (all $p < .001$). All other main or interaction effects were not significant (all $F < 1$; $p > .4$). For the latencies, there was no significant effect (all $F < 1.3$; $p > .3$). The pattern of results is substantiated by the cross-validation procedure, where no effect of the cross-validation factor was found (all $F < .5$; $p > .4$).

P3-effects: Analyzing the P3-amplitudes it is shown that potentials were higher at electrode FCZ (8.4 ± 0.1), compared to Fz (7.5 ± 0.2) (main effect electrode: $F(1,89) = 19.95$; $p < .001$; $\eta = .02$). The main effect trial type ($F(2,178) = 121.95$; $p < .001$; $\eta = .56$) revealed that amplitudes were highest in the AY condition ($9.8 \pm 0.2\,\mu V$) and lower in the BX ($8.7\,\mu V \pm 0.1$) and AX condition ($5.1 \pm 0.2\,\mu V$) ($p < .009$). The main effect delay ($F(1,89) = 174.34$; $p < .001$; $\eta = .60$) revealed that the P3 amplitude was larger on short ($8.8 \pm 0.2\,\mu V$) than on long delay ($7.2 \pm 0.1\,\mu V$) intervals. Also the

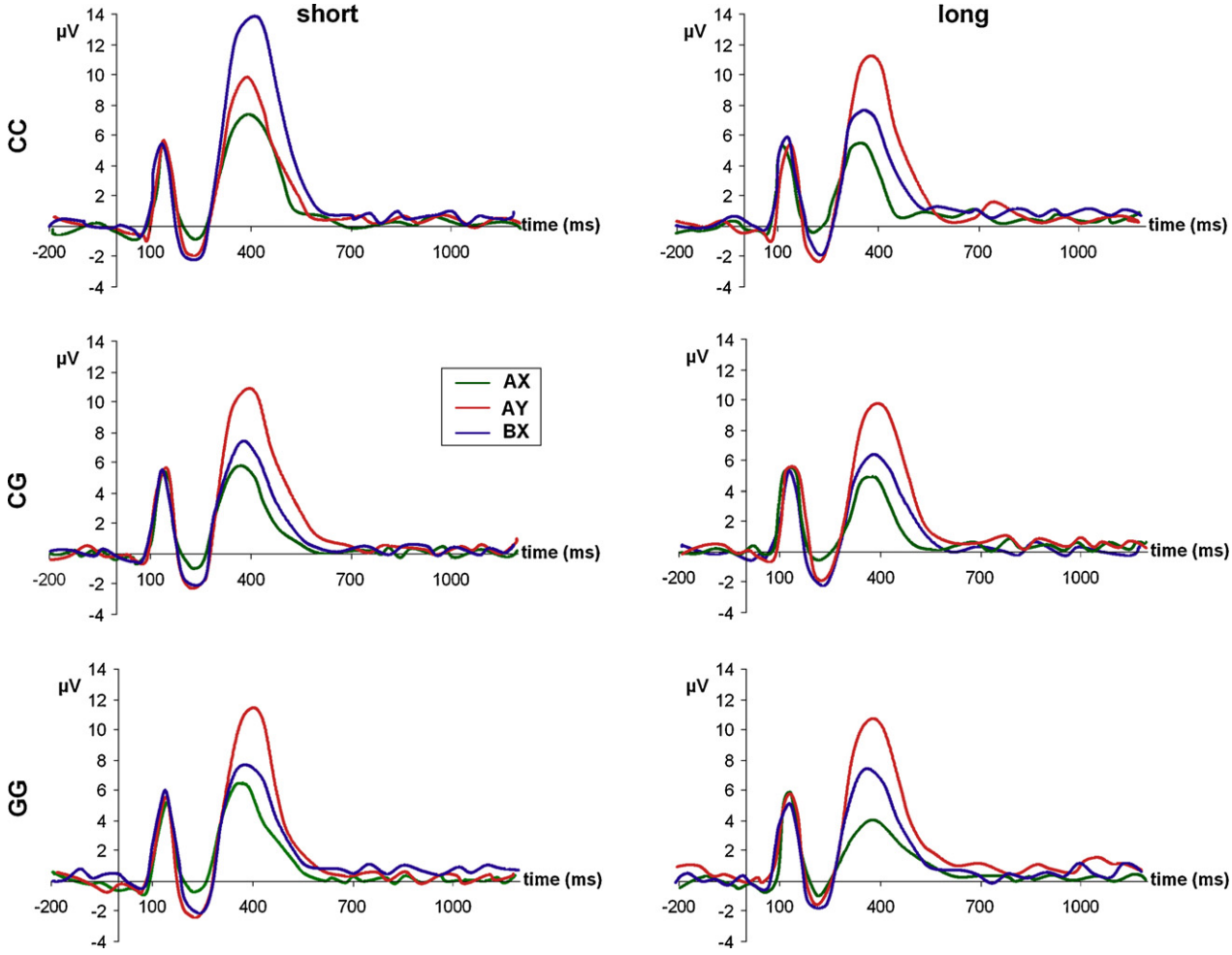

Fig. 2. Event-related potentials (ERPs) at electrode Fz. The different ERP-traces denote the different experimental condition (i.e., AX, AY, BX). The short delay condition is depicted on the left side of the panel, and the long delay condition on the right side of the panel. In the rows, the different genotype groups (i.e., CC, CG, GG) are given. Time point 0 denotes the time point of target stimulus delivery.

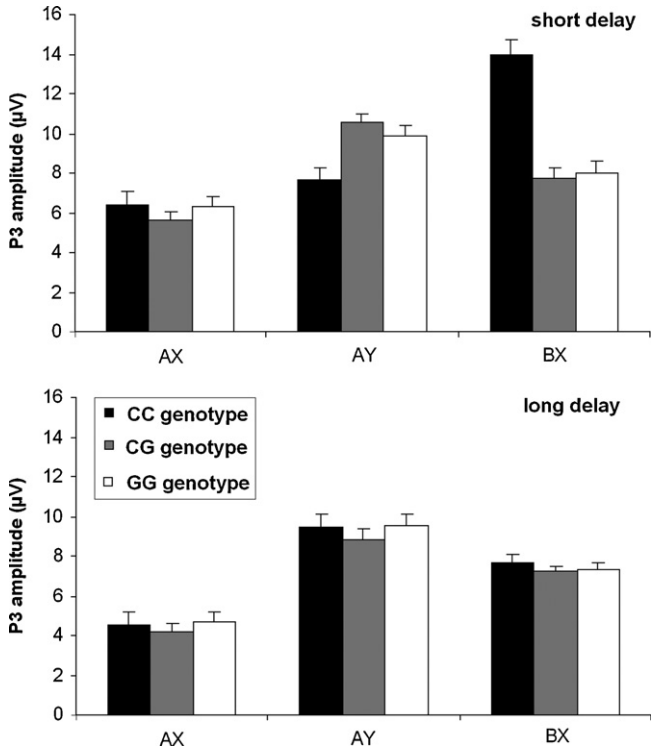

Fig. 3. Amplitudes of the P3 potential separated for the different experimental conditions (i.e., AX, AY, BX) and genotype groups (i.e., CC, CG, GG). Amplitudes of the short delay are shown at the top, the amplitudes of long delay condition at the bottom.

main effect genotype group was significant ($F(2,89) = 8.56$; $p < .001$; $\eta = .16$) showing that amplitudes were greater in the CC genotype group ($8.8 \pm 0.2\,\mu V$), compared to the CG ($7.4 \pm 0.2\,\mu V$) and GG genotype groups ($7.7 \pm 0.3\,\mu V$) ($p < .008$), which did not differ from each other ($p > .8$). As the highest interaction, the ANOVA revealed an interaction trial type × delay × group ($F(4,178) = 26.99$; $p < .001$; $\eta = .33$). This interaction is plotted in Fig. 3.

To explore this interaction further, subsequent univariate ANOVAs examining genotype-group differences were run. In the long delay condition the genotype groups did not differ from each other in either of the trials (i.e., AX, AY and BX) (all $F < 1$; $p > .3$).

For the short delay condition, the groups did not differ in the AX condition ($F(2,89) = 1.11$; $p > .2$; $\eta = .04$). For the AY condition the P3 amplitude was lower in the CC genotype group ($7.6 \pm 0.6\,\mu V$), compared to the CG ($10.5 \pm 0.4\,\mu V$; $p = .001$) and GG ($10.4 \pm 0.5\,\mu V$; $p = .001$) genotype groups. The latter groups did not differ from each other ($p > .8$) ($F(2,89) = 8.17$; $p = .001$; $\eta = .15$). For the BX condition, the pattern of results was reversed. Here, the amplitude of the P3 was largest in the CC genotype group ($14 \pm 0.7\,\mu V$) ($p < .001$) and attenuated in the CG ($7.7 \pm 0.5\,\mu V$) and GG ($8.2 \pm 0.6\,\mu V$) genotype groups, which again did not differ from each other ($F(2,89) = 23.20$; $p < .001$; $\eta = .34$). To estimate the relation of P3 amplitude variations with behavioural performance, correlational analyses (Pearson correlations) were conducted. These analyses show that variations in P3 amplitude were inversely related to variations in error rates in AY and BX trials in each genotype group. The correlation coefficients are given in Table 2.

Concerning the latencies of the P3, there was a main effect of delay ($F(1,90) = 63.45$; $p < .001$; $\eta = .41$) showing that latencies were shorter for the short (363 ± 4 ms), than for the long delay (372 ± 6 ms). No other main or interaction effects were significant (all $F < 0.9$; $p > .3$). All effects described above were validated by the cross-validation procedure, which again revealed no significant interaction effect with the cross-validation factor (all $F < .5$; $p > .4$).

Table 2
Results of the correlational analyses of P3 amplitude and performance in AY and BX-trials in the short and long delay condition for each genotype group.

	AY (short delay)	AY (long delay)	BX (short delay)	BX (long delay)
CC	−.464	−.480	−.501	−.481
CG	−.477	−.590	−.594	−.509
GG	−.465	−.496	−.477	−.511

CNV effects: The CNV for each delay length, genotype group and electrode is given in Fig. 4A.

A repeated measures ANOVA revealed a main effect electrode showing that the CNV was stronger at electrode Cz ($-9.1 \pm 0.2\,\mu V$), compared to Pz ($-7.5 \pm 0.2\,\mu V$) ($F(1,89) = 14.70$; $p < .001$; $\eta = .14$). The CNV was also stronger at short ($-8.7 \pm 0.1\,\mu V$) than at long delays ($-7.9 \pm 0.1\,\mu V$) ($F(1,89) = 14.68$; $p < .001$; $\eta = .13$). Furthermore, there was an interaction "electrode × delay length × genotype group" ($F(2,89) = 9.86$; $p < .001$; $\eta = .18$). This interaction is illustrated in Fig. 4B. Subsequent Bonferroni-corrected post-hoc tests showed that this interaction was due to the fact that selectively for short delays the CNV was stronger at electrode Cz, but only in the CC genotype group ($p < .01$); all other post-hoc tests were not significant (all $p > .2$). In the above analysis, the mean amplitude of the CNV in the time interval −100 ms before target presentation was analyzed. However, Fig. 4A suggests that in the long delay condition, the CNV was more negative in the time interval between −800 and −1000 ms in the CC genotype group than in other genotype groups. This is underlined by the statistical analysis of the mean amplitudes in this time interval in the long delay condition. There was an interaction electrode × delay length × genotype group ($F(2,89) = 4.11$; $p < .01$; $\eta = .09$). Post-hoc tests also revealed that the CNV was again larger for the CC genotype group and also selectively for electrode Fz (CC: $-8.9 \pm 0.5\,\mu V$; CG: $-9.2 \pm 0.6\,\mu V$; GG: $-8.5 \pm 0.5\,\mu V$) ($p < .01$); all other post-hoc tests were not significant (all $p > .4$). The cross-validation procedure again revealed no significant interaction with the cross-validation factor (all $F < .5$; $p > .4$) in all of the above conducted CNV-analyses.

3.3. Regression analyses

The above findings suggest a robust effect of the 5-HT1A C(−1019)G polymorphism on context-dependent cognitive control processes. Given the reported relation of response inhibition processes with anxiety-related personality traits (Sehlmeyer et al., 2010), we conducted linear regression analyses examining the relative importance/relation of the 5-HT1A C(−1019)G polymorphism and anxiety sensitivity (ASI) (McNally, 2002) with behavioural performance and neurophysiological processes in AY and BX trials. Multiple regression analyses are useful when having predictors that are not independent from each other (e.g. Freedman, Pisani, & Purves, 2007), since genotype and anxiety are known to be associated. For the current study the 'inclusion method' was used for regression analyses. Genotype was used as categorical predictor in the regression analyses.

For BX-trials the analysis revealed a significant regression model ($F(2,89) = 24.81$; $p < .001$). Both the genotype group ($\beta = .52$; $t = 6.05$; $p < .001$) and the ASI-score ($\beta = .26$; $t = 3.08$; $p = .003$) were significantly related to performance (error rates) in BX-trials, but the influence of genotype group was larger that the influence of anxiety-sensitivity.

For the AY trials also a significant model was obtained ($F(2,89) = 7.50$; $p = .001$). Again, the influence of genotype group ($\beta = -.40$; $t = -3.58$; $p = .001$) was larger than the impact of anxiety sensitivity ($\beta = -.20$; $t = -2.01$; $p = .02$). However, because of the antagonistic conception of BX and AY-trails (Braver & Barch, 2002),

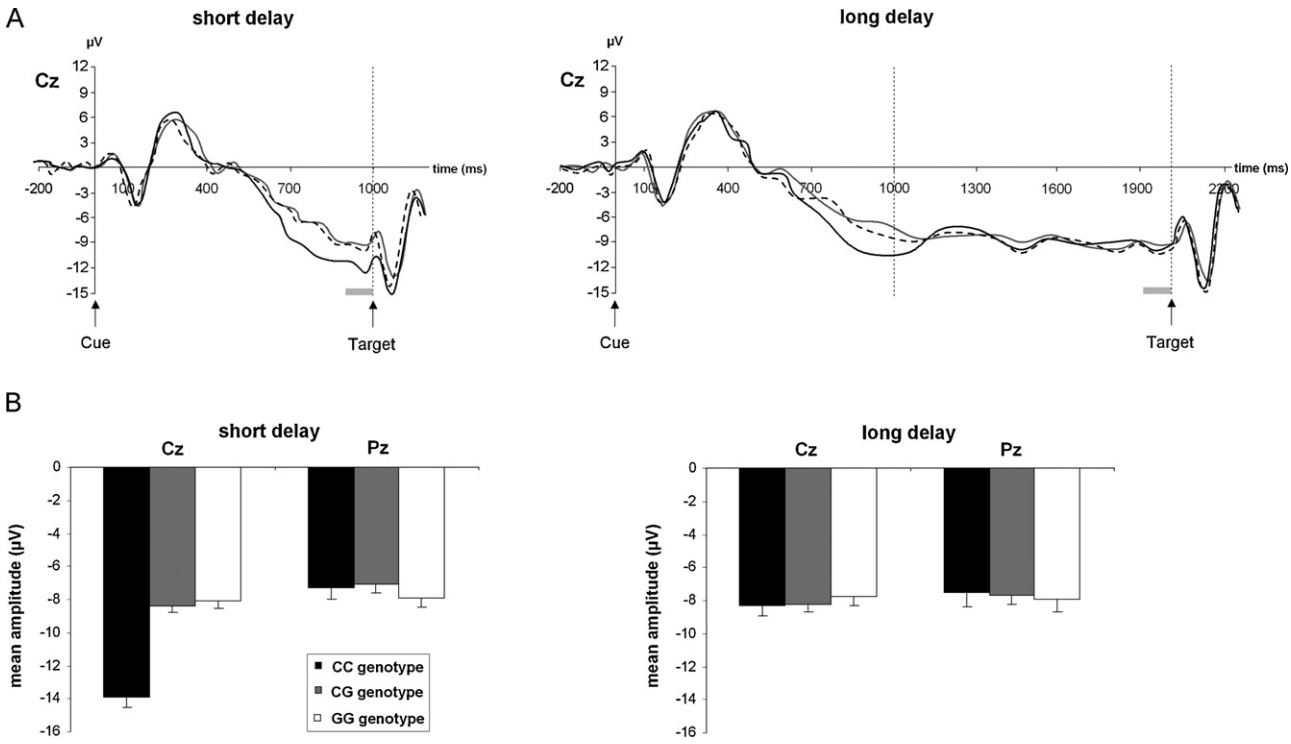

Fig. 4. (A) The contingent negative variation (CNV) at electrode Cz is depicted (Left panel short delay, right panel long delay). Time point 0 denotes the time point of cue stimulus delivery. Dashed dotted lines denote the time point of target stimulus delivery. In case of the long delay interval, the time point of target presentation for the short delay condition (i.e., 1000 ms before target presentation) is also denoted. The grey horizontal bar marks the interval used for CNV amplitude quantification. (B) The mean amplitude of the CNV for electrodes Cz and Pz, separated for the different delay lengths and genotype groups (i.e., CC, CG, GG) is given.

the direction of relation was in opposite direction in BX and AY trials.

Concerning neurophysiological processes, the P3 in AY and BX trials was examined, since this component revealed condition × genotype dependent modulations. For the BX-trials the factor genotype group ($\beta = -.61$; $t = -7.61$; $p < .001$) was again more influential than anxiety sensitivity ($\beta = -.19$; $t = -2.42$; $p = .018$) ($F(2,89) = 33.70$; $p < .001$). On AY trials, the influence of genotype group ($\beta = -.25$; $t = 2.61$; $p = .011$) and anxiety sensitivity ($\beta = -.26$; $t = -2.71$; $p = .008$) on the amplitude of the P3 was similarly strong ($F(2,91) = 7.71$; $p = .001$). As with the behavioural data, the direction of relation was opposite in BX and AY-trials. Regression analyses for long delay intervals did not reveal any significant model (all $F < 0.5$; $p > .5$).

4. Discussion

In the current study we examined modulations of contextual response inhibition processes by the functional serotonin 1A receptor polymorphism (5-HT1A C(−1019)G) on a neurophysiological level. The results show that the genotype groups differed in task performance depending on trial type (AY or BX) and delay length. For short delay intervals, the CC genotype group revealed worse performance on AY trials, compared to the CG and GG genotype group. On BX trials, the pattern reversed. On BX-trials, the CC genotype group revealed better performance (i.e., fewer errors) than G allele carriers. On a neurophysiological level, these effects were paralleled by modulations of the P3 component. Besides 5-HT1A C(−1019)G genotype, also anxiety sensitivity (AS) was related to AX-CPT task performance.

This is the first study suggesting that variations in the functional serotonin 1A receptor polymorphism affect cognitive control functions such as response inhibition in a context-dependent manner. It has been suggested that in AX-trials occurring with high frequency, context representations evoke robust response tendencies prior to the onset of the probe (Braver & Barch, 2002). This leads to an increased probability of false alarms in cases where 'A' is not followed by an 'X' probe (i.e., AY-trials). Against this background, the finding that the CC genotype group revealed worse performance on AY trials suggests that context representations are stronger in the CC genotype, compared to G allele carriers. Response inhibition is only successful in BX trials when the cue is correctly maintained in working memory (Braver & Barch, 2002). Therefore, robust working-memory functions are necessary to enable high performance in BX-trials. The result that the CC genotype group revealed better performance on BX trials compared to G allele carriers simply reflects the antagonistic conception of AY and BX trials (for review: Braver & Barch, 2002) for which strong contextual representation have adverse or beneficial effects, respectively.

On a neurophysiological level (ERPs), the above effects were paralleled by modulations of the P3 amplitude. The results are specific for the P3-data, since the N2 did not show trial and genotype dependent modulations. Modulations of the P3-component by the serotonergic system in response inhibition have previously been shown by the 5-HTTLPR polymorphism (Fallgatter et al., 1999). The neurophysiological data reveals an increased CNV in the CC genotype group in the short delay condition, compared to −1019G allele carriers. The CNV, denoting preparatory processes (e.g. Brunia & van Boxtel, 2001), was weaker in G allele carriers, compared to the CC genotype group. These weaker preparatory processes in G allele carriers may contribute to a weaker bias to respond on probe presentation. Consequently, the CG and GG genotype groups performed better on these AY-trials, as can be seen in the lower rate of false alarms and increased P3 amplitudes in these G allele carriers compared to the CC genotype group. The P3 amplitudes have frequently been found to be higher when response inhibition performance was better (i.e., error rates were lower) (e.g. Beste et al., 2008a; Beste, Dziobek, Hielscher, & Falkenstein, 2009; Sehlmeyer

et al., 2010). In the current data, the amplitude of the P3 was related to error rates underlining the above relation of the inhibition of motor processes and the P3. The reduction of the P3 in long, compared to short delay intervals is in line with this interpretation, as performance was worse in the long delay condition. The increase in the P3 in BX and AY compared to AX trials most likely reflects effects of trial number (oddball effects). The P3 observed in trials requiring the inhibition of a response has been assumed to reflect the process of motor inhibition (e.g. Smith, Johnstone, & Barry, 2008; Zordan, Sarlo, & Stablum, 2008) closely related to the outcome evaluation of inhibition processes (e.g. Band and van Boxtel, 1999; Beste et al., 2008a; Roche et al., 2005; Schmajuk et al., 2006). In this way variation in the 5-HT1A C(−1019)G genotype modulates neurophysiological processes related to motor inhibition and hence affects behavioural performance. However, the N2 component, likely reflecting pre-motor inhibition processes (Falkenstein et al., 1999), was not affected by 5-HT1A C(−1019)G genotype. Such a differential modulation of the Nogo-N2 and Nogo-P3 component has been observed in several studies examining neurobiological factors related to these cognitive functions (e.g. Beste, Willemssen, et al., 2010; Beste, Baune, Domschke, Falkenstein, & Konrad, 2010). It has been suggested that processes reflected by these components are mediated via different basal ganglia-neocortical systems (Beste et al., 2010a). As such, the results may reflect differences in serotonin 1A receptor related neural transmission in these systems. As the functional effect of the 5-HT1A C(−1019)G polymorphism is specific for autoreceptors located in the dorsal raphe nucleus (DRN) (e.g. Czesak et al., 2006; Parsey et al., 2006), the results may also reflect a differential modulation of these systems by projections originating from the DRN.

The DRN modulates serotonergic tone in limbic structures (e.g. Alex & Pehek, 2008; Beste, Domschke, Falkenstein, & Konrad, 2010; Varnäs, Halldin, & Hall, 2004) and dorsolateral prefrontal areas (e.g. de Almeida, Palacios, & Mengod, 2008; Michelsen, Prickaerts, & Steinbusch, 2008). These areas are important for response inhibition processes (e.g. Beste et al., 2008a; Beste, Saft, Andrich, Gold, & Falkenstein, 2008b; Beste, Dziobek, Hielscher, et al., 2009; Beste, Willemssen, et al., 2010; Beste, Baune, et al., 2010; Botvinick, Cohen, & Carter, 2004; Bush, Luu, & Posner, 2000; Ridderinkhof et al., 2004; Rushworth et al., 2004) and play a crucial role in maintaining information (e.g. Sawaguchi & Goldman-Rakic, 1991; Seamans & Yang, 2004) to guide cognitive control (Braver & Barch, 2002). It is therefore reasonable that variations in the functional 5-HT1A C(−1019)G polymorphism affect context-dependent response-control processes.

The presence of a −1019G allele is accompanied by a derepression of 5-HT1A autoreceptor expression by disruption of an inhibitory transcription-factor binding site. This entails reduced serotonergic neurotransmission (Albert & Lemonde, 2004; Lemonde et al., 2003). The current results therefore suggest that higher levels of serotonin 1A receptor-related neural transmission is beneficial for performance in BX trials, whereas lower levels are beneficial for performance in AY trials. The observed differences in AY and BX trial performance within each genotype group can be explained similarly: In the CC genotype group for example, putatively higher levels of serotonin promote performance in BX trials. As a downside of this effect, performance is worse in AY trials, since AY and BX trials are conceptualized antagonistically. It has been proposed that short and long delay intervals reflect the ability to represent context information and to maintain these representations (Braver & Barch, 2002). Therefore, the current results suggests that 5-HT1A C(−1019)G genotype mostly affects the contextual representation and not the maintenance of information. The present findings suggest that only the CC genotype group develops a stable contextual representation (AY performance was worse, compared to BX performance), since G allele carriers do not reveal this pattern, even at short delays. The results suggest that the relatively low serotonergic neural transmission in G allele carriers compromises the development of contextual representations in working memory. For the maintenance of information, the dopaminergic system is of crucial importance (Seamans & Yang, 2004). It can therefore not be ruled out that the effects observed emerge due to close interaction of the serotonergic and dopaminergic system in the PFC (e.g. Remington, 2008), which is known to work in the seconds range (e.g. Seamans & Yang, 2004). In this regard it has been shown that low doses of 5-HT1A receptor agonist 8-OHPAT increase firing rates of dopaminergic neurons (Alex & Pehek, 2008). Also, other evidence suggests that serotonergic neurotransmission is important for working memory processes, and hence the maintenance of information used to drive executive control processes (Robbins & Arnsten, 2009; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006). The fact that neither 5-HT1A C(−1019)G genotype group seems to be able to maintain context information in working memory in the long delay condition suggests that processes necessary to maintain information in working memory are not sufficiently triggered by serotonin 1A receptor-mediated neural transmission. This possible interaction of the dopaminergic and serotonergic system should be investigated in future research.

The double-edged effects of the functional 5-HT1A C(−1019)G polymorphism on cognitive control described above emerge as a function of different effects of contextual information in AY and BX trials. This has important implications from a genetic point of view. The −1019G allele of the 5-HT1A C(−1019)G polymorphism is supposed to be a risk allele for the development of mood and anxiety disorders (e.g. Domschke et al., 2006; for review: Albert & Lemonde, 2004) and thus confers strong negative effects to its carriers. Yet, to be evolutionarily sustained, any allele has to confer some advantage to its carriers. The current results suggest that the G allele confers a benefit to its carriers in terms of a higher accuracy in response-control processes in conditions where stable context representations compromise performance, since they induce attentional expectancies (Edwards et al., 2010) that may drive pre-potent target responses in these non-target trials. In this way the results suggest that the question whether a certain allele confers a risk or a benefit to its carriers depends on the context in which the effect of the variant on cognitive functions is examined. However, it can only be speculated on how superior AY performance could give G allele carriers an advantage in real-world survival. For high performance in AY-trials stable context representations are disadvantageous and it is beneficial to let behaviour be driven by the stimulus. It may be speculated that real-world situations where 'strategy' is useful occur quite often, which leads to an evolutionarily conservation of the G allele.

With respect to the above mentioned trial-type dependent variations by 5-HT1A C(−1019)G genotype, it is important to note that the regression analyses revealed that also 'anxiety sensitivity' (AS) (McNally, 2002) was related to performance. Depending on trial type (AY vs. BX-trials), higher ASI scores were positively or negatively related to performance and P3 amplitude. In particular it has been shown that AY performance was positively correlated with AS whereas BX was negatively correlated with AS. In this way the results suggest that higher levels of AS deteriorate performance, when robust contextual information is disadvantageous for response inhibition processes. The results corroborate the findings by Sehlmeyer et al. (2010) showing that the P3 component is correlated with anxiety-related personality traits. Yet, the relative association between AS and task performance was weaker than the association between genotype and task performance. This suggests that the 5-HT1A C(−1019)G genotype may be a stronger modulator than individual variation in AS for contextual response inhibition processes.

In summary, the current study examined the relevance of the serotonin 1A receptor system and anxiety-related personality traits for different mechanisms of cognitive control by examining associations of the functional serotonin 1A receptor polymorphism (5-HT1A C(−1019)G) with AX-CPT performance. The results show that the −1019G allele differentially modulates cognitive control, depending on context information. In cases where context information is helpful to drive behavioural control, carriers of the −1019G allele are compromised in their performance, while they show better performance when stable context-representation compromise behavioural control. Likewise, anxiety sensitivity is related to behavioural performance in contextual response inhibition and reflects similar antagonistic effects when the context is manipulated. On a neurophysiological level, the results suggest that especially processes underlying the Nogo-P3 response, hence processes related to the inhibition of a motor program and/or evaluation of a successful inhibition, are modulated by 5-HT1A C(−1019)G genotype. Future studies may use pharmacological accounts to clarify the neurobiological basis in more detail. Importantly the study shows that a genotype can exert opposing effects on cognitive functions, depending on the contextual information. These results suggest that, even though certain alleles increase the risk to develop neuropsychiatric disorders, these alleles may also confer a benefit for some cognitive processes at the same time. This implication should be a target for future research.

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