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CHRM2 Genotype Affects Inhibitory Control Mechanisms During Cognitive Flexibility

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Abstract

The cholinergic system is one of the most important neurotransmitter systems, but knowledge about the relevance of the cholinergic muscarinergic receptor system for cognitive functions is still scarce. Evidence suggests that the cholinergic muscarinic 2 receptor (CHRM2) plays an important role in the processing of cueing/prior information that help to increase the efficacy of lower-level attentional processes. In the current study, we investigated whether this is also the case for higher-level cognitive flexibility mechanisms. To this end, we tested $N = 210$ healthy adults with a backward inhibition task, in which prior information needs to be used to guide cognitive flexibility mechanisms. Testing different polymorphisms of the *CHRM2* gene, we found that variation in this gene play a role in cognitive flexibility. It could be demonstrated that rs8191992 TT genotype carriers are better able to suppress no longer relevant information and to use prior information for cognitive flexibility, compared to A allele carriers. We further found that rs2350780 GG genotype carriers performed worse than A allele carriers. The results broaden the relevance of the CHRM2 system for cognitive functions beyond attentional selection processes. Corroborating recent theories on the relevance of the cholinergic system for cognitive processes, these results suggest that CHRM2 is important to process of "prior information" needed to inform subsequent cognitive operations. Considering the importance of prior information for adaptive behavioral control, it is possible that CHRM2 also modulates other instances of higher-level cognitive processes as long as these require the processing of "prior information."

Keywords *CHRM2* · Cognitive flexibility · Inhibition · Genotype · Choline · Muscarinergic

Introduction

The cholinergic system is one of the most important neurotransmitter systems. Cholinergic receptors are divided into nicotinergic and muscarinergic types. The muscarinic receptors are transmembrane G protein-coupled receptors located in neurons of the nervous system, cardiac, and smooth muscles [1, 2]. Single-nucleotide polymorphisms (SNPs) of the type 2 (M2) cholinergic muscarinic receptor gene (*CHRM2*) have been demonstrated to show associations with the pathophysiology of major depressive disorder [3–5], bipolar disorder [3, 5], schizophrenia [6], and Alzheimer's disease [7]. One of the common symptoms underlying these neuropsychiatric diseases is an impairment of attention, as seen in major depressive disorder [8–12], in bipolar disorder [13], in schizophrenia [14–17], and in Alzheimer's disease [18–20]. The functional relationship between the cholinergic system/receptor and attentional processes is also supported by studies employing pharmacological methods [21–25].

Though knowledge on the differential effects of the nicotinergic and the muscarinergic system on cognitive processes is still scarce, evidence suggest that both receptor types fulfill different functions: while nicotinergic receptors mainly modulate arousal and selective attention, muscarinic receptors seem to primarily modulate higher-level visual processing of stimulus characteristics [24]. Furthermore, some evidence suggests that the muscarinergic system plays a role in the guidance of attentional selection mechanisms by prior information (i.e., "cues") [26]. This has been shown examining the rs8191992 SNP of the *CHRM2* gene, which is located in the 3′ untranslated region (UTR) [4]. Cues can be of different sort [27] and are, by definition, are external events that are

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extracted from the sensory input and indicate that some behaviorally relevant property is going to change. It was shown that the effect of prior information was strongest in the rs8191992 TT genotype carriers. This suggests that varying efficiency in the M2 receptor caused by this *CHRM2* variation could selectively influence muscarinic presynaptic inhibition [26]. Yet, an open question is whether the muscarinergic receptor system, and the *CHRM2* genotype in particular, are important for the processing of cueing/prior information only in the context of attentional processes [26], or whether this neurobiological system plays a more general role in the processing of prior information—not confined to spatial attentional selection processes. Given that the cholinergic system has been suggested to play a general role in the assessment of the validity of prior (cueing) information [28], this might well be possible.

The processing of prior information plays a central role in "active inference" mechanisms as a guiding principle of cognitive functions [29]. This mechanism affects higher-level cognitive control processes, including functions that are important for adaptive behavioral control [30]. One major instance of adaptive behavioral control is "cognitive flexibility" [31]. During cognitive flexibility, it is not only important to switch between different tasks but also to inhibit competing task rules that have become obsolete, as they are no longer relevant. The so-called backward inhibition (BI) effect describes the time cost of overcoming the inhibition of a recently abandoned task set that has just become relevant again [32]. In experimental settings, this is typically observed in situations in which a task A is repeated from n-2 trials (e.g., ABA task triplet/backward inhibition condition), compared to when that task A has no n-2 trial sequence history (e.g., DBA task triplet/baseline condition). If the inhibitory effect of the n-1 trial on the n-2 trial is strong, costs to overcome this inhibition are high. Therefore, a strong BI effect is disadvantageous, as it leads to lower accuracy and larger RTs [32]. Importantly, the task rule to be applied in a backward inhibition task is often signaled by a cue. Using this prior information, it is possible to determine whether a previous task rule needs to be suppressed or whether the previously inhibited task rule needs to be activated again. The processing of this prior information is therefore central for the size of the BI effect. Since the *CHRM2* SNP rs8191992 TT genotype has been shown to modulate how "prior information" is processed, we hypothesizes that it could also have modulating influence on backward inhibition processes. Interestingly, it has been shown that variation in *CHRM2* is also implicated in inhibitory control problems associated with various psychiatric disorders, like substance abuse [5, 33–38]. This provides further evidence for the assumption that varying efficiency in the M2 receptor due to *CHRM2* sequence variations could also have modulating effects on performance in backward inhibition. In the current study, we investigated different *CHRM2* genotype effects on backward inhibition by analyzing the *CHRM2* SNPs rs20061174, rs324650, rs8191992, and rs2350780. Based on the previously reported association of the rs8191992 TT genotype with better processing of prior information [26], we hypothesized that especially this genotype could be associated with better cognitive flexibility and thus showing better performance in a backward inhibition paradigm (i.e., the TT group should have a smaller BI effect) as compared to persons carrying at least one A allele.

Material and Methods

Sample

A total of $N = 210$ healthy young participants of Caucasian descent (146 ♀, 64 ♂) between 18 and 32 years of age (mean 23.85, SD 3.3) was included in this study. All participants stated to have normal or corrected-to-normal vision and reported no psychiatric or neurologic diseases. Depression was ruled out using the Beck Depression Inventory (BDI) [39] scores (mean = 4.5, SD = 4.17). Each participant received a financial reimbursement of 25 €. Informed consent was obtained from all individual participants included in the study. The study was approved by the local ethics committee of the TU Dresden, Germany.

Genotyping

Genomic DNA was extracted from whole-blood samples, and the four *CHRM2* SNPs rs8191992, rs20061174, rs324650, and rs2350780 were genotyped using polymerase chain reaction-restriction fragment-length polymorphism (PCR-RFLP).

Experimental Setup

During the experiment, the participants sat in front of a 17-in. CRT computer monitor with a viewing distance of 57 cm. White stimuli were presented on a black background in the middle of the screen. Participants were asked to respond with two keys (left and right Ctrl key) on a regular QWERTZ keyboard with their left and right index fingers. The software "Presentation" (version 14.9. of Neurobehavioral Systems, Inc.) was used for stimulus presentation and response recording.

Backward Inhibition Task

We used a backward inhibition paradigm, which was first introduced by Mayr and Keele [32] and later adapted by Koch et al. [40]. The experimental paradigm used in this study is based on the latter and detailed in Fig. 1.

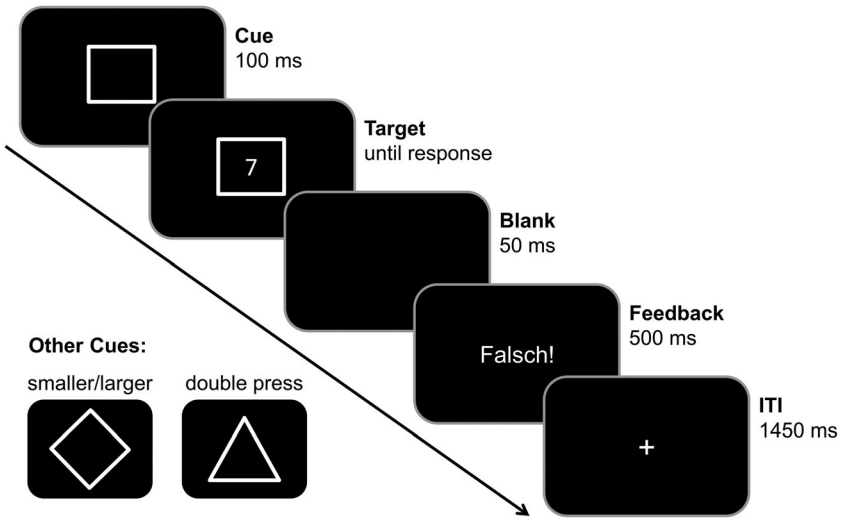

Fig. 1 Illustration of the experimental paradigm. Each trial began with the presentation of a target stimulus, which was terminated upon the first response or when 2000 ms had elapsed (in this case, the trial was coded as a "miss"). This was followed by a blank screen for 700 ms, a response feedback ("+" for correct and "−" for incorrect or missed responses) for 500 ms and another 500 ms blank before the start of the next trial

A square, diamond, and triangle frame were used as a task cues. They indicated task A (odd/even rule), task B (smaller/larger rule), or task D (double press rule), respectively. The target stimuli consisted of the digits 1 to 9 with the exception of 5. After a stimulus onset asynchrony (SOA) of 100 ms, during which the participants only saw the cue frame, a target digit was presented centrally within the cue frame. Cue and stimulus remained on the screen until a response was made. After that, there was a fixed response stimulus interval (RSI) of 1500 ms until the next cue was presented. During the RSI, a fixation cross was displayed in the center of the screen. For the parity judgment (i.e., odd/even rule in task A), a left key press was required when an odd target digit was presented and a right key press was required when the presented target digit was even. For the magnitude judgment (i.e., smaller/larger rule in task B), participants had to press the left key when the target stimulus was smaller than 5, and the right key when the target stimulus was larger than 5. For the double-press task D (i.e., double-press rule), participants were asked to press both keys simultaneously within 1000 ms after target onset. If they did not meet this requirement, a warning sign (German word "Schneller!", translating to "Faster!") appeared above the frame, asking the participants to react more quickly. Furthermore, participants also received feedback with the words "zu langsam!" (translating to "too late!") in the middle of the screen, in case they replied after this warning sign appeared. In case of a response error (i.e., wrong button press in tasks A or B, and too slow or nonsimultaneous responses separated by more than 50 ms in task D), an error message (German word "falsch!", translating to "wrong!") was presented on the screen for 500 ms. The experiment consisted of 768 trials, which were divided into eight equally sized blocks. After each block, participants received feedback about their mean response time (RT) during the last block. Within each block, the task (cue) sequence and stimulus sequence were randomized, except for n-1 repetitions, which means that both cues and stimuli could not be the same in two consecutive trials (e.g., a trial with a square cue and a stimulus 7 followed by a trial with a square cue and a stimulus 9 could not occur due to the same cue; likewise, a trial with a diamond cue and a stimulus 3 followed by a trial with a triangle cue and a stimulus 3 could not take occur due to the same stimulus). Each cue and stimulus, as well as every possible combination of both, was presented equally often. It was also ensured that the stimulus in the current trial was different from the stimulus used in the last trial with the same cue (e.g., a square cue with any stimulus except 4 was allowed in the current trial when the stimulus in the last square cue trial was 4). With the exception of the first two trials, every trial constituted a triplet with the last two previous trials. Within all blocks, all 12 possible triplet combinations (ABA, ADA, BAB, BDB, DAD, DBD, DBA, BDA, DAB, ADB, BAD, ABD) were presented equally often (± 1 triplet for two triplet conditions in each block). Triplets where the last trial had the same cue as the first trial were categorized as backward inhibition triplets, while triplets without this n-2 cue repetition were categorized as baseline triplets. To ensure that participants understood the instructions and followed the rules, task instructions were given both verbally by the test instructor and visually by reading the instructions on the screen. Afterwards, participants performed a practice block of 12 trials. Participants were encouraged to respond as quickly and accurately as possible. The RT and response accuracy of each condition were separately collected for behavioral analysis.

The first two trials of each block were discarded, and only triplets with correct responses in all three trials were included in the analyses [41–44]. Therefore, the chance level is at 12.5%. Moreover, trials with RTs higher than 2500 ms or lower than 100 ms were discarded. The mean number of the triplets used for data analysis was above 40 for all triplet conditions (ABA 44.8 ± 0.7; BAB 45.1 ± 0.7; DBA 46.6 ± 0.7; DAB 47.1 ± 0.7; ADA 45.8 ± 0.7; BDB 47.8 ± 0.6; BDA 47.4 ± 0.7; ADB 47.0

± 0.7; DBD 49.2 ± 0.6; DAD 46.8 ± 0.6; ABD 48.1 ± 0.7; BAD 47.7 ± 0.7). As explained in the "Introduction," we intended to investigate genotype effects on the size of the BI effect. Given that the BI effect seems to only be found when response selection is required in the n-1 trial [40, 45], we did not analyze triplets with a double-press in the n-1 trial (backward inhibition triplets ADA/BDB vs. baseline triplets BDA/ADB), as double-press trials require no response selection [40, 45]. In line with the study by [40], we analyzed triplets known to show the strongest BI effects (i.e., backward inhibition triplets ABA/BAB vs. baseline triplets DBA/DAB). We separately averaged the two BI triplets and the two baseline (BASE) triplets to obtain a measure for each condition. After that, we calculated the RT and accuracy differences between the BI and BASE conditions as a variable depicting the BI effect [mean (ABA, BAB) − mean (DBA, DAB)].

Statistical Analyses

The behavioral data (RT and accuracy) was analyzed using SPSS Statistics 24. We ran separate mixed-effects ANOVAs with the between-subject factor "genotype group" (AA vs. AT vs. TT for rs8191992 and rs324650; CC vs. CT vs. TT for rs20061174; AA vs. AG vs. GG for rs2350780) and the within-subject factor "condition" (backward inhibition vs. baseline). Greenhouse–Geisser corrections were applied whenever necessary. In the "Results" section, the reported mean values are followed by the standard error of the mean (SEM) as a measure of variance.

Results

Genotype Groups

Of the initial $n = 210$ participants, 50 were homozygous for the rs8191992 A allele, 105 were A/T carriers, and 55 were homozygous for the T allele. For rs20061174, the observed frequencies for C and T allele were 34.4% and 65.6%, respectively. Of the initial 209 participants, 24 were homozygous for the C allele, 92 were T/C carriers, and 93 were homozygous for the T allele. For rs324650, the observed frequencies for A and T allele were 47.6% and 52.4%, respectively. Of the initial 209 participants, 48 were homozygous for the A allele, 99 were A/T carriers, and 62 were homozygous for the T allele. For rs2350780, the observed frequencies for A and G allele were 64.3% and 35.7%, respectively. Of the initial 209 participants, 92 were homozygous for the A allele, 86 were A/G carriers, and 31 were homozygous for the T allele. All examined SNPs of *CHRM2* were in Hardy-Weinberg equilibrium ($p > 0.05$).

Task Performance Data

The behavioral performance is shown in Fig. 2. For all SNPs, the analysis of hit RTs and accuracy revealed a main effect of condition (all $F \geq 13.05$, $p < .001$), with higher accuracy and lower hit RTs in the baseline condition as compared to backward inhibition condition (see Fig. 2a).

Response accuracy further showed a condition × genotype interaction ($F(2,206) = 3.47$; $p = .033$; $\eta_p^2 = 0.033$) for SNP rs324650. Post hoc t tests revealed that all genotype groups showed an effect of backward inhibition with higher accuracy in the baseline condition (AA 76.0% ± 1.7; AT 74.0% ± 1.5; TT 76.4% ± 1.8) as compared to backward inhibition (AA 71.0% ± 2.1; AT 72.2% ± 1.5; TT 74.5% ± 2.0) (all $t \geq |3.74|$; all $p \leq .015$), but this difference between the baseline and the backward inhibition condition was larger in the AA genotype group (4.2% ± 1.0), compared to the AT (1.8% ± 0.7) and TT genotype groups (1.9% ± 0.7) $t(145) = 1.87$; $p = .032$). There was no difference between the AT and TT group ($t(159) = -0.05$; $p = .959$).

For rs8191992, the accuracy measure showed a main effect of genotype group ($F(1,207) = 4.12$; $p < .018$; $\eta_p^2 = 0.038$). Post hoc t tests showed that the accuracy of the TT group (79.0% ± 1.7) was significantly higher than that of the AT group (74.5% ± 1.4; $t(158) = 2.01$; $p = .046$), but not compared to the AA group (73.1% ± 2.6; $t(103) = 1.21$; $p = .118$). There were no significant accuracy differences between the AA and AT group ($t(153) = -0.50$; $p = .615$). Importantly, a condition × group interaction was also found for SNP rs8191992 ($F(2,207) = 5.67$; $p = .004$; $\eta_p^2 = 0.052$). Subsequent post hoc t tests showed a significant backward inhibition effect (i.e., condition difference) for the AA group ($t(49) = 4.29$; $p < .001$; BASE = 74.7% ± 1.8; BI = 69.2% ± 2.0) and the AT group ($t(104) = 2.80$; $p = .006$; BASE = 73.4% ± 1.4; BI = 71.4% ± 1.5). However, there was no significant condition difference for the TT group ($t(54) = 1.44$; $p = .155$; BASE = 79.0% ± 1.8; BI = 78.0% ± 2.0) (refer Fig. 2b).

For rs2350780, hit RTs showed a condition × genotype interaction ($F(2,206) = 3.79$; $p = .024$; $\eta_p^2 = 0.035$). Post hoc t tests showed that all genotype groups had a significant backward inhibition effect (i.e., condition difference; all $t \geq 7.42$; $p < .001$). Further post hoc t test showed that the GG group had a larger backward inhibition effect (BI minus BASE; 81 ms ± 11) than the AA group (52 ms ± 5; $t(121) = 2.76$; $p = .007$) and the AG group (54 ± 6; $t(115) = 2.30$; $p = .023$). Yet, the BI effect did not differ between the AA and AG group ($t(176) = 0.23$; $p = .823$) (refer Fig. 2c).

For rs20061174, no main effects or interactions were found for the genotype factor (all $F < 1.78$; $p > .171$).

Taken together, the rs8191992 SNP showed reliable genotype-related effects on accuracy, as the TT group

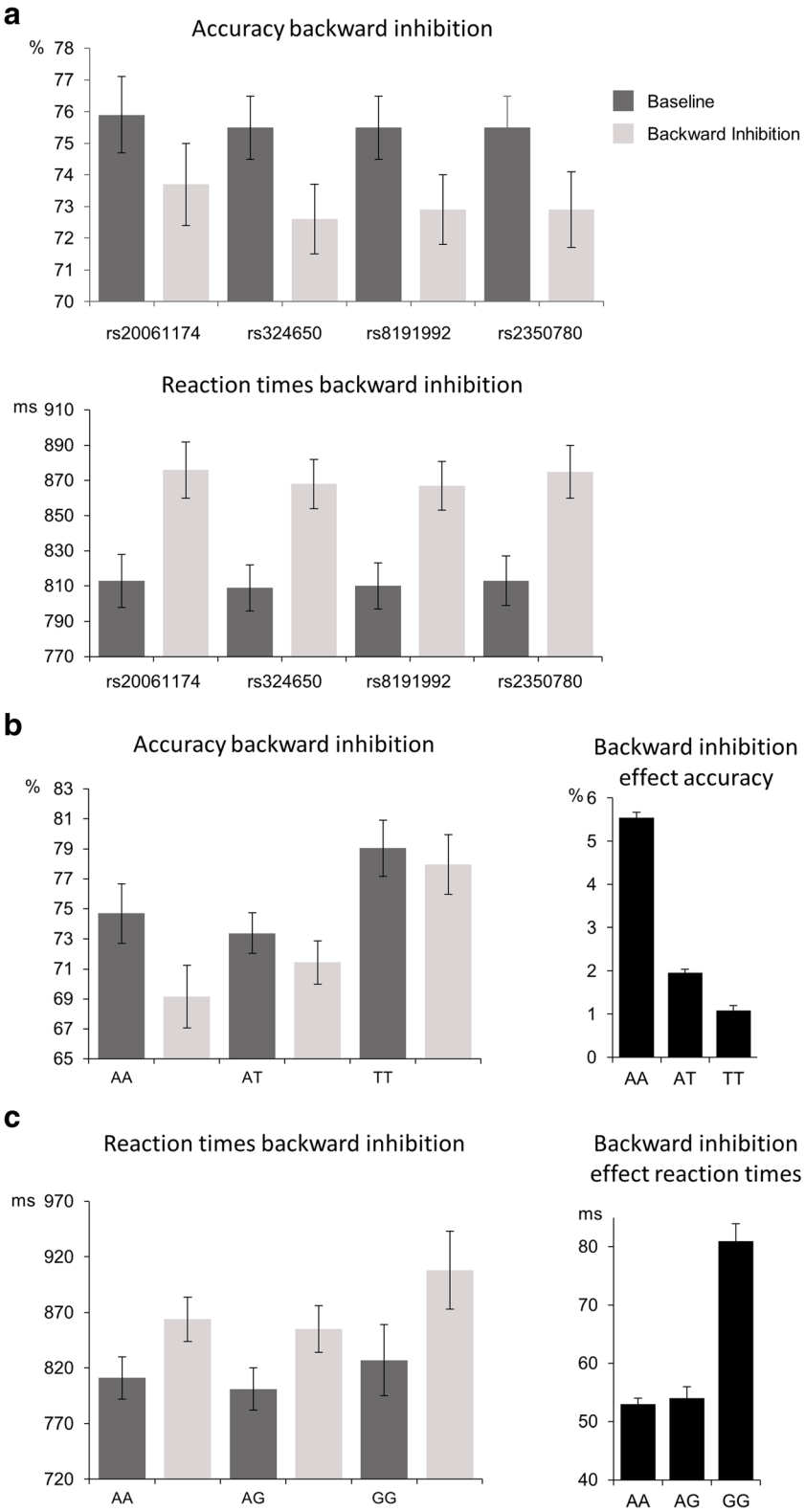

Fig. 2 Behavioral differences in the backward inhibition effect. **a** Accuracy (in %) and reaction times (RTs) in milliseconds for the backward inhibition (BI) and baseline condition for the SNPs rs8191992, rs20061174, rs324650, and rs2350780. **b** rs8191992-related accuracy differences between the BI and baseline conditions (left) and the BI effect (BASE-BI condition) (right) for the AA, AT, and TT groups. **c** rs2350780-related RT differences between the BI and baseline conditions (left) and the BI effect (BI-BASE condition) (right) for the AA, AG, and GG groups

did not only outperform the AA and AT groups but also showed no significant backward inhibition effect. The rs2350780 SNP showed genotype-related differences in RT, as the GG group showed a larger backward inhibition effect than the AA and AG groups. For rs324650, only marginal significant accuracy effects were obtained and rs20061174 did not seem to modulate backward inhibition at all.

Discussion

In the current study, we investigated the effects of different *CHRM2* genotypes on inhibitory control processes during cognitive flexibility (i.e., backward inhibition). Although the relationship between cholinergic system function and attentional processes has been supported by numerous studies [21–25, 46, 47], there is little knowledge about the specific effects of the cholinergic muscarinic receptor system on higher cognitive control processes that rely on prior or cuing information. Yet, theoretical work suggested that this is likely to be the case [28].

For the analyzed SNPs (rs20061174, rs324650, rs8191992, and rs2350780), all genotypes showed typical backward inhibition effects, i.e., decreased accuracy and/or prolonged RTs during BI trials, as compared to BASE trials. Importantly, however, only the SNPs rs2350780 and rs8191992 showed significant genotype-related differences in the magnitude of the BI effect: Although there were no differential effects of the rs8191992 genotype on RTs, the TT group did not only react more accurately than the AT and AA groups but also showed no BI effect on accuracy, i.e., no significant performance difference between BI and BASE trials. In contrast to this, the AA and AT genotype groups had a significantly higher accuracy in BASE than in BI trials. For the rs2350780 SNP, however, differential BI effects were only found for RT, where the GG group had a larger BI effect than the AA and AG groups.

As outlined in the "Introduction," a strong BI effect (i.e., lower accuracy and longer RTs in the BI condition) is considered disadvantageous and reflects reduced cognitive flexibility [32]. As mentioned, the BI effect reflects the time cost of overcoming the inhibition of a recently abandoned task set that has become relevant again [32], i.e., when the inhibitory effect of the n-1 trial on the n-2 trial is strong, costs to overcome this inhibition are high. Against this background, the results suggest that TT genotype carriers of the rs8191992 SNP and A allele carriers of the rs2350780 SNP are better able to reverse ("undo") the inhibitory effect of the n-1 trial on the n-2 trial than A allele carriers (rs8191992) or GG homozygotes (rs2350780). It can therefore be argued that especially in situations when previously inhibited task sets are relevant again, TT homozygotes (rs8191992) and A allele carriers (rs2350780) might benefit more from processing prior information (i.e., cues) than AA and AT genotype carriers (rs8191992) and GG homozygotes (rs2350780), respectively. This finding of better cognitive abilities in rs8191992 TT genotype carriers is in line with previous findings also suggesting that prior information can best be used by rs8191992 TT genotype carriers to guide perceptual and attentional selection processes [26]. Moreover, muscarinergic receptors were shown to be involved in the visual processing of stimulus characteristics [24]. Importantly, it has recently been shown that an efficient inhibitory perceptual gating of incoming information strongly modulates the efficacy of backward inhibition processes [48–50]. Other electrophysiological evidence suggests that CHRM2 modulates inhibitory neural networks and processes [51]. Autoradiographic data from postmortem depressive patients' brain tissue suggests that modulations of CHRM2 receptor binding in frontal cortices are strongest in inferior frontal regions [52, 53]. Notably, exactly these regions have been shown to be associated with inhibitory perceptual gating of incoming information during backward inhibition [48, 49]. The possible reason why the rs8191992 TT genotype does not only modulate the processing of prior information on a perceptual–attentional level [26] but also seemingly unrelated inhibitory control process during cognitive flexibility, may relate to the fact that the inhibitory gating and categorization of sensory input using informational priors plays an important role in both cases. This fits well into the concept that the acethylcholinergic system is involved in the processing of "cueing" or "prior information" in general [28]. Considering the importance of prior information for higher level cognitive control processes, including functions important for adaptive behavioral control [30], it may be speculated that CHRM2 also modulates other instances of higher level cognitive processes as long as these require the processing of "prior information."

The finding that only the rs8191992 and rs2350780 SNP showed genotype-related behavioral differences during task switching indicates a special role of these SNPs. Yet, nothing is known about their potential functional role. However, rs8191992 located in the 3UTR could for example affect microRNA-binding sites. Creating or destroying miRNA binding to its target site modulates the microRNA-mRNA interaction, which can have strong effects on the phenotype [54]. A likely functional impact of these SNPs is further corroborated by other studies showing that especially rs8191992 and rs2350780 were found to be associated with differences in intelligence [4, 55] and inhibitory control deficits in substance use disorders [5, 33–38] and especially nicotine addiction [36]. Currently, there is no study examining backward inhibition processes in nicotine addiction and/or craving. However, as far as CHRM2 receptor turnover is modulated (e.g., during nicotine craving), the cognitive processes examined in the current study may be useful as a diagnostic tool to monitor nicotine withdrawal. However, a central aspect in the experiment conducted is related to the processing of cues. This function has been shown to be affected by various drug including alcohol-related effects [56, 57]. It is thus possible that the cognitive functions investigated may have a broader relevance beyond its usage in nicotine addiction.

In summary, the results show that different *CHRM2* genotypes play a role in cognitive flexibility and that inhibitory control processes during cognitive flexibility are strongly modulated by these sequence variations. The results suggest

that variation in the *CHRM2* gene could have a broad relevance beyond attentional selection processes. The range of cognitive processes being modulated suggests that the muscarinergic system affects mechanisms relevant for a broad range of cognitive functions. This common mechanism may relate to the processing of "prior information" needed to inform subsequent cognitive operations.

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Compliance with Ethical Standards

The study was approved by the local ethics committee of the TU Dresden, Germany.

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