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The Presynaptic Regulation of Dopamine and Norepinephrine Synthesis Has Dissociable Effects on Different Kinds of Cognitive Conflicts

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Abstract

Goal-directed behavior requires the ability to resolve subliminally or consciously induced response conflicts, both of which may benefit from catecholamine-induced increases in gain control. We investigated the effects of presynaptic differences in dopamine and norepinephrine synthesis with the help of the *tyrosine hydroxylase* (TH) rs10770141 and the *dopamine-β-hydroxylase* (DBH) rs1611115, rs6271, and rs1611122 polymorphisms. Conscious and subliminal response conflicts were induced with flanker and prime distractors in ($n = 207$) healthy young participants while neurophysiological data (EEG) was recorded. The results demonstrated that the increased presynaptic catecholamine synthesis associated with the *TH* rs10770141 TT genotype improves cognitive control in case of consciously perceived (flanker) conflicts, but not in case of subliminally processed (prime) conflicts. Only norepinephrine seemed to also modulate subliminal conflict processing, as evidenced by better performance of the *DBH* rs1611122 CC genotype in case of high subliminal conflict load. Better performance was linked to larger conflict-induced modulations in post-response alpha band power arising from parietal and inferior frontal regions, which likely helps to suppress the processing of distracting information. In summary, presynaptic catecholamine synthesis benefits consciously perceived conflicts by improving the suppression of distracting information following a conflict. Subliminal conflicts were modulated via the same mechanism, but only by norepinephrine.

Keywords Conflict · DBH · Dopamine · Norepinephrine · Subliminal · TH

Introduction

The ability to exert volitional cognitive control is indispensable for living an independent and successful life. Cognitive control processes are however known to be quite error-prone as they can often not be completely shielded from the effects of either consciously or subliminally processed distracting information [1–9]. These two kinds of distracting information have been shown to evoke different kinds of conflicts: While consciously perceived distractors may trigger consciously initiated top-down control processes, this is not the case for subliminally perceived conflicts [8, 10, 11]. Yet, it is increasingly recognized that conscious and subliminal information processing can conjointly modulate interference control and conflict processing [8], suggesting that both sources of conflict might share a common neurobiological basis [8, 10, 11].

Catecholamines are a likely candidate for this common basis, as increased postsynaptic dopamine and norepinephrine concentrations have been suggested to improve the neural signal-to-noise ratio and thereby support gain control [12–17]. Gain control fosters cognitive control processes [16–21], strengthens inhibitory influences on districting response representation [22–24, 25–28], and therefore facilitates task-relevant processing. It is hence possible that both consciously and subliminally evoked response conflicts can be attenuated by increases in catecholaminergic signaling, as this improves gain control. There is, however, evidence that catecholamines might differentially modulate the two kinds of conflict: In the presence of consciously perceived distractors, dopamine supports the top-down selection of correct responses [29], while norepinephrine supports signal detection and plays

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an important role in conflict monitoring [30]. In contrast to this, subliminally triggered conflicts have been suggested to be rather unaffected by these two catecholamines, as demonstrated via methylphenidate (MPH) administration [31].

Unfortunately, those findings do however not allow to draw specific conclusions about the potentially different effects of dopamine and norepinephrine on the two kinds of conflict. The main reason for this is that drugs that cross the blood-brain barrier and may be used in humans usually modulate postsynaptic dopamine and norepinephrine levels in a non-selective fashion [32–35]. Moreover, drugs like MPH only act postsynaptically by manipulating catecholamine reuptake but do not interfere with presynaptic synthesis. Given that differences in presynaptic synthesis are an important determinant of the neurotransmitter amounts which can be released by a given neuron upon stimulation, synthesis may however also heavily contribute to postsynaptic effects [36, 37]. As both aspects may substantially increase our functional understanding of how catecholamines may improve cognitive control functions, modulators of presynaptic catecholamine synthesis, as well as functional differences between dopamine and norepinephrine, should receive more attention.

Against this background, we set out to investigate and distinguish the effects of dopamine and norepinephrine on consciously vs. subliminally triggered conflicts by applying a molecular genetics approach in combination with high-density EEG-recordings, time-frequency decomposition, and source localization (beamforming) methods. By investigating polymorphisms in both the *tyrosine hydroxylase* (TH) and the *dopamine ß-hydroxylase* (DBH) gene, it is possible to not only investigate the effects of presynaptic differences in catecholamine synthesis but to also dissociate the modulatory effects of dopamine and norepinephrine on subliminally and consciously induced conflicts. TH is the rate-limiting enzyme in the biosynthetic pathway of both dopamine and norepinephrine, as dopamine is not only an active neurotransmitter but also the biochemical precursor of norepinephrine [38, 39]. DBH is an enzyme that is found in norepinephrinergic neurons, where it converts dopamine into norepinephrine. Via this mechanism, it has a direct influence on the biosynthesis of norepinephrine, but not of dopamine [40]. Effects that are found to be only modulated by the TH, but not by DBH, suggest an important role of dopamine, but not of norepinephrine. Effects that are found to be modulated by both TH and DBH, or by DBH alone, suggest a stronger involvement of norepinephrine in the respective function.

To assess general effects in presynaptic catecholamine synthesis, we investigated the functional single nucleotide polymorphism (SNP) rs10770141 (C-824T), which is located in the promoter region of the *TH* gene and affects binding sites of transcription factors MEF2, FOXD1, and SRY32. Rao et al. [41] demonstrated that carriers of the minor T allele show higher amounts of TH than carriers of the C allele, thus resulting in an upregulation of presynaptic dopamine/norepinephrine production and release [41]. Based on the observation that an MPH-induced increase in postsynaptic dopamine and norepinephrine levels has been shown to decrease consciously, but not subliminally induced conflicts [31], we hypothesized that carriers of the minor *TH* rs10770141 T allele should show comparable effects (i.e., selectively decreased consciously processed conflicts as compared to carriers of the C allele). Since TH does however not allow to dissociate the functional roles of dopamine and norepinephrine, we further assessed three SNPs in the *DBH* gene: The SNP rs1611115 (-1021C/T) has been identified as the main predictor of DBH activity in plasma where it explains 30–50% of interindividual variance in DBH activity [42]. The common C allele of this SNP is known to be the high-activity allele [42] and should, therefore, diminish conscious (and potentially also subliminal) conflict effects, as compared with the rare T allele that contributes to greatly lowered DBH activity. The non-synonymous exonic SNP rs6271 (Arg535Cys) in exon 11 of *DBH* has also been reported to influence plasma DBH activity (but with a considerably smaller effect). Here, also, the C allele coding for arginine is considered as the high activity allele [42]. We hence hypothesized the C allele to diminish conscious (and potentially also subliminal) conflict effects, as compared with the rare T allele coding for cysteine. Additionally, we analyzed the *DBH* rs1611122 SNP, since earlier studies found this SNP to play an important role in schizophrenia, which is known to be associated with increased catecholaminergic signaling [43].

To investigate effects of *TH* and *DBH* polymorphisms on subliminally and consciously induced response conflicts as well as their interaction, we applied an experimental paradigm that combines response-relevant targets with two different kinds of distractors (i.e., subliminal primes and consciously perceived flankers) [10, 11, 31]. On a neurophysiological level, cognitive control processes have been suggested to be implemented via oscillations in the theta frequency band. Theta oscillations implied in cognitive control typically originate from medial frontal structures [44–50] and are thought to reflect decision processes during response selection in many response conflict situations [45, 47, 51]. As medial frontal theta band power is known to increase in case of a response conflict [45], it can be hypothesized that larger behavioral conflicts should be associated with larger theta band power. Given that we expect increases in catecholaminergic signaling to decrease conscious conflicts and potentially to also decrease subliminal conflicts (albeit to a smaller degree), we hypothesized that this should be associated with a decrease in theta power modulation. Aside from the theta frequency band, oscillations in the alpha frequency band are known to reflect a basic processing mode that controls the flow of information in the cortex [52–54]. Alpha oscillations have been suggested to reflect inhibitory control processes regulating

access of information to a knowledge system [52–54]. More specifically, alpha band power has been shown to be inhibited in situations where conflicting information needs to be suppressed [55]. While this suppression is commonly found directly after the conflict-inducing stimulus, it can also be delayed and found after the response [55]. Because alpha band activity likely implements processes to inhibit distracting information, it reflects a process critical to online conflict processing and resolution. The neuroanatomical sources of such differences in theta and alpha power may be identified by means of beamforming [56–58]. Medial frontal regions are well-known to be involved in conflict monitoring processes as reflected by theta [59] and should therefore also underlie any catecholamine-associated modulations of theta band power. While alpha band power is typically found to be largest over parietal and occipital sites, orbitofrontal and inferior frontal regions may also play an important role and be associated with catecholaminergic conflict modulation, as those regions have been found to be an important part of an alpha-driven inhibitory control network [60–62].

In short, the objective of this study is to investigate and differentiate the functional relevance of dopamine and norepinephrine for both consciously and subliminally triggered response conflicts, as both neurotransmitters have been shown to modulate gain control in neuronal processing and may, therefore, modulate response conflicts. For this purpose, we examined functional SNPs in the *TH* and *DBH* genes, which modulate the biosynthesis and therefore the amount of presynaptic dopamine and norepinephrine. We hypothesized to find that increases in both catecholamines might especially benefit consciously induced conflicts, while subliminally induced conflicts might only be modulated by norepinephrine, which improves signal detection and might, therefore, enhance the processing of subliminal information. Moreover, we hypothesized to find these effects to be reflected in the theta and alpha frequency bands and associated medial frontal as well as parietal and/or inferior frontal structures.

Material and Methods

Participants

A group of $n = 207$ genetically unrelated healthy young participants (mean age 23.7; SD 3.12; range 18 to 32 years; 149 females) of western European/Caucasian descent participated in the study. All participants were right-handed, had normal vision or corrected-to-normal vision, and had been recruited using flyers and online ads at the local university (TU Dresden, Germany). None of the participants reported any psychiatric disorders or neurological diseases. Each participant gave written informed consent and was reimbursed with either 10€ or course credits for taking part in the study. The study was approved by the ethics committee of the Faculty of Medicine of TU Dresden and conducted in accordance with the Declaration of Helsinki.

Genotyping

The candidate SNP in the *TH* gene, rs10770141 (C-824 T), as well as the three candidate SNPs in the *DBH* gene, rs1611115 (-1021C/T), rs6271 (Arg535Cys), and rs1611122, were selected based on their potential functional impact found in earlier studies [43, 63, 64]. Genotyping was performed by PCR-RFLP techniques. Primers were designed with Primer Express 2.0 software (Applied Biosystems). All other details of the methodology and primer sequences are available upon request.

Task

The task was based on a paradigm developed by Boy et al.. [10] and identical to that used in previous studies of our group [8, 11, 31]. It allows to investigate conflicts evoked by consciously and subliminally perceived distractor stimuli as it combines the target stimulus with a subliminal prime and consciously perceived flankers.

Participants were seated at a distance of 57 cm from a 17-in. CRT monitor and were asked to respond using a regular QWERTZ keyboard. Participants had to rest their index fingers on the response buttons (right and left Ctrl buttons) during the entire experiment. To present stimuli, record the behavioral responses, and synchronize with the EEG, we used "Presentation" software (Version 17.1 by Neurobehavioral Systems, Inc.). Before the start of the experiment, subjects completed a supervised task practice until they were able to sufficiently comply with the task instructions. During the practice, feedback about the accuracy of the given response was provided. The experiment/data collection did not comprise such response feedback and was started as soon as the subjects had no further questions. Each trial started with a 100 ms presentation of a central white fixation cross on a black background (see Fig. 1). It was followed by the prime (a central white arrow pointing either right or left), which was presented for 30 ms; a mask (an array of randomly distributed white lines), which was presented for another 30 ms; and the combination of the target (a central white arrow pointing either right or left) and two flankers (identical white arrows located above and below the target), which were presented for 100 ms. Participants were asked to indicate the pointing direction of the target by pressing the right Ctrl button with the right index or middle finger when the target arrow pointed to the right and pressing the left Ctrl button with the left index or middle finger when the target pointed to the left. Each trial ended with the first given response or after 2000 ms had elapsed (in this case, the trial was coded as a "miss"). The

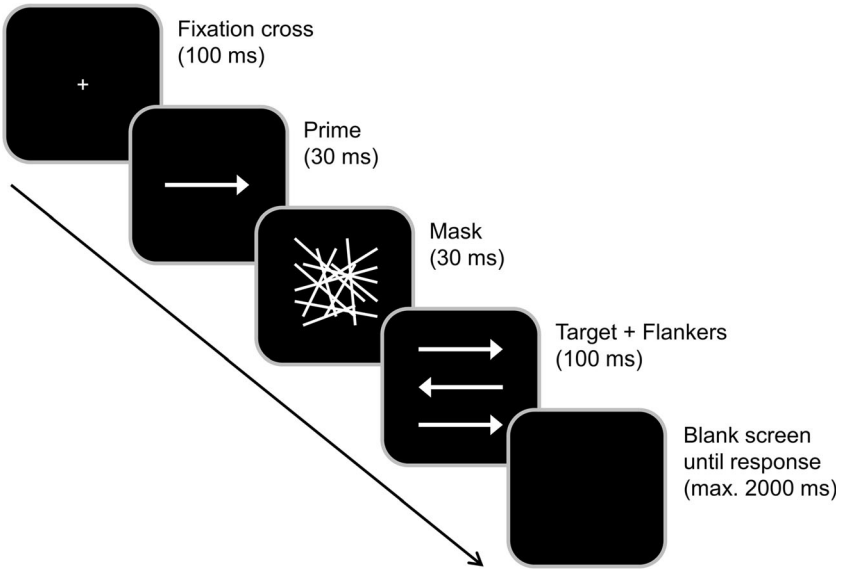

Fig. 1 Experimental paradigm. Each trial began with a 100 ms presentation of a fixation cross, which was followed by a prime (middle arrow) for 30 ms and a mask array for 30 ms. The target (middle arrow) was then presented for 100 ms together with the flanker stimuli. After the presentation of the target, the screen turned black. Primes pointing in the same direction as the target were rated as compatible, while flankers that pointed in the same direction as the target were rated as congruent.

response-stimulus interval between the first response and the onset of the following trial randomly varied between 1000 and 1200 ms. The trial was rated as compatible whenever prime and target pointed in the same direction, and as incompatible in case they pointed in opposite directions. Additionally, trials where flankers and target pointed in the same direction were classified as congruent and as incongruent when they pointed in opposite directions. All possible combinations of prime compatibility, flanker congruency, and target pointing direction occurred with equal frequency and in a randomized order. In total, the experiment consists of 384 trials (subdivided into four equal blocks) and took approximately 15 min to complete. After finishing the task, the participants were asked whether they had consciously perceived the prime stimulus (i.e., whether they had consciously perceived any visual stimulus preceding the mask, which we termed "scrambled lines" for the sake of better understanding). This was denied by all of them, which matches the reports by Boy et al. [10], who reported no conscious perception of the prime at a stimulus onset asynchrony (SOA) of 70 ms (i.e., even 10 ms longer than in our study).

EEG Recording and Time-Frequency Decomposition

EEG data was acquired using a QuickAmp amplifier (Brain Products, Inc.). Data was recorded from 60 Ag-AgCl electrodes at standard equidistant scalp positions against a reference electrode at position Fpz. All electrode impedances were kept below 5 kΩ. The sampling rate was 500 Hz. Brain Vision Analyzer 2.1 was used for offline data pre-processing and ERP data analyses. During this process, the recorded data were down-sampled to 256 Hz, and a band-pass filter was applied (0.5 to 20 Hz at a slope of 48 dB/oct each). Subsequently, rare technical or muscular artifacts were eliminated using a manual raw data inspection. Afterwards, an independent component analysis (ICA) was used to remove periodically recurring artifacts (horizontal and vertical eye movements, blinks, and ECG artifacts) using the infomax algorithm. Lastly, a second raw data inspection was conducted to manually remove any residual artifacts. The pre-processed data were then segmented in a target-locked fashion. Each segment started 2000 ms before the onset of the target and ended 2000 ms thereafter. Only correct trials were included in the data analysis. An automated artifact rejection excluded all segments with amplitudes below − 100 μV or above 100 μV, value differences of more than 200 μV in a 200 ms interval, or value differences of less than 0.5 μV in a 100 ms interval. In order to eliminate the reference potential, a current source density (CSD) transformation was applied. The CSD works as a spatial filter identifying the electrodes that best reflect activity related to the respective power [65, 66].

In the next step, the time-frequency analysis was conducted by means of a continuous wavelet transform (CWT), employing Morlet wavelets (w) in the time domain to different frequencies (f):

$$w(\mathrm{t},\mathrm{f}) = \mathrm{A}\exp\left(-\mathrm{t}^2/2\sigma_\mathrm{t}^2\right)\exp(2i\pi\mathrm{ft})$$

with t = time, $A = (\sigma_t\sqrt{\pi})^{-1/2}$, σ_t = wavelet duration, and $i = \sqrt{-1}$. Furthermore, a Morlet parameter of $f_0/\sigma_f = 5.5$ was used to plot the time-frequency (σ_f = width of Gaussian shape in the frequency domain; f_0 = central frequency). The analysis was conducted in the frequency range from .5 to 20 Hz. A central frequency at .5-Hz intervals was employed. For different f_0, time and frequency resolutions (or wavelet duration and spectral bandwidth [67]) can be calculated as $2\sigma_t$ and $2\sigma_f$, respectively. σ_t and σ_f are related by the equation $\sigma_t = 1/(2\pi\sigma_f)$. For example, for $f_0 = 1$ Hz, $2\sigma_t = 1770$ ms, and $2\sigma_f = 0.36$ Hz; for $f_0 = 3$ Hz, $2\sigma_t = 580$ ms, and $2\sigma_f = 1.09$ Hz; for $f_0 = 5$ Hz, $2\sigma_t = 350$ ms, and $2\sigma_f = 1.82$ Hz. The time-frequency

decomposition was applied to the single trial data of each of the segmented conditions in order to calculate the total wavelet power. For the time-frequency analysis, we focused on fronto-central theta oscillations as well as on parieto-occipital alpha oscillations, which are both known to play an important role in executive control functions [45, 68]. Electrodes were chosen based on the visual inspection of the scalp topography. Within the theta band, we quantified the absolute power at a frequency of 6 Hz in the timeframe from 300 to 410 ms at electrode FCz, where the theta power, as well as any conceivable differences, reached their maximum. Alpha band oscillations were analyzed at 10.5 Hz and quantified at electrodes PO1, PO2, O1, O2, and Oz. Mean alpha band power (pooled across electrodes) was quantified both in the timeframe from 250 to 350 ms after target onset (i.e., when alpha suppression was maximal), as well as in an the interval from 1450 to 1550 ms after target presentation, in which maximal alpha band power was evident (refer to Figs. 3 and 5).

Beamforming

For the alpha oscillations that showed strong activity, a beamforming analysis was performed to provide neural sources. For this purpose, we made a wavelet transformation as described above without prior CSD-transformation of the data because both the CSD-transformation and the beamformer work as a spatial filter [65]. Thus, the time-frequency decomposition was applied on average-referenced data [69] on the same time-frequency window. The spectral analysis was conducted using a multitaper frequency transformation to compute the power and the cross-spectral density matrix. Therefore, alpha band core frequency was set to 10.5 Hz with a smoothing window of 1.00 Hz. This frequency range corresponds with the frequency identified for the electrode-level TF-analysis. A time interval of 600 ms from 1200 to 1800 ms including three full wave cycles was used to reflect the time window of 1450 to 1550 ms that was used for TF alpha band analysis. To reconstruct the cortical sources of the oscillatory theta band activity, we applied a dynamical imaging of coherent sources (DICS) beamformer [69]. This linear beamforming approach was successfully applied to reconstruct the sources of frequency specific activity in several EEG and MEG studies [56–58]. DICS beamforming computes the estimates of sources in the frequency domain. The beamformer-based source reconstruction relies on a spatially adaptive filter that is subject to the unit-gain constraint. Due to the filter characteristics, the amount of activity at any given location in the brain can be estimated while activity from other locations is maximally suppressed. DICS beamforming was implemented using the MATLAB toolbox "Fieldtrip" [70]. Fieldtrip includes a MNI brain template-based forward model. The model construction of this boundary element method-based forward model is described in detail by [70]. EEG electrodes were realigned to this head model. The leadfield matrix was computed by partitioning the forward model's brain volume into a grid with 6 mm resolution. Consecutively, the leadfield matrix was calculated for each grid point. A common spatial filter based on all conditions with the regularization parameter set to 5% was applied on each condition separately to estimate the power of the sources. The DICS beamformer was exclusively applied to significant TF intervals that were identified in the analyses of the wavelet data. Beamformer contrasts were computed as the ratio between conditions normalized by the sum:

$$P_{\text{ratio}} = \frac{P_{\text{cond1}} - P_{\text{cond2}}}{P_{\text{cond1}} + P_{\text{cond2}}}$$

where P_{cond1} and P_{cond2} are the contrasted conditions. This approach cancels out a possible noise bias and reduces the effect of outliers by assuming that the noise is distributed equally in both conditions. These alpha source power estimates are given in MNI coordinates [70, 71]). The procedure is comparable to other studies [46, 50].

Statistics

For the behavioral and neurophysiological analyses, we used only correct trials with RTs between 100 and 1000 ms in order to exclude trials with premature responses and to reduce the effect of outliers on mean hit RTs. Separate mixed effects ANOVAs were performed to analyze behavioral and neurophysiological data. All behavioral analyses used prime compatibility (compatible vs. incompatible) and flanker congruency (congruent vs. incongruent) as within-subject factors. The genotype group was included as between-subject factor. Genotypes of each SNP were analyzed as additive (+/+ vs. +/− vs. −/−) and dominant (+/+ plus +/− vs. −/−). All performed post hoc tests were Bonferroni-corrected, and Greenhouse-Geisser correction was applied, whenever necessary. As *t* tests following the ANOVA are calculated using the pooled variance implied in the ANOVA's null hypothesis, rather than variance from the specific groups compared for a single test statistic, further multiple testing correction is not necessary. For all descriptive statistics, the mean and standard error of the mean (SEM) are given as a measure of variability.

Results

Replication of General Behavioral Task Effects

In line with previous studies using the same experimental paradigm [11, 31], we were able to reproduce significant behavioral effects of both prime compatibility and flanker congruency, as well as their interaction: The analysis of the accuracy

(percentage of hits) revealed main effects of prime compatibility ($F_{(1,206)} = 166.79$, $p < .001$, $\eta_p^2 = .447$; compatible = 99.13% ± 0.09; incompatible = 95.30% ± 0.32) and flanker congruency ($F_{(1,206)} = 107.40$, $p < .001$, $\eta_p^2 = .343$; congruent = 98.01% ± 0.15; incongruent = 96.42% ± 0.23). Furthermore, an interaction of prime compatibility × flanker congruency ($F_{(1,206)} = 59.77$; $p < .001$; $\eta_p^2 = .225$) was found. Post hoc t tests showed that all conditions differed significantly from each other (all $t \geq 5.50$; $p \leq .001$). As in previous studies [11], we however found an effect of subliminal conflict load, as the flanker effect (i.e., congruent minus incongruent) was significantly larger in trials with incompatible primes (2.57% ± 0.26) than in trials with compatible primes (0.60% ± 0.10) ($t(206) = 7.73$; $p < .001$).

The analysis of RTs in correct trials revealed main effects of prime compatibility ($F_{(1,206)} = 529.31$, $p < .001$, $\eta_p^2 = .720$; compatible = 410 ms ± 2, incompatible = 450 ms ± 2) and flanker congruency ($F_{(1,206)} = 574.40$, $p < .001$, $\eta_p^2 = .736$; congruent = 421 ms ± 2, incongruent = 439 ms ± 2). There was however no significant interaction of prime compatibility × flanker congruency for hit RTs ($F_{(1,206)} = 0.04$; $p = .842$).

In order to keep the "Results" section concise, the following sections on genotype effects will be limited to main and interaction effects of the respective between-subject factor (i.e., genotype group).

Genotype Groups

In the sample of $n = 207$ subjects, the observed frequencies of the *TH* rs10770141 C and T alleles were 53.9% and 46.1%, respectively. The CC group comprised $n = 70$, the CT group comprised $n = 81$, and the TT group comprised $n = 54$ participants. For add-on analyses, all T allele carriers were also combined in one group.

The observed frequencies of the *DBH* rs1611122 C and G alleles were 55.1% and 44.9%, respectively. G allele carriers were combined in one group for add-on analyses. The CC group comprised $n = 65$, the CG group comprised $n = 98$, and the GG group comprised $n = 44$ participants.

For *DBH* rs1611115, frequencies of the C and T alleles were 78.5% and 21.5%, respectively. The CC group comprised $n = 130$, the CT group comprised $n = 65$, and the TT group comprised $n = 12$ participants. As the TT genotype group was too small for additive single genotype analyses, all T allele carriers were combined (all three genotypes were hence not investigated separately).

The frequencies of *DBH* rs6271 C and T alleles were 92.2% and 7.8%, respectively. The CC group comprised $n = 177$, the CT group comprised $n = 28$, and the TT group comprised $n = 2$ participants. Again, all T allele carriers were combined in one group as the TT group was too small for additive single genotype analyses (all three genotypes were hence not investigated separately).

Except for one, the tested SNPs did not deviate from the Hardy-Weinberg equilibrium (HWE). However, the genotyping results for TH rs10770141 showed a higher frequency of the rare T allele than expected. This deviation can be caused by many factors, one of which is genotyping error. Since we can exclude this, we assume that the deviation is attributable to a cohort bias: Horiguchi et al. [63] previously reported the C allele to be associated with lower IQ. The fact that the vast majority of the included participants were university students (which likely included substantially fewer individuals with low IQ than the overall population) could explain why the rare functional T allele was found with a disproportionate frequency in our sample.

TH rs10770141: Behavioral Analyses

The analysis of the accuracy (percentage of hits) revealed no significant main effects and interactions of the group factor (all $F \leq 2.06$; $p \geq .130$) (see Fig. 2).

The mixed effects ANOVA for RTs in correct trials revealed an interaction of flanker congruency × *TH* genotype group ($F_{(2,202)} = 3.54$, $p = .031$, $\eta_p^2 = .034$) (see Fig. 2). Post hoc tests indicated that the flanker congruency effect (i.e., congruent minus incongruent) was smaller in the TT genotype group (15.1 ms ± 1.2) than in both the CT genotype group (19.7 ms ± 1.2) ($t(127.53) = 2.56$; $p = .009$) and the CC genotype group (19.7 ms ± 1.4) ($t(121.82) = 2.42$; $p = .017$). The flanker effect did not differ between the CT and CC genotype groups ($t(140.71) = 0.007$; $p > .9$). All other main and interaction effects of the *TH* rs10770141 group were not significant (all $F \leq 0.22$; $p \geq .799$).

Due to the fact that we found no significant main or interaction effects of TH rs10770141 group when combining the less frequent TT and CT genotypes in one group (all $F \leq 1.50$; $p \geq .221$), we chose to conduct no neurophysiological analyses for the combined *TH* rs10770141 TT and CT group (see Fig. 2).

TH rs10770141: Neurophysiological Analyses

As behavioral data showed that the *TH* genotype modulates flanker-related conflicts, but not prime-related conflicts, we excluded the factor of prime compatibility from our subsequent neurophysiological analyses. Wavelet plots illustrating the time-frequency decomposition of the target-locked EEG segments for the flanker effect in each *TH* genotype group are depicted in Fig. 3.

In the theta band at 6 Hz (from 300 to 410 ms), there was a main effect of flanker congruency ($F_{(1,202)} = 70.71$; $p < .001$; $\eta_p^2 = .259$), as theta power was larger in incongruent

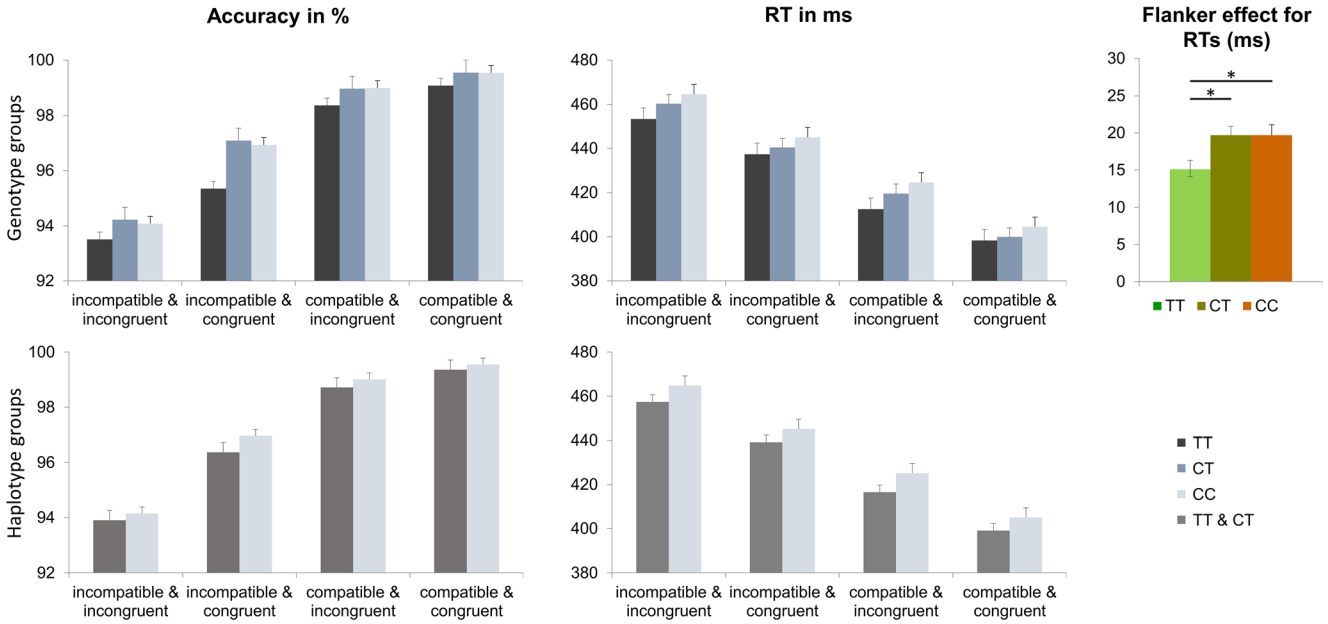

Fig. 2 Behavioral data of *TH* rs10770141 groups. The data of single genotype groups are given in the first row, while the data of combined genotype groups are given in the second row. Accuracy (mean percentage of correct responses) is shown in the left graphs and hit reaction times (RTs) are shown in the middle column. For the genotype group, the flanker congruency effect (incongruent minus congruent) on RTs is shown in the right graph. As indicated in this graph, we found the TT genotype group to display a significantly smaller flanker effect on RTs than carriers of the C allele (denoted with an asterisk). Error bars show the standard error of the mean (SEM) as a measure of variability

(387.68 $\mu V/m^2 \pm 17.00$) than in congruent (342.67 $\mu V/m^2 \pm 15.34$) trials. All other main and interaction effects were not significant in the theta band (all $F \leq 2.79$; $p \geq .064$).

In the analyses of alpha band power at 10.5 Hz in the early time window (250 to 350 ms), none of the investigated factors or interactions reached significance (all $F \leq 2.28$; $p \geq .104$). However, the analyses of alpha band power at 10.5 Hz in the late time window (1450 to 1550 ms) revealed an interaction of flanker congruency × *TH* genotype group ($F_{(2,202)} = 0.14$; $p = .018$; $\eta_p^2 = .039$). Post hoc tests showed that the flanker congruency effect (i.e., congruent minus incongruent) was significantly larger in the TT genotype group (-155.38 $\mu V/m^2 \pm 72.80$) than in both the CT genotype group (70.95 $\mu V/m^2 \pm 62.36$) ($t(117.42) = 2.36$; $p = .020$) and the CC genotype group (45.94 $\mu V/m^2 \pm 1.4$) ($t(74.69) = 2.51$; $p = .014$). The flanker effect size did not differ between the CT and CC genotype groups ($t(120.29) = 0.354$; $p > .7$). All main effects were non-significant in the post-response alpha time window (all $F \leq 0.14$; $p \geq .704$).

Beamforming analyses were run to plot flanker-associated activation differences in all genotype groups that showed a significant post-response alpha power difference between congruent and incongruent flankers. While this was not the case for the CT genotype group ($t(80) = 1.138$; $p = .259$) or in the CC genotype group ($t(69) = 1.389$; $p = .169$), the TT genotype group showed significantly larger post-response alpha power in the incongruent condition (1991.12 $\mu V/m^2 \pm 435.64$), as compared to the congruent condition (1835.37 $\mu V/m^2 \pm 373.70$) ($t(53) = 2.134$; $p = .037$). The subsequent analysis of flanker-induced post-response alpha power differences in the TT group revealed that this increase was related to an activation increase in a broad area within the right frontal lobe (peak MNI coordinates in mm: 126/142/62) (see bottom of Fig. 3).

In summary, the behavioral data showed that genetically determined differences in TH biosynthesis modulate consciously perceived (flanker-induced) conflicts, but not subliminally processed (prime-induced) conflicts. Specifically, we found that the flanker congruency effect in RTs was smaller in the TT genotype group. On a neurophysiological level, this was mirrored by larger alpha band modulations arising from the right frontal lobe ~ 1500 ms after target onset.

DBH rs1611122: Behavioral Analyses

The accuracy analysis revealed no main effects or interaction effects of the *DBH* rs1611122 genotype group (all $F \leq 2.21$; $p \geq .111$) (see Fig. 4).

For RTs of correct responses, we found an interaction of flanker congruency × *DBH* genotype group ($F_{(1,204)} = 3.74$; $p = .025$; $\eta_p^2 = .035$) (see Fig. 4). Post hoc tests indicated that the flanker congruency effect (i.e., congruent − incongruent) was larger in the GG genotype group (22.3 ms ± 1.9) than in the CG genotype group (17.8 ms ± 0.9) ($t(140) = 2.35$; $p = .020$) and the CC genotype group (16.7 ms ± 1.4) ($t(84.42) = 2.28$; $p = .025$). The flanker effect did not differ between the CG and CC genotype groups ($t(116.78) = 0.614$; $p > .5$). All other main and interaction effects of the

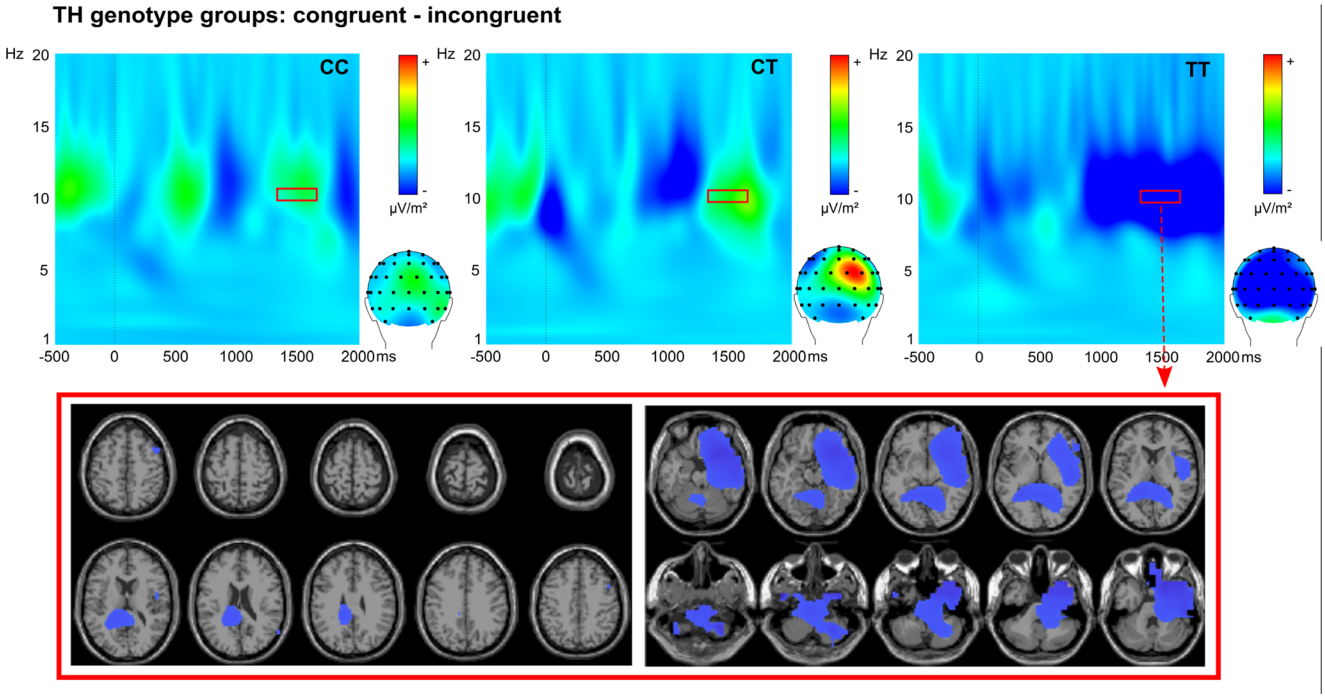

Fig. 3 Time frequency decomposition and beamforming results for *TH* rs10770141 groups. Alpha band activity was quantified at electrodes where it reached its maximum, namely at PO1, PO2, O1, O2, and Oz. Here, we pooled those electrodes and quantified the power in the time interval from 1450 to 1550 ms at 10.5 Hz. The *x*-axis of each time frequency plot shows the time in milliseconds (time point zero denotes the onset of the target stimulus), while the *y*-axis denotes frequency, and the color coding denotes power. Scalp topography plots are given for every condition at 10.5 Hz in the time interval from 1450 to 1550 ms after target presentation (this quantification interval is marked with rectangular boxes in each TF plot). The graphs show the TF decomposition of the flanker effect, i.e., the difference between trials with congruent and incongruent flankers. The flanker effect of the CC genotype group is shown in the left graph, the CT group flanker effect is shown in the middle graph, and the TT group flanker effect is shown in the right graph. The TT group was the only genotype group to show significant alpha differences (i.e., smaller alpha band power at 10.5 Hz in congruent than in incongruent trials). The sources of those differences are illustrated in the maps below, where blue color denotes significant activation differences in a broad area within the right frontal lobe.

DBH rs1611122 genotype group were not significant (all $F \leq 0.56$; $p \geq .080$).

The repeated measures ANOVA for accuracy (percentage of hits) showed no main or interaction effects of the combined *DBH* rs1611122 genotype group (all $F \leq 3.35$; $p \geq .062$) (see Fig. 4). For the hit RTs, there was a significant interaction of prime compatibility × flanker congruency × *DBH* group ($F_{(1,205)} = 5.01$, $p = .026$, $\eta_p^2 = .024$) (see Fig. 4). To analyze this interaction, we conducted separate analyses for prime incompatible trials and prime compatible trials. In prime incompatible trials, there was an interaction of flanker × *DBH* group ($F_{(1,205)} = 8.61$, $p = .004$, $\eta_p^2 = .040$). Post hoc testing showed that the flanker effect (incongruent minus congruent) was more pronounced in the CG and GG group (20.3 ms ± 0.9) than in the CC group (14.7 ms ± 1.8) ($t(205) = 2.93$; $p = .004$). In prime compatible trials, there was only a main effect of flanker congruency ($F_{(205)} = 236.35$, $p < .001$; $\eta_p^2 = .536$; congruent = 404 ms ± 3; incongruent = 423 ms ± 3), but no such interaction of flanker congruency × *DBH* group ($F_{(1,205)} = 0.08$, $p = .778$, $\eta_p^2 = .000$) (see Fig. 4). All other main and interaction effects of the combined *DBH* rs1611122 group were not significant (all $F \leq 2.21$; $p \geq .139$).

DBH rs1611122: Neurophysiological Analyses

Given that only the combined *DBH* rs1611122 analysis revealed a significant interaction with both the prime and flanker conflicts, we subsequently analyzed the neurophysiological data using prime compatibility, flanker congruency, and combined *DBH* rs1611122 group as factors. Wavelet plots showing the time-frequency decomposition of the target-locked EEG segments for the flanker effect in the two *DBH* groups are given in Fig. 5 for trials with incompatible primes.

In the theta band at 6 Hz (from 300 to 410 ms), there was a main effect of prime compatibility ($F_{(1,205)} = 100.39$; $p < .001$; $\eta_p^2 = .329$), as the theta power was larger in incompatible (401.24 μV/m² ± 19.08) than in compatible (338.28 μV/m² ± 15.95) trials. There was also a main effect of flanker congruency ($F_{(1,205)} = 105.99$; $p < .001$; $\eta_p^2 = .341$), with larger theta power in incongruent (399.86 μV/m² ± 19.08) than in congruent (339.66 μV/m² ± 15.87) trials. Furthermore, an interaction of prime compatibility × flanker congruency ($F_{(1,205)} = 4.41$; $p = .037$; $\eta_p^2 = .021$) was found. In line with the behavioral results, post hoc *t* tests showed that all conditions differed significantly from each other (all $t \geq 8.56$;

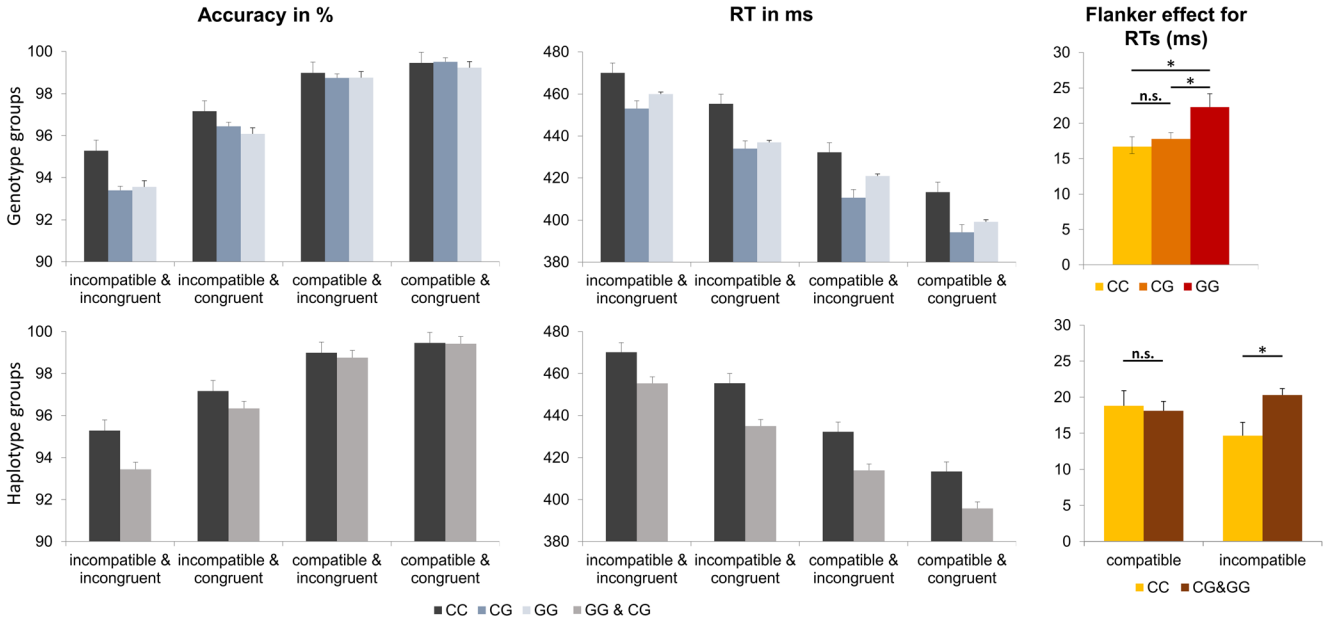

Fig. 4 Behavioral data of *DBH* rs1611122 groups. The data of genotype groups are given in the first row, while the data of combined genotype groups are given in the second row. Accuracy (mean percentage of correct responses) is shown in the left column; hit reaction times (RTs) are shown in the middle column. In the right column, the flanker congruency effect (incongruent minus congruent) on RTs is shown. In the genotype analyses, we found the GG group to display a significantly larger flanker effect than carriers of the C allele (top graph; significant differences are denoted with an asterisk). In the combined genotype analyses, we found an interaction of genotype, flanker, and prime. Here, we found the CC group to display a significantly smaller flanker effect, but only in case of high conflict load, as induced by incompatible primes (bottom graph; significant differences are denoted with an asterisk). Error bars show the standard error of the mean (SEM) as a measure of variability

$p \leq .001$). However, the flanker effect (i.e., incongruent minus congruent) was larger in incompatible primes (73.16 ± 7.19) than in compatible primes (53.52 ± 6.25) ($t(206) = 2.47$; $p = .014$). All other main effects and interactions were not significant (all $F \leq 2.08$; $p \geq .150$).

In the analyses of alpha band power at 10.5 Hz in the early time window (250 to 350 ms), none of the investigated factors or interactions reached significance (all $F \leq 3.12$; $p \geq .079$). However, the analyses of alpha band power at 10.5 Hz in the late time window (1450 to 1550 ms) showed an interaction of flanker congruency × prime compatibility × *DBH* group ($F_{(1,203)} = 6.81$; $p = .010$; $\eta_p^2 = .032$). To analyze this interaction, we conducted separate analyses for prime incompatible trials and prime compatible trials. In line with the behavioral results, we found no interaction of flanker congruency × *DBH* group in trials with compatible primes ($F_{(1,203)} = 1.00$, $p = .318$, $\eta_p^2 = .005$), but in prime incompatible trials ($F_{(1,203)} = 4.30$, $p = .039$, $\eta_p^2 = .021$). Post hoc tests showed that in trials with incompatible primes, the flanker congruency effect (i.e., congruent − incongruent) was larger in the CC group ($54.97\ \mu V/m^2 \pm 32.60$) than in the CG and GG group ($-44.56\ \mu V/m^2 \pm 28.71$) ($t(156.28) = 2.29$; $p = .023$). All other main effects and interactions were not significant (all $F \leq 3.77$; $p \geq .054$). Additional beamforming analyses were however not run as differences between flanker congruent and incongruent trials in case of incompatible primes failed to reach significance when separately tested within each group (all $t \leq 1.686$; $p \geq .097$).

DBH rs1611115: Behavioral Analyses

For the combined *DBH* rs1611115 groups, we found no significant main or interaction effects in the accuracy data (all $F \leq 0.55$; $p \geq .456$), or in the hit RTs (all $F \leq 1.55$; $p \geq .213$). To decrease the risk for false positive main effects and interactions, we hence chose to conduct no neurophysiological analyses for *DBH* rs1611115.

DBH rs6271: Behavioral Analyses

For the combined *DBH* rs6271 groups, we also found no significant main or interaction effects in the accuracy data (all $F \leq 2.06$; $p \geq .152$), or in the hit RTs (all $F \leq 1.35$; $p \geq .246$). To decrease the risk for false positive main effects and interactions, we hence chose to conduct no neurophysiological analyses for *DBH* rs6271.

In summary, we found no behavioral effects of the *DBH* rs6271 and rs1611115 polymorphisms. Instead, we found that the *DBH* rs1611122 SNP modulated flanker-related conflicts and was furthermore sensitive to conflict load (i.e., prime compatibility). This effect was however only selectively found for the combined *DBH* rs1611122 groups. With respect

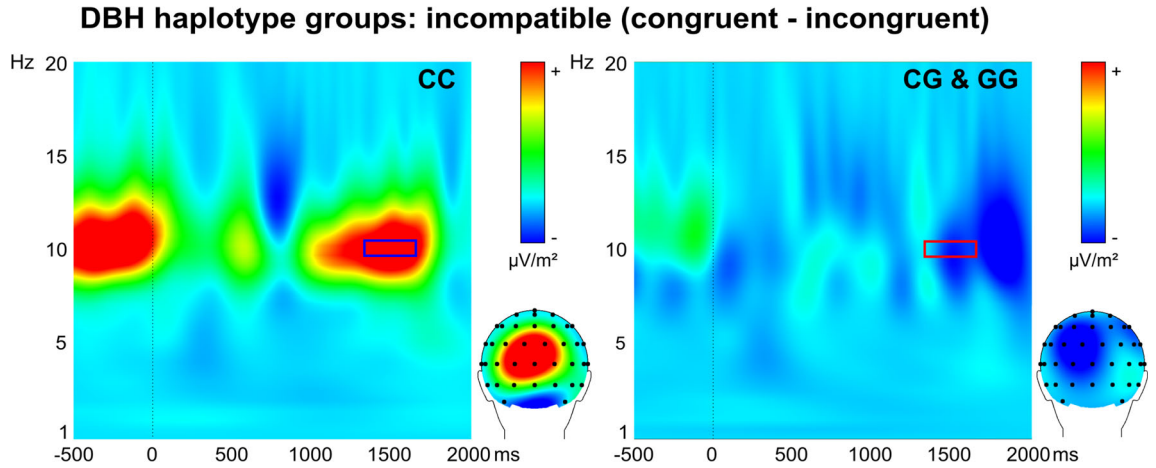

Fig. 5 Time frequency decomposition for *DBH* rs1611122 groups. Alpha band activity was quantified at electrodes where it reached its maximum, namely at PO1, PO2, O1, O2, and Oz. Here, we pooled those electrodes and quantified the power in the time interval from 1450 to 1550 ms at 10.5 Hz. The *x*-axis of each time frequency plot shows the time in milliseconds (time point zero denotes the onset of the target stimulus), while the *y*-axis denotes frequency and the color coding denotes power. Scalp topography plots are given for every condition at 10.5 Hz in the time interval from 1450 to 1550 ms after target presentation (this quantification interval is marked with rectangular boxes in each TF plot). The graphs show the TF decomposition of the flanker effect, i.e., the difference between trials with congruent and incongruent flankers in case of incompatible primes. The flanker effect of the CC genotype group is shown in the left graph, and the flanker effect of the combined CG and GG genotype group is shown in the right graph. While The CC group had significantly larger alpha differences between congruent and incongruent flankers in incompatible primes (as compared with the CG and GG group), none of the condition differences reached significance within the respective groups, so that we refrained from conducting a beamforming source estimation for this effect

to this interaction of flanker congruency, prime compatibility, and combined *DBH* rs1611122 group, we found corresponding effects in the alpha band ~ 1500 ms after target onset.

Discussion

In the current study, we investigated the modulating effects of dopamine and norepinephrine on consciously and subliminally induced response conflicts. On a postsynaptic level, volitional cognitive control mechanisms have been demonstrated to be heavily modulated by dopamine and norepinephrine, while subliminally triggered conflicts haven been suggested to be rather unaffected by MPH-induced postsynaptic increases in catecholaminergic signaling [31]. It has, however, remained largely unclear whether presynaptic differences in catecholamine synthesis modulate conflicts in the same way. Most importantly, however, the functional roles of dopamine and norepinephrine for the modulation of response selection conflicts have never been dissociated in humans.

We examined the effect of functional *TH* (rs10770141) and the *DBH* (rs1611122, rs1611115, rs6271) SNPs using a paradigm that combines consciously and subliminally induced conflicts [10, 31]. Importantly, this molecular genetics approach does not only allow to investigate the effect of presynaptic variations in catecholamine synthesis, but it also allows to dissociate the functional effects of dopamine and norepinephrine. Given that most human studies on catecholamine effects are limited to non-specific drugs like MPH, which indiscriminately increase postsynaptic dopamine and norepinephrine levels [32–35] and also cannot account for differences in presynaptic transmitter synthesis, our approach provides an important contribution to a better functional understanding of catecholamine effects on cognition.

We started by investigating the effects of genetically determined differences in catecholamine biosynthesis with the help of the *TH* rs10770141 polymorphism. Summing up the main findings, we found that homozygous carriers of the T allele, which increases TH levels and thereby upregulates of catecholaminergic neurotransmission (characterized by increased catecholamine production and release [41]), show decreased behavioral conflicts, as compared to carriers of the C allele. Importantly, this effect could only be observed for response times in consciously evoked response conflicts (i.e., the flanker effect), but not for subliminally evoked conflicts (i.e., the prime effect). In line with previous studies of our group showing that MPH only modulates consciously but not subliminally induced conflicts [31], this suggests that increases in catecholamine biosynthesis and the level of presynaptic catecholamines decrease consciously induced conflicts, but play no role for subliminally evoked conflicts. With respect to the underlying neurophysiological mechanisms, we found that the flanker conflict modulated mid-frontal theta power in the expected direction, as reflected by significantly increased theta power in case of incompatible flankers [45]. However, we did not find theta band power to be modulated by differences in catecholamine synthesis, because there were no differences between genotype groups. Given that mid-frontal theta oscillations reflect the degree of cognitive control and effort associated with a given conflict [45], the lack of *TH* genotype

effects suggests that the beneficial effects of increased catecholamine synthesis on consciously processed conflicts were not mainly based on alterations in cognitive control processes. Instead, we found post-response modulations in the alpha band ~ 1500 ms after target onset (i.e., in the inter-trial-interval): Here, the TT genotype group, who had shown a significantly smaller behavioral flanker effect than carriers of the C allele, presented with larger flanker-associated condition differences than carriers of the C allele. Alpha oscillations help to control the flow of information in the cortex and regulate the access of information to a knowledge system via inhibitory control processes [52–54, 72, 73] that help to suppress the processing of distracting information [74]. As TT carriers were the only group to present with significantly larger post-response alpha band power in flanker incompatible trials as compared with flanker compatible trials, our results suggest that individuals with increased catecholamine synthesis are better able to inhibit interference by suppressing distracting and/or irrelevant information following a consciously perceived response conflict [75, 76]. Since this effect does not seem to occur until after the response, it seems to reflect reactive control processes helping to prevent interference from previous trials and to prepare response selection in upcoming trials [52–54, 75]. Because alpha-band activity likely implements processes to inhibit disruptive information, alpha-band activity reflects a process that is critical to online conflict processing and resolution. Corroborating this interpretation, the beamforming analysis showed that alpha band modulations were associated with areas in the right inferior frontal lobe and parietal areas. These areas are known to be part of an alpha-modulated network controlling the access to and inhibition of task sets [75, 77–81].

As the *TH*-based approach alone does not allow to dissociate the roles of dopamine and norepinephrine, we further assessed the functional role of long-term differences in norepinephrine by investigating several functional SNPs of the *DBH* gene, which plays a key role in the biosynthesis of norepinephrine by converting dopamine into norepinephrine [40]. With respect to our behavioral results, we found no behavioral modulation of conscious or subliminal conflicts by *DBH* rs1611115 or rs6271 genotype groups. While this lack of *DBH*-associated effects in the first two investigated SNPs suggests that dopamine plays a much more important role for consciously perceived response conflicts than norepinephrine, it should not go unmentioned that we had obtained rather low frequencies of the T allele. As a consequence, we had to form combined genotype groups containing a small number of TT and a much larger number of CT genotypes. Given that the C allele of both SNPs has been shown to increase DBH activity [42], this pooling might have masked effects associated with the T allele and should, therefore, be treated with ample caution. In contrast to the first two investigated *DBH* SNPs, the *DBH* rs1611122 polymorphism yielded similar frequencies for both alleles as well as a clear-cut effect: On the behavioral level (reaction times), we found the CC genotype to be associated with decreased consciously induced (flanker) conflicts in the genotype analyses. Furthermore, we also found an effect of subliminal conflict load in the combined genotype analyses. Here, the CC group showed a significant flanker effect in case of additional subliminal conflict load, as induced by the primes. This suggests that homozygote carriers of the C allele seem to especially benefit from their genetic disposition in case control requirements are high. It is thus still possible that the subliminal conflict size is modulated by presynaptic norepinephrine. As the functional effects of this SNP have not yet been investigated, this effect can however not (yet) be clearly attributed to increases in norepinephrine biosynthesis. The fact that the *TH* gene did not show a comparable interaction with the prime factor, however, indicates that subliminally induced conflicts might be selectively modulated by norepinephrine (but this is masked by the combined effects of catecholamines) because only norepinephrine improves detection of less salient information [30]. As signal detection is especially important for processing stimuli with low saliency, this might be especially important in case of subliminally (i.e., only briefly) presented stimuli, where better signal detection might increase the processing of subliminal information. Interestingly, the behavioral results obtained for combined *DBH* rs1611122 genotype groups were again not reflected by theta band power, even though our analyses revealed clear-cut effects for both types of conflict in theta band, which were in the expected direction (i.e., larger theta power in case of either kind of conflict). Instead, the results of smaller behavioral conflict size in the CC group were reflected by larger conflict-associated modulations in the post-response alpha band, which reflects a lingering inhibition of distracting and conflict-producing information, thereby increasing gain control. It is thus conceivable that an increase in presynaptic norepinephrine levels may support the inhibition of distracting information via gain control [22–28]. Gain control mechanisms can be thought of as amplifying the ability of a given information processing system to efficiently process input signals and to reduce neuronal noise. As recent data suggests that catecholamines modulate these processes [19, 31], it is likely that lingering inhibitory control tendencies reflect the enhanced gain control due to norepinephrine, and possibly also to dopamine.

Even though we found solid evidence that the processing of subliminally induced conflicts is more strongly related to the norepinephrine level than to the dopamine level, the sample was unfortunately not sufficiently large to investigate potential epistasis effects of the interaction of the two SNPs.

Therefore, we cannot provide information on how the alleles of the *TH* rs10770141 and *DBH* rs1611122 SNPs interact in the formation of the observed phenotypic differences on cognitive conflicts.

It should furthermore be noted that candidate gene approaches are limited to genes that are relatively well-researched and have already been shown to have a specific effect on a physiological function of interest. While this allows us to specifically investigate functional systems of interest, there is of course always a risk to overlook functional contributions of less well-researched SNPs in seemingly unrelated genes, which would be better detected by large genome-wide association studies (GWAS). Another distinction is that the SNPs investigated in our candidate gene approach are functionally related, rather than being independent of each other, so that we chose not to conduct corrections for multiple testing.

In summary, we dissociated the modulating effects of presynaptic dopamine and norepinephrine on consciously and subliminally induced response conflicts using a molecular genetics approach. The results demonstrated that increased presynaptic catecholamine synthesis selectively improves cognitive control in case of consciously perceived conflicts, but not in case of subliminally processed conflicts. While this is in line with previous findings on the effects of experimental postsynaptic catecholamine increases, we further found that norepinephrine, but not dopamine, seemed to modulate subliminal conflict processing. Interestingly, neither of those effects was rooted in common cognitive control processes as reflected by theta band power. Instead, better performance was linked to larger conflict-induced modulations in post-response alpha band power arising from parietal and inferior frontal regions helping to suppress the processing of distracting information in order to prepare for upcoming control requirements. Our findings hence suggest that presynaptic catecholamine synthesis benefits consciously perceived conflicts by improving the suppression of distracting information following a conflict. Subliminal conflicts were however only modulated by norepinephrine, albeit via the same mechanism.

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Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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