Behavioral/Cognitive

DRD1 and *DRD2* Genotypes Modulate Processing Modes of Goal Activation Processes during Action Cascading

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Dopamine plays an important role in action selection, but little is known about the influence of different dopamine receptor systems on the subprocesses occurring during the cascading of actions. Because action selection and cascading can be accomplished in a serial manner or a parallel manner, we investigated the potential effects of DRD1 (rs4531) and DRD2 (rs6277) receptor polymorphisms on this dimension. We gathered behavioral and neurophysiological data from healthy human subjects ($n = 162$) and applied mathematical constraints to quantify their action selection strategy on a serial-parallel continuum. The behavioral results show a more serial and more effective action cascading strategy in homozygous DRD1 G allele carriers, who are assumed to have a higher D1 receptor efficiency than carriers of the A allele. In the group of homozygous DRD2 T-allele carriers, who have a higher striatal density of D2 receptors than C-allele carriers, we found a less effective and more parallel action cascading strategy. These findings suggest that, within the same sample, a higher D1 efficiency seems to shift the action cascading strategy toward a more serial processing mode, whereas the D2 receptors seem to promote a shift in the opposite direction by inducing a more parallel processing mode. Furthermore, the neurophysiological analysis shows that the observed differences are not based on attentional differences or basic inhibition. Instead, processes linking stimulus processing and response execution seem to differentiate between more serial and more parallel processing groups.

Key words: **action cascading; action selection; dopamine; EEG; genetics; P3**

Introduction

In everyday life, action selection is a multicomponent process. When coping with multiple response options, different task goals need to be activated and chained to properly organize behavior (Verbruggen et al., 2008). The strategies applied for this chaining have been shown to operate on a continuum and either tend toward a more serial, step-by-step fashion (i.e., a task goal is activated after the previous one has been carried out) or toward a more parallel, overlapping fashion (i.e., a task goal is activated while the previous is carried out; Verbruggen et al., 2008; Mückschel et al., 2013). Compared with serial processing, parallel processing might cause different task goals to interfere and thus hamper responding. It has often been argued that processing mode differences could be due to a shared, limited capacity that needs to be allotted to multiple task goal inputs in case of parallel processing. It is, however, hard to determine whether and to what extent parallel processing relies on limited or unlimited capacities (Verbruggen et al., 2008).

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Action selection seems to heavily depend on frontostriatal networks (Bar-Gad et al., 2003; Beste et al., 2009, 2012; Cameron et al., 2010; Willemssen et al., 2011; Ravizza et al., 2012) and there are neurophysiological differences between serial and parallel processing modes (Mückschel et al., 2013). The neurobiological foundations of these differences are still widely unknown, but the functionality of frontostriatal networks has been demonstrated to be modulated by changes in dopamine levels (Frank et al., 2009; Schulz et al., 2012). In this context, computational models suggest that dopamine D1 and D2 receptors serve different subprocesses in action selection (Humphries et al., 2006; Maia and Frank, 2011) and induce different processing characteristics ("states") in neuronal networks (Seamans and Yang, 2004; Durstewitz and Seamans, 2008): A highly active "D2 state" leads to interference-prone representations, but also facilitates switching between them. In contrast, representations are more stable in the "D1 state," but this state is also more rigid, so fewer items can be represented in the network (Seamans and Yang, 2004; Durstewitz and Seamans, 2008). Following from this, strong dopamine D1 states may induce a stepwise mode of serial task goal activation processes, whereas in strong dopamine D2 states, task goals may be activated with more overlap (parallel processing).

Here, we test this hypothesis using a molecular genetic approach in combination with electrophysiological recordings (EEG) in a stop–change paradigm providing a classification of an individual's processing mode using mathematical constraints.

Homozygous *DRD2* rs6277 T-allele carriers have been shown to display greater striatal dopamine D2 receptor density (Hirvonen et al., 2005; Frank et al., 2009), whereas the *DRD1* G allele (rs4532) is associated with higher D1 receptor efficiency (Dolzan et al., 2007; Novak et al., 2010). Regardless of potential capacity limitations, we therefore expect that *DRD2* T-allele carriers should be more inclined toward a D2 state (i.e., more parallel and less effective processing), whereas *DRD1* G-allele (rs4532) carriers should experience a stronger D1 state (i.e., less overlapping and better performance; Verbruggen et al., 2008; Mückschel et al., 2013).

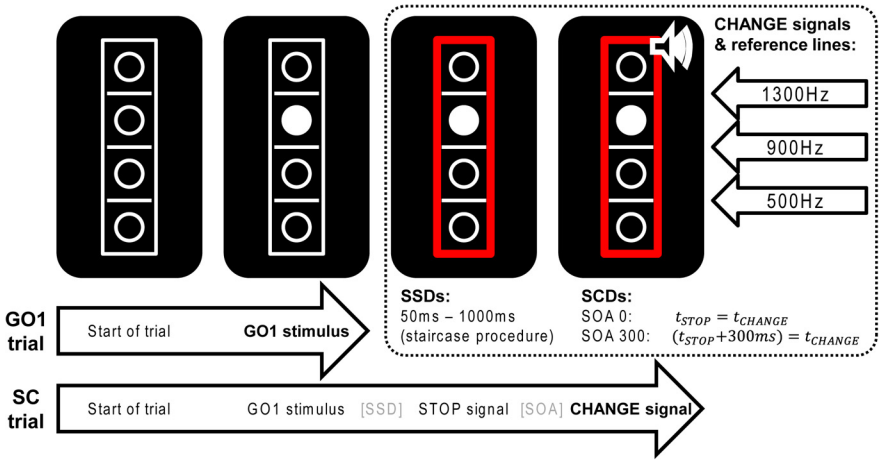

Figure 1. Schematic illustration of the SC paradigm (compare Stock et al., 2014a, 2014b). A response to the GO1 stimulus ended GO1 trials while responses to the CHANGE stimulus ended SC trials. The SSD between the GO1 stimulus and the STOP signal was adjusted by means of a staircase procedure (Logan and Cowan, 1984; Verbruggen et al., 2008). The SCD between the onset of the STOP and CHANGE stimuli was fixed and set to 0 ms in half of SC trials and to 300 ms in the other half. The three CHANGE stimuli were associated with one of the three reference lines (top right).

Materials and Methods

Participants. A total of 162 genetically unrelated participants (96 females, 66 males) of western European/Caucasian descent were included in the study. For the *DRD*1 receptor polymorphism rs4532, genotyping revealed 61 AA (38 females), 78 AG (47 females), and 23 GG (11 females) genotype carriers. For the *DRD*2 receptor polymorphism rs6277, genotyping revealed 47 CC (32 females), 86 CT (44 females), and 27 TT (19 females) genotype carriers [for this single nucleotid polymophism (SNP), we failed to obtain results for two of the participants]. All participants were right handed as measured via the Edinburgh handedness inventory (Oldfield, 1971; 89.8 ± 16.0) and reported no history of psychological and/or neurological illness as assessed by experienced neuropsychologists.

All participants gave written consent and received either 10 Euros or study credits for their participation in the experiment. The study was approved by the ethics committee of the medical faculty of the Ruhr-University Bochum (Germany) and was performed in accordance with the Declaration of Helsinki.

Genotyping. The two candidate SNPs in *DRD1* and *DRD2* were selected from previous results due to their potential functional impact (Batel et al., 2008; Bolton et al., 2010; Doll et al., 2011; Davis et al., 2012; Ota et al., 2012; Voisey et al., 2012; Colzato et al., 2013; Prasad et al., 2013; Zhu et al., 2013; Trampush et al., 2014). SNP rs4532 is located in the 5′ untranslated region of *DRD1* and rs6277 is a synonymous SNP (Pro319Pro) within the coding sequence of *DRD2*. 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.

Stop–change paradigm. The paradigm used in this study was adapted from Verbruggen et al. (2008) and has already been used in previous studies on the psychophysiological processes underlying the different processing modes in goal activation during action cascading (Stock et al., 2014b; Mückschel et al., 2013). Here, we used the same paradigm as in the Mückschel et al. (2013) study. It is illustrated in Figure 1.

The task consists of a total of 864 trials that are divided into six equally sized blocks. For the duration of each trial, a white rectangle of 20 × 96 mm was presented on black background in the center of a 17 inch CRT screen. Within that rectangle were 4 vertically aligned circles (8 mm diameter) and 3 horizontal reference lines (line thickness 1 mm, width 8 mm) that separated the circles from each other. At 250 ms after the rectangle appeared on the screen, one of the four circles was filled with white color, thus becoming the GO1 target stimulus. Participants were instructed to respond with their right hand on a custom-made response panel to indicate whether the target was located above (right middle finger) or below (right index finger) the middle reference line.

Two thirds (576) of the trials were simple GO trials. In these trials, the frame and GO1 stimulus remained visible until the participant either responded with the right hand or 2500 ms had elapsed. In case no response was made within 1000 ms after the onset of the target stimulus presentation, the German word "Schneller!" (translating to "faster!") was presented above the box until the participant responded, thus ending the trial.

The remaining third (288) of the trials consisted of stop–change (SC) trials. Like the GO trials, they started with the presentation of the GO1 target stimulus. In addition, they comprised the presentation of a STOP signal (a red rectangle replacing the usual white frame; depicted gray in Fig. 1) after a variable "stop-signal delay" (SSD). Participants were requested to try to stop/inhibit their right hand responses in reaction to the STOP stimulus. However, this was not always possible due to the SSD adaption. The initial SSD was set to 450 ms and adapted to the participants' performance by means of a "staircase procedure" (see next paragraph or Verbruggen et al., 2008) aiming at an ~50% probability of successfully inhibited GO1 responses. Regardless of whether the response to the GO1 trials was successfully inhibited, every STOP signal was combined with one of three possible CHANGE stimuli that turned the GO1 stimulus into a GO2 stimulus. These CHANGE stimuli were 100 ms sine tones presented via headphones at 75 dB SPL and could be high (1300 Hz), medium (900 Hz), or low (500 Hz). Each tone was presented equally often and was associated with one of the reference lines (Fig. 1). Participants were instructed to use their left hand to indicate whether the GO2 stimulus (the previous GO1 stimulus that remained on the screen throughout the trial) was located above (left middle finger) or below (left index finger) the reference line "denoted" by the respective CHANGE signal. As a further experimental variation, there were two different stimulus onset asynchronies (SOAs) constituting two different SC delays (SCDs). In half of the trials, there was an SOA of 300 ms between the STOP and the CHANGE stimuli (SCD300 condition). In the other half of the SC trials, STOP and CHANGE stimuli were presented simultaneously (SCD0 condition). In case the participants did not respond within 2000 ms after the onset of the CHANGE stimulus, the German word "Schneller!" was presented above the box until the participant responded to end the trial.

After the end of each SC trial, the SSD for the succeeding SC trial was calculated by means of a staircase algorithm (Logan and Cowan, 1984). In case of an entirely correct SC trial performance (correct inhibition of the GO1 response before the presentation of the CHANGE stimulus and correct left hand GO2 response thereafter), 50 ms were added to the previously used SSD. In case of any errors (button presses before the presentation of the CHANGE stimulus and/or incorrect GO2 response thereafter), 50 ms were subtracted from the previous SSD. For practical reasons, SSD values were confined to vary between 50 and 1000 ms. After each trial, a fixation cross was presented in the center of the screen for the

duration of the intertrial interval (fixed duration of 900 ms). All conditions were presented in a randomized order and participants were instructed to respond as fast and accurately as possible.

Estimating the degree of overlap in task goal activation. Based on Verbruggen et al. (Verbruggen and Logan, 2008; Verbruggen et al., 2008) and our own previous studies (Stock et al., 2014a; Mückschel et al., 2013), we calculated an individual slope value for each participant. This measure describes the differences between GO2 response times (RTs) in the SCD0 and SCD300 conditions and is calculated using the following equation:

$$slope = \frac{Go2\,RT_{SCD0} - Go2\,RT_{SCD300}}{SOA_0 - SOA_{300}}$$

In the vast majority of cases, SCD0 RTs are slower than SCD300 RTs. Therefore, the slope is usually negative and becomes steeper the more these two RTs differ.

Variations in this measure are thought to arise from response selection differences on a serial-parallel continuum in the SCD0 condition. This can be better understood when taking a look at the makeup of the two SCD conditions. The SCD300 condition enforces a serial processing of STOP- and CHANGE-related cognitive processes because the STOP process is usually finished at the time the CHANGE stimulus appears. In contrast to this, the SCD0 condition does not enforce a serial or parallel processing mode because the STOP and CHANGE stimuli are presented simultaneously. In this condition only, the question of how to cascade STOP- and CHANGE-associated processes is up to the participants. Models addressing this issue suggest that response selection strategies can be more serial (cognitive substeps being executed one after another) or more parallel (cognitive substeps being processed in parallel so that there is a temporal overlap of processes; Verbruggen et al., 2008; Wu and Liu, 2008; Miller et al., 2009). Assuming that response selection depends on a restricted resource, different processing strategies should result in different GO2 RTs in the SCD0 condition, because each active task goal representation consumes a certain proportion of the presumably limited processing capacities. Therefore, fewer of the resources can be allocated to the each of the task goals in case of a larger overlap of STOP- and CHANGE-associated processes (more parallel processing). In addition, there is a risk of interference between the tasks goals when processed in parallel (i.e., the GO2 processes might be hindered or even cancelled by the ongoing STOP processes; Verbruggen et al., 2008). In case of interference or if fewer resources can be "spent" on performing the associated responses of stopping and changing, SCD0 RTs should be longer and—as a consequence—the slope value should be steeper. In case of less overlap (more serial processing), there should be less interference and more of the restricted resource should be available for the relevant processes. This should lead to faster SCD0 RTs and thus to a flatter slope (for further elaboration on this topic, see Verbruggen et al., 2008; Mückschel et al., 2013). Based on that logic, a slope value between 0 and −1 suggests some/an incomplete temporal overlap of the CHANGE-associated GO2 response processes and the termination of the inhibitory process of stopping the GO1 response. Within this range, slope values closer to 0 indicate a more serial processing mode, whereas slope values closer to −1 indicate a more parallel (less efficient) processing mode. However, it needs to be noted that the slope value does not provide the possibility of distinguishing between nondeterministic serial processes and parallel processing stratgies (cf. Verbruggen et al., 2008 for a detailed discussion on this issue).

EEG recording and analysis. As in Mückschel et al. (2013), EEG data were recorded by means of 65 Ag-AgCl electrodes (standard 10–20 scalp positions) against a reference electrode at FCz. Electrode impedances were kept at $<5\ k\Omega$.

For data analysis, the sampling rate was reduced (from 1000 to 256 Hz) and a band-pass filter (IIR filter from 0.5 to 20 Hz at a slope of 48 db/oct) was applied. Technical artifacts were removed during a manual raw data inspection. As a next step, periodically recurring artifacts such as pulse and eye movements were removed with the help of an independent component analysis (Infomax algorithm). After these corrections, stimulus-locked segments (locked to the STOP signal) were formed. Within these segments, an automatic rejection procedure was run. The criteria used were a maximum voltage step of $>60\ \mu V$/ms, a maximal value difference of 150 μV in a 250 ms interval, or activity $<1\ \mu V$. After the artifact rejection, a CSD transformation was run. This transformation yields a reference-free evaluation of the electrophysiological data and thereby helps to identify the electrodes showing the strongest effects. A prestimulus baseline was set to the interval from −900 to −700 ms to receive a baseline that was positioned before the onset of the GO1 stimulus. The P1, N1, and P3 ERPs were quantified based on the scalp topography; that is, electrodes used for data quantification were selected in a data-driven manner. According to this, the visual P1 and N1 were measured at electrodes PO7 and PO8 (P1: 0–140 ms; N1: 150–250 ms), the auditory N1 at C5 and C6 (0–500 ms), and the P3 at Cz (200–600 ms). The ERP components were quantified relative to the prestimulus baseline. All components were quantified in peak amplitude and latency on the single subject level. This data analysis procedure is identical to that used in Mückschel et al. (2013).

In similar contexts, the (Nogo)-N2 occurring with a latency of 200–300 ms after the inhibitory signal (Falkenstein et al., 1999; van Boxtel et al., 2001) has frequently been analyzed to investigate inhibitory control processes. In the current paradigm, a Nogo-N2-like component is only evident in the SCD300 condition and cannot be detected in the SCD0 condition due to the simultaneously occurring change processes. Because the (Nogo)-N2 is not quantifiable in all conditions, it is not included in the analysis.

Statistical analysis. Behavioral data including stop-signal reaction times (SSRTs) were analyzed using mixed and univariate ANOVAs. In all analyses, "genotype group" was used as a between-subjects factor. In the mixed ANOVAs, the factor "SCD" (SCD0 vs SCD300) was used as a within-subject. For the analysis of neurophysiological data, the additional within-subject factor "electrode" (PO7 vs PO8 or C5 vs C6) was introduced wherever necessary. All *post hoc* tests were Bonferroni corrected. Kolmogorov–Smirnov tests revealed that all relevant variables were normally distributed (all $z < 0.5$; $p > 0.4$; 1-tailed). The SEM is provided as a measure of variability.

Results

DRD1

For the *DRD*1 receptor polymorphism rs4532, genotyping revealed 61 AA, 78 AG, and 23 GG genotype carriers. The distribution of genotypes did not differ from Hardy-Weinberg equilibrium ($p > 0.5$).

The behavioral data were analyzed using a mixed-effects ANOVA of RTs (to the GO1 stimulus in simple GO trials and to the GO2 stimulus in both kinds of SC trials).

This ANOVA revealed a main effect of condition ($F_{(2,314)} = 499.44$; $p < 0.001$; $\eta^2 = 0.765$) showing that GO2 RTs were longer for the SCD0 (1099 ± 18) than for the SCD300 condition (944 ± 17; $p < 0.001$). Furthermore, RTs in both SCD conditions were longer than in the GO1 condition (485 ± 13). Importantly, there was an interaction of condition × genotype ($F_{(4,321)} = 4.11$; $p = 0.01$; $\eta^2 = 0.055$; Fig. 2*A*). Subsequent univariate ANOVAs for the GO1, SCD0, and SCD300 conditions reveal that only in the SCD0 condition did RTs differ across genotype groups ($F_{(2,159)} = 5.63$; $p = 0.011$ $\eta^2 = 0.045$). Bonferroni-corrected pairwise comparisons revealed that AA (1150 ± 23) and AG genotype groups (1145 ± 19) did not differ from each other ($p > 0.9$), but differed from the GG genotype group (988 ± 30; $p < 0.012$). Therefore, the SCD slope values differed between genotype groups ($F_{(2,159)} = 5.22$; $p = 0.006$; $\eta^2 = 0.060$; Fig. 2*B*). Bonferroni-corrected pairwise comparisons showed that the slope of the SCD-RT function was flatter in the GG genotype group (0.19 ± 0.07) than in the AG (0.56 ± 0.09) and AA (0.56 ± 0.07) genotype groups, which did not differ from each other ($p > 0.5$). This shows that the GG genotype group reveals quicker GO2 RTs in the SCD0 condition, which are probably due to a more

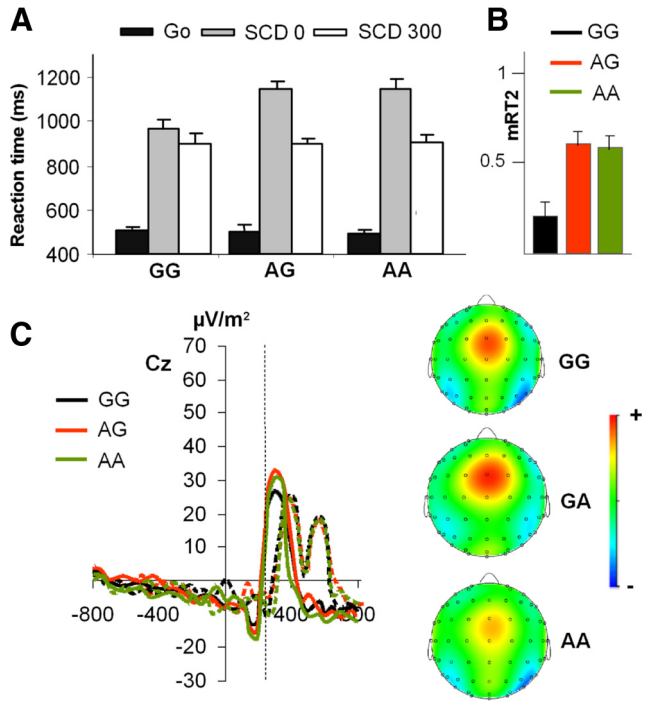

Figure 2. ***A***, RT data (mean ± SEM) for the different DRD1 genotypes (AA, AG, and GG) for the GO1 condition (black), the SCD0 condition (gray), and the SCD300 condition (white). ***B***, Slope of the SCD RT2 function (mRT2) for the GG genotype group (black), the AG genotype group (orange), and the AA genotype group (green). ***C***, The P3 event-related potential at electrode Cz for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; GG genotype = black, AG genotype = orange, AA genotype = green). Time point zero denotes the time point of stop-signal presentation. In addition, the vertical dashed line denotes the onset of the change stimulus in the SCD300 condition. Scalp topography maps depict the peak of the P3 amplitude in the SCD0 condition for each genotype group.

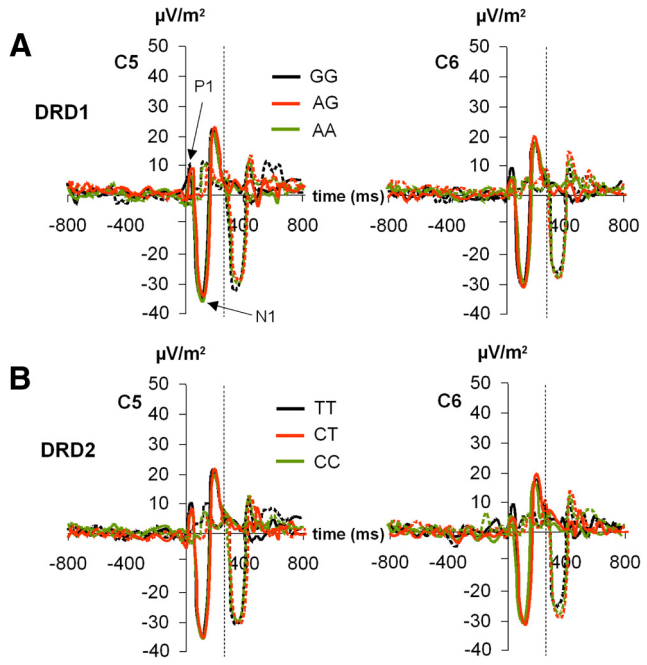

Figure 3. ***A***, Auditory P1 and N1 ERP for the DRD1 genotype groups at electrodes C5 and C6 for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; GG genotype = black, AG genotype = orange, AA genotype = green). ***B***, Auditory P1 and N1 ERP for the DRD2 genotype groups at electrodes C5 and C6 for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; TT genotype = black, CT genotype = orange, CC genotype = green). Time point zero denotes the time point of stop-signal presentation; the vertical dashed line denotes the onset of the change stimulus in the SCD300 condition.

serial mode of goal-activation processes compared with A-allele carriers. To control for a possible speed-accuracy trade-off, we furthermore examined GO2 error, but there was no difference in the error rates between genotype groups ($p > 0.7$). Because of the applied staircase procedure, GO1 error rates cannot differ (Mückschel et al., 2013). SSRT values (overall 216 ms ± 7.4) did not differ across genotype groups ($F_{(2,159)} = 0.28$; $p = 0.754$ $\eta^2 = 0.004$).

The electrophysiological P3 data at electrode Cz are shown in Figure 2*C*. This electrode revealed maximum P3 amplitude as confirmed by the scalp topography plots. The P3 was analyzed in a mixed-effects ANOVA using the between-subject factors SCD condition (SCD0 vs SCD300) and the between-subject factor group. There was a main effect of SCD condition ($F_{(1,155)} = 158.15$; $p < 0.001$; $\eta^2 = 0.489$), showing that the P3 was larger in the SCD0 (29.12 ± 0.65) than in the SCD300 condition (17.33 ± 0.46). There was also a main effect of genotype group ($F_{(2,155)} = 7.5$; $p = 0.001$; $\eta^2 = 0.081$), showing that the P3 amplitude was larger in the AA (25.55 ± 0.49) and AG genotype groups (24.55 ± 0.39) than in the GG genotype group (20.99 ± 0.56; $p = 0.001$). Importantly, there was an interaction of SCD interval × genotype group ($F_{(2,155)} = 7.54$; $p < 0.001$; $\eta^2 = 0.093$). Subsequent univariate ANOVAs revealed that the genotype groups only differed in the SCD0 condition ($F_{(2,155)} = 10.77$; $p < 0.001$; $\eta^2 = 0.133$), but not in the SCD300 condition ($F_{(2,155)} = 0.70$; $p > 0.4$; $\eta^2 < 0.01$). In the SCD0 condition, the GG genotype revealed a smaller P3 amplitude (24.33 ± 1.14; $p < 0.001$) than the AG (30.99 ± 0.71) and AA genotype groups (32.55 ± 0.84), which did not differ from each other ($p > 0.2$). There was no effect of genotype on the latencies of the P3 in the SCD0 and SCD300 conditions (all $F < 0.5$; $p > 0.3$). When using the RT as covariate in the model, the results remain unchanged (all $F < 0.9$; $p > 0.2$). In addition to this, we correlated the slope values obtained with the help of the SCD RT function with slope values calculated on P3 amplitudes at electrode Cz. This analysis showed that there was a positive correlation ($r = 0.49$; $R^2 = 0.24$; $p < 0.001$) across the entire sample ($n = 162$), which parallels the results obtained in the study by Mückschel et al. (2013), who reported $r = 0.42$ in a sample of $n = 24$ healthy young adults.

The auditory and visual P1 and N1 were quantified at electrodes PO7 and PO8 because these electrodes revealed maximum activity (Fig. 3*A*). The auditory P1 and N1 are shown in Figure 4*A* and were quantified at electrodes C5 and C6, again, based on maximum activity in the topographical maps. We did not find any SCD main effect or interaction with the genotype group for either the visual or the auditory P1 and N1 components (all $F < 1.2$; $p > 0.2$).

DRD2

For the *DRD2* receptor polymorphism rs6277, genotyping revealed 47 CC, 86 CT, and 27 TT genotype carriers. The distribution of genotypes did not differ from Hardy-Weinberg equilibrium ($p = 0.19$).

The main effect of the condition is identical to the *DRD1* receptor analysis, because the sample is the same. Differential effects can therefore only emerge with respect to the genotype group. There was again an interaction of condition × genotype group ($F_{(2,314)} = 5.33$; $p = 0.007$; $\eta^2 = 0.042$; Fig. 5*A*). Subsequent univariate ANOVAs revealed that only in the SCD0 condition did the RTs differ between genotypes ($F_{(2,159)} = 3.44$; $p = 0.03$; $\eta^2 = 0.056$), whereas no genotype effects were observed in the GO1 and SCD300 conditions (all $F < 0.3$; $p > 0.5$). In the SCD0 condition, RTs were longer in the TT genotype group (1228 ± 34) than in the CT (1089 ± 25) and CC (1115 ± 31; $p =$

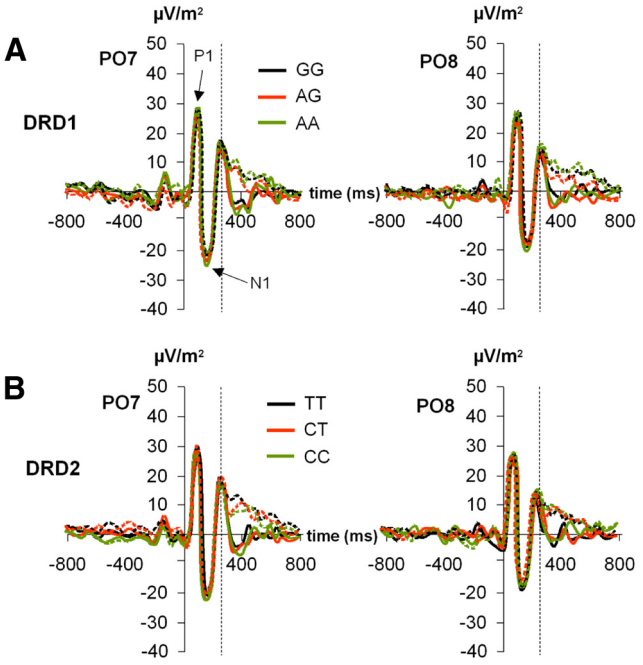

Figure 4. ***A***, Visual P1 and N1 ERP for the DRD1 genotype groups at electrodes PO7 and PO8 for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; GG genotype = black, AG genotype = orange, AA genotype = green). ***B***, Visual P1 and N1 ERP for the DRD2 genotype groups at electrodes PO7 and PO8 for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; TT genotype = black, CT genotype = orange, CC genotype = green). Time point zero denotes the time point of stop-signal presentation; the vertical dashed line denotes the onset of the change stimulus in the SCD300 condition.

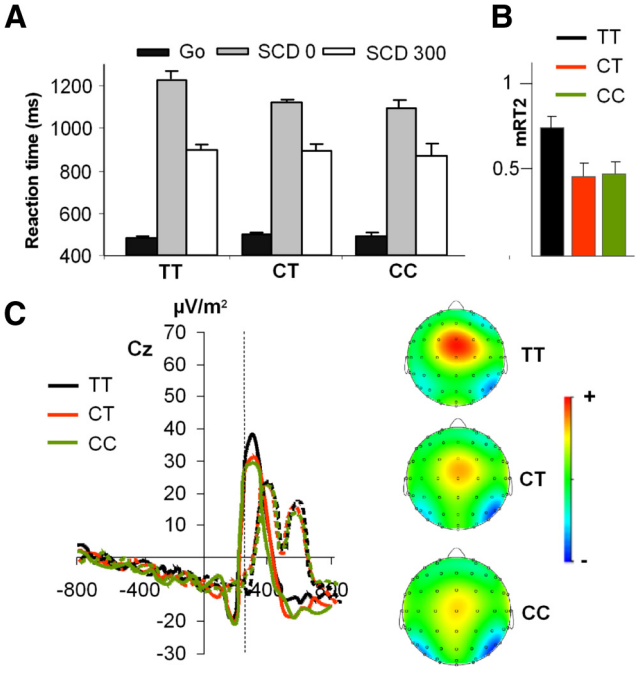

Figure 5. ***A***, RT data (mean ± SEM) for the different DRD2 genotypes (CC, CT, and TT) for the GO1 condition (black), the SCD0 condition (gray), and the SCD300 condition (white). ***B***, Slope of the SCD RT2 function (mRT2) for the TT genotype group (black), the CT genotype group (orange), and the CC genotype group (green). ***C***, P3 event-related potential at electrode Cz for the SCD0 condition (solid lines) and the SCD300 condition (dashed lines; TT genotype = black, CT genotype = orange, CC genotype = green). Time point zero denotes the time point of stop-signal presentation. In addition, the vertical dashed line denotes the onset of the change stimulus in the SCD300 condition. Scalp topography maps depict the peak of the P3 amplitude in the SCD0 condition for each genotype group.

0.014) genotype groups, which did not differ from each other ($p = 0.078$). The SCD slope differed across genotype groups ($F_{(2,159)} = 5.66$; $p = 0.004$; $\eta^2 = 0.070$). Bonferroni-corrected pairwise comparisons revealed that the slope was steeper in the TT genotype group (0.77 ± 0.09) than in the CT (0.45 ± 0.07) and CC genotype groups (0.41 ± 0.11; $p < 0.020$; Fig. 5*B*), which, again, did not differ from each other ($p = 0.350$). This shows that the TT genotype group has slower GO2 RTs in the SCD0 condition, which are probably due to a more parallel processing mode than in the other genotype groups. Again, there was no evidence for a speed/accuracy trade-off ($p > 0.4$) and SSRT values did not differ across genotype groups ($F_{(2,157)}$=.322; $p = 0.725$ $\eta^2 = 0.004$).

The P3 at electrode Cz is plotted in Figure 5*C*. This electrode showed the maximum P3 amplitude as revealed by the scalp topography plots. Given that it is identical to the effects provided in the DRD1 results section, the main effect of SCD condition is not reported here.

There was also a main effect of genotype group ($F_{(2,155)} = 6.7$; $p = 0.001$; $\eta^2 = 0.071$), showing that the P3 was smaller in the CC (22.12 ± 0.44) and CT genotype groups (22.31 ± 0.40) than in the TT genotype group (27.67 ± 1.01; $p = 0.001$). Importantly, there was again an interaction of SCD condition × genotype group ($F_{(2,155)} = 6.23$; $p < 0.001$; $\eta^2 = 0.076$), which is shown in Figure 5*C*. Subsequent univariate ANOVAs revealed that the genotype groups only differed in the SCD0 condition ($F_{(2,155)} = 8.77$; $p < 0.001$; $\eta^2 = 0.098$), but not in the SCD300 condition ($F_{(2,155)} = 0.67$; $p > 0.4$; $\eta^2 < 0.01$). In the SCD0 condition, the TT genotype group revealed a larger P3 amplitude (40.04 ± 0.16; $p < 0.001$) than the CT (32.33 ± 0.74) and CC (33.33 ± 0.66) genotype groups, which did not differ from each other ($p > 0.4$). There was no effect of genotype on P3 latencies in the SCD0 and SCD300 conditions (all $F < 0.5$; $p > 0.3$). As for the analysis of the DRD1 data, there was no influence of RT on the P3 results when RT was used as a covariate in the model (all $F < 0.8$; $p > 0.2$).

The auditory and visual P1 and N1 were again quantified at C5/C6 and PO7/PO8 and are shown in Figures 3*B* and 4*B*, respectively. We did not find any SCD main effect or interaction with the genotype group for either the visual or the auditory P1 and N1 components (all $F < 1.2$; $p > 0.3$).

Discussion

This study suggests a possible effect of the *DRD1* rs4532 and *DRD2* rs6277 polymorphisms on the dopaminergic modulation of task goal activation processes during action cascading. Summing up the main findings of the study, all of the observed differences between the assessed genotype groups were confined to the SCD0 condition. Because SCD0 is the only condition in which participants can cascade their actions according to their "preferred" processing strategy (see Materials and Methods), this allows for the interpretation that the effects were confined to specific variations in response selection/action cascading processes on a serial-parallel continuum, which could be caused by a limited processing resource, effects of task goal interference, or both (cf. Verbruggen et al., 2008; Mückschel et al., 2013). The main results reveal opposing effects: compared with the CC and CT genotype groups, the *DRD2* TT genotype group showed a less efficient and more parallel response selection strategy as measured via slower SCD0 RTs and a steeper slope. In contrast, the *DRD12* GG genotype group showed faster SCD0 RTs and a flatter slope, suggesting that the GG group was more efficient and had a more serial processing strategy than the AA and GA groups.

Carriers of the *DRD2* T allele are described to present with a higher striatal density of D2 receptors (Hirvonen et al., 2005; Frank

et al., 2009), which has previously been associated with decreased executive functioning (Kehagia et al., 2010). It can be assumed that they are more inclined toward a dopamine D2 state (Durstewitz and Seamans, 2002, 2008) than the CT and CC groups. According to the dual-state theory (Durstewitz and Seamans, 2002, 2008), several items (e.g., task goals) can be represented simultaneously in frontostriatal networks in the D2 state. This may greatly facilitate flexible switching between the representations. However, the parallel representation of several task goals produces high costs because they may interfere with each other and/or need to share processing capacity (Meyer and Kieras, 1997; Brisson and Jolicoeur, 2007; Sigman and Dehaene, 2008; Verbruggen et al., 2008). Therefore, the selection of an action on the basis of the activation of task goals becomes more difficult. This slows down task goal activation processes and ultimately leads to the observed delay of the SCD0 response. Applying this to the SC paradigm, the TT genotype group seems to deal with STOP- and CHANGE-associated cognitive processes in a more parallel manner so that interference between these two task goals ultimately results in prolonged times to activate task goals and thus longer RTs. Because morphologic changes with the striatum have already been demonstrated to affect the performance in the SC task (Beste and Saft, 2013), it seems very likely that genotypes differing in their striatal D2 receptor densities affect task performance.

As to the examined *DRD1* polymorphism, the *DRD1* G allele is associated with increased D1 receptor efficiency (Dolzan et al., 2007; Novak et al., 2010), which has previously been linked to improved executive functioning (Kehagia et al., 2010). The *DRD1* GG genotype group should be more inclined to the dopamine D1 state than the AG and GG genotype groups. The D1 state is characterized by a rather serial representation of items in prefrontal networks (Durstewitz and Seamans, 2002, 2008). Contrary to what happens in the D2 state, this rather serial representation impedes flexible switching between different items (e.g., task goals), but, at the same time, a represented task goal should interfere less and/or need to share less capacities with competing task goals. Following from this lack of competition or interference between different task goals, serial action selection is faster (compared with a more parallel processing mode). In the context of the SC task, less interference of the STOP and CHANGE task goals should thus result in faster RTs in the GG group, compared with the other groups. Together, these findings suggest that response flexibility is not the key aptitude of the performance in the SC paradigm. Instead, the fashion in which task goal representations are activated and processed seems to determine the speed at which they can be selected and performed. Given that behavioral task performance does not allow for reliable inferences about underlying processing capacity limitations (for a detailed discussion, see Verbruggen et al., 2008), it is more appropriate to consider task goal interference as the primary cause for the observed behavioral effects.

On the neurophysiological level, the difference between a more serial versus a more parallel processing mode is reflected by genotype group differences in the P3 amplitude. This event-related potential is thought to reflect the link between stimulus evaluation and response selection and has repeatedly been shown to depict different processing modes in the SC task (Mückschel et al., 2013) and to be modulated by dopamine (Falkenstein et al., 1994a, 1994b; Verleger et al., 2005; Brisson and Jolicoeur, 2007; Polich, 2007; Sigman and Dehaene, 2008). The more serial and efficient processing mode of the *DRD1* GG genotype was associated with a smaller P3 component, whereas the more parallel and less efficient *DRD2* TT genotype group had a larger P3 component. This finding is consistent with previous studies that also demonstrated a reduced P3 amplitude in more serial processing and a larger P3 in more parallel processing (Beste and Saft, 2013; Mückschel et al., 2013; Stock et al., 2014b). The observation that subjects with a better behavioral performance have repeatedly been shown to display a reduced P3 amplitude might suggest that less effort is needed in case of a more serial action cascading strategy. This would also match the assumption that serial processing evokes fewer conflicts, less interference, and less mutual inhibition between the representations of different response options.

Altogether, the neurophysiologic results suggest that *DRD1* and *DRD2* genotypes exert their effects at the stage of task goal selection. Furthermore, there were no genotype group differences in the SSRTs or the P1 and N1 ERP components, which suggests that the observed differences in task performance are neither based on aspects of mere inhibition or on attentional effects (cf. Herrmann and Knight, 2001; Gajewski et al., 2013). Therefore, the differentiation of serial and parallel processing strategies does not seem to start until after the stages of initial stimulus processing. Even though we were able to demonstrate opposing effects of *DRD1* and *DRD2* polymorphisms in the same sample, the sample is not sufficiently large to investigate potential epistasis effects of the interaction of the two investigated SNPs (the smallest combination of genotypes, GG/TT, comprised only three subjects). Therefore, we cannot provide information on how the *DRD1* and *DRD2* alleles interact in the formation of the observed phenotypic trait differences on a serial-parallel continuum. Furthermore, it needs to be mentioned that that the functional role of our polymorphisms has remained somewhat unclear (Le Foll et al., 2009) and that changes in D2 receptor density and D1 receptor binding have also been suspected to globally modulate executive functioning (Kehagia et al., 2010).

Summing up this study, we could demonstrate that dopamine D1 and D2 receptors, as examined via functional *DRD1* (rs4532) and *DRD2* (rs6277) receptor polymorphisms, seem to modulate goal activation processes in action cascading on a serial-parallel continuum. Individuals with a higher D1 receptor efficiency seem to process task goals in a more serial and more efficient manner, whereas subjects with higher striatal D2 receptor density were more inclined toward a parallel and less efficient processing mode. This difference was based on the link between stimulus processing and response selection, not on attentional differences. These findings are consistent with previous observations and with predictions of the dual-state theory of dopaminergic modulation. They demonstrate that the stable representation of task goals, rather than the general possibility to flexibly switch between them, seems to determine performance in multicomponent behavior.

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