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Original Article

Effects of DRD2/ANKK1 and COMT Val158Met polymorphisms on stabilization against and adaptation to unexpected events

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Abstract

Genetic variations affecting dopaminergic neuromodulation such as the DRD2/ANKK1 and the COMT Val158Met polymorphisms contribute to goal-directed behavior that requires a balance between stabilization and updating of current states and behaviors. Dopamine is also thought to be relevant for encoding of surprise signals to sensory input and adaptive learning. A link between goal-directed behavior and learning from surprise is therefore plausible. In the present fMRI study, we investigated whether DRD2 and COMT polymorphisms are related to behavioral responses and neural signals in the caudate nucleus and dlPFC during updating or stabilizing internal models of predictable digit sequences. To-be-detected switches between sequences and to-be-ignored digit omissions within a sequence varied by information-theoretic quantities of surprise and entropy. We found that A1 noncarriers and Val-carriers showed a lower response threshold along with increased caudate and dlPFC activation to surprising switches compared with A1-carriers and Met-homozygotes, whose dlPFC activity increased with decreasing switch surprise. In contrast, there were overall smaller differences in behavioral and neural modulation by drift surprise. Our results suggest that the impact of dopamine-relevant polymorphisms in the flexibility-stability trade-off may result in part from the role of dopamine in encoding the weight afforded to events requiring updating or stabilization.

Key words: frontostriatal circuits; dopamine; genes; prediction error; stability-flexibility.

Introduction

It is crucial to adapt our behavior to environmental changes in daily life without losing sight of our action goals. On the one hand, we need to stabilize our predictions in the face of potential distractors. On the other hand, we need to adapt these stable predictions to changing circumstances. Neurocomputational models and brain imaging studies suggest that this balance between stability and flexibility is supported by activity in frontostriatal circuits (see Cools and D'Esposito 2011, for a review). Specifically, separate loops that work in parallel have been proposed linking widely distributed cortical areas via the basal ganglia and thalamus to premotor and prefrontal regions to support various cognitive and motor functions (Alexander et al. 1986). These loops presumably accomplish two things: on the one hand, input about external states of the environment from numerous cortical regions is integrated through the basal ganglia and fed to frontal regions, and on the other hand, updated predictions from frontal regions are fed back to the striatum, thereby maintaining and focusing coordinated behavior. Tonic and phasic supplies of dopamine are thought to substantially modulate activity within these frontostriatal circuits

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(Cools and D'Esposito 2011). Put simply, high dopamine levels in the prefrontal cortex (PFC) favor stabilization of predictions but are detrimental for flexible updating, whereas high dopamine levels in the striatum promote flexibility but impair stability. The opposing effects of dopamine may be mediated by the different topology of the various dopamine receptor types, which are commonly divided into two classes: the D1 family (D1, D5 receptors; D1Rs) and the D2 family (D2, D3, D4 receptors; D2Rs). The highest D2Rs density is found in the striatum, whereas D1Rs expression is enriched in the PFC, the hippocampus, and the visual cortex (Hall et al. 1994).

As to its specific functional profile, dopamine has been ascribed a role in coding the weight (or "precision") of prediction errors that represent the mismatch between expected and actual sensory input (Friston et al. 2012). Precision can be driven by internal or external factors such as attention, behavioral relevance, and/or the statistical properties of the sensory signal (Hsu et al. 2020). Increasing the precision of sensory input can be achieved by an enhancement of the neurons' signal-to-noise ratio through synaptic gain modulation (Ott and Nieder 2019) in the course of learning (Daw et al. 2011; Adams et al. 2020). By controlling the gain of postsynaptic neurons, dopamine determines how strongly prediction errors are weighted and, consequently, whether they lead to an updating or, on the contrary, stabilization of current internal states. In line with this suggestion, dopaminergic signaling in the striatum was found to adopt a gating function to pass on only relevant information for updating representations in the PFC and to adapt one's behavior accordingly (Miller and Cohen 2001; Chatham et al. 2014). Dopamine is therefore also considered important for learning which action to select (Frank 2005). According to computational models on the basal ganglia's role in action selection, high dopamine transmission leads to a high gain within corticostriatal loops, due to amplification effects of D1Rs in the direct pathway and compression effects of D2Rs in the indirect pathway (Hauser et al. 2016).

Different modes of dopamine action depending on the respective receptor type in the striatum cannot be easily transferred to the effects of dopamine in cortical regions. As for the PFC, neurocomputational models suggest that tonic D1R activation stabilizes the current internal state by increasing the threshold that must be exceeded to switch to another network state (Durstewitz and Seamans 2008). Only substantial phasic dopamine input to D2Rs can render the state susceptible to incoming new information and ease changing to a new state. More or less stable or flexible states might correspond to predictions of varying precision, being more or less susceptible to updating (Yu et al. 2013).

The role of dopamine for balancing flexibility and stability can be addressed based on the large intraindividual variability in dopamine availability, which depends, among other factors, on different variants of single nucleotide polymorphisms (SNPs). One well-studied polymorphism influencing striatal dopamine is the DRD2/ANKK1-TaqIA that modulates the density and availability of D2Rs (Jönsson et al. 1999; Gluskin and Mickey 2016). Carriers of the A1 allele (A1+) have up to 30–40% reduced D2Rs density compared with homozygous A2 allele carriers (A1−), particularly in the striatum (Pohjalainen et al. 1998). In keeping with this, studies investigating flexibility and stability provide evidence for the differential performance of these two genotypes. For example, A1 carriers outperformed noncarriers regarding backward inhibition during switching (Markett et al. 2011) and also show lower switching costs (Stelzel et al. 2010), with better performance accompanied by increased lateral frontal activity and increased frontostriatal functional connectivity. In contrast, noncarriers showed superior performance and increased striatal signaling during reversal learning (Jocham et al. 2009) and long-term memory updating (Persson et al. 2015).

Another candidate gene codes for catechol-O-methyl transferase (COMT), the central enzyme contributing to the degradation of dopamine in the PFC (Männistö and Kaakkola 1999; Weinshilboum et al. 1999). The polymorphism of the COMT Val158Met gene includes a functional missense mutation at codon 158 that results in a substitution of methionine (Met) for valine (Val) (Chen et al. 2004). The Met allele is associated with reduced COMT activity leading to increased dopamine baseline levels in the PFC. Individuals with the Met allele tend to stabilize better in working memory delay or inhibition tasks (Egan et al. 2001; Bruder et al. 2005). On the other hand, individuals with the Val allele demonstrate greater flexibility (Nolan et al. 2004; Colzato et al. 2014).

Taken together, previous studies suggest that the delicate balance between cognitive flexibility and stability depends on optimal dopamine levels in frontostriatal circuits and that, therefore, genotypes associated with dopaminergic neurotransmission contribute differentially to these functions. However, different operationalization approaches for flexibility and stability make it difficult to gain consistent insights into dopaminergic involvement in the trade-off between flexibility and stability (Miyake et al. 2000). In the present study, we therefore hypothesized that dopaminergic neurotransmission influences the need to either update or stabilize current predictions in response to prediction errors. Specifically, in light of current models of the role of dopamine in the precision weighting of predictions and prediction errors, we extended previous studies by assuming that this influence depends on the respective precision of predictions relative to the precision of prediction errors, which is reflected in a specific activation pattern of the dlPFC and caudate nucleus, respectively. In addition, we examine the influence of the intrinsic relevance of the stimulus itself, i.e. whether it involves an update or a stabilization of the current prediction, which (in many cases) involves the execution or inhibition of motor responses, respectively. We investigated how variants of the two dopamine-relevant SNPs modulate

participants' response to unexpected events of varying surprise that require either stabilization or updating of current predictive models. Across a small series of studies, we collected genetic data from participants including healthy subjects and patients with Parkinson's disease and schizophrenia, who performed the so-called "serial switch-drift paradigm." The task required to track predictable digit sequences, which serve as an explicit internal model of the current visual input, in order to indicate the occurrence of sequential model "switches" while ignoring model-uncritical omissions of single digits ("drifts"). To assess the effects of varying precision of these events, both the relative proportion of switch vs. drift occurrences (i.e. their respective probability) and the absolute frequency of unpredicted vs. predicted digits (i.e. predictability) varied throughout the experiment. The probability and predictability of digits were quantified as information-theoretic quantities of Shannon's "surprise" and "entropy," respectively (Shannon 1948). While we calculated surprise to quantify the participants' different behavioral and neural responses to particular event types (i.e. drift or switch) with regard to their respective (un-)expectedness, entropy derives from the probabilistic distribution of "all" possible events. It thus reflects event processing in a specific environment independent of a specific event type. Due to the high information content of unexpected input per se, highly surprising events could be easier to detect (as for switches) but more difficult to ignore (as for drifts). Moreover, in the context of high entropy, switches and drifts occur both equally frequently and very frequently, particularly requiring increased control demands.

In line with the suggested role of dopamine in coding the weight of sensory input, we tested whether the detection of switches and the rejection of drifts would be differentially modulated by surprise in variants of the DRD2 and COMT polymorphisms. We focused on the dlPFC and caudate nucleus as part of the "cognitive loop" described by Alexander et al. (1986) and assessed how activity within these regions was modulated by surprise. Given the existing evidence and the prevalent interpretation on striatal involvement in flexible updating in response to novel or changing input on the one hand, and frontal involvement in distractor inhibition on the other, as well as the specific functional distinction between caudate nucleus and dlPFC, two basic hypotheses emerge: (H1) Regarding flexibility, switch surprise positively covaries with the hit rate for switches, and more with activity in caudate nucleus than with activity in dlPFC. In contrast, (H2) regarding stability, drift probability positively covaries with the rejection rate for drifts, and more with activity in dlPFC than with activity in caudate nucleus. In terms of possible differences between genotypes, we had the following two hypotheses: (H3) A1 non-carriers (vs. A1 carriers) and Val carriers (vs. Met homozygotes) show a higher flexibility, as tested in (H1). In contrast, (H4) A1 carriers (vs. A1 noncarriers) and Met carriers (vs. Val homozygotes) show a higher stability, as tested in (H2). Since we tested all hypotheses in a single model, we assumed a 3-way interaction between genotype, event type and level of surprise on behavioral performance, and between genotype, event type, and region on the neural activity parametrically modulated by surprise. Finally, we assessed differential effects of stimulus entropy on overall error rate and striatal and prefrontal activation to explore potential differences between the genotypes in the adjustment of learning, dependent on environmental volatility.

Materials and methods

Participants

The data of the present sample of 91 participants in total (34 females, mean age = 44.29 years, $SD = 17.23$, range = [20, 74]) were collected in three independent studies (I–III). Note that behavioral and neural results independent of genetic polymorphisms were partly reported in previous publications (Trempler et al. 2017, 2018); Standke et al. 2021). The subsamples of these studies consisted of (I) 21 young healthy participants (YH, 7 females, 14 males), (II) 19 participants that were diagnosed with the akinetic-rigid subtype of idiopathic Parkinson's disease (PD, 6 females, 13 males), and 18 healthy elderly control participants matched for age and gender (HC_1, 6 females, 12 males), and (III) 17 patients with schizophrenia (SZ, 6 females, 11 males) and 16 age- and gender-matched healthy control participants (HC_2, 4 females, 12 males). Two participants (both female) of the SZ sample were excluded due to poor behavioral performance (see 2.6 Behavioral data analysis). Apart from the respective diagnosis within the samples, no participant had a history of other neurological or psychiatric diseases. All participants were native German speakers. Table 1 depicts the demographic and clinical data of the final subsamples.

There were no significant differences regarding the DRD2 genotype distribution between the subsamples, $\chi^2(4) = 4.281$, $P = 0.369$, as well as no significant differences when considering the distribution of healthy participants (YH, HC_1, HC_2) vs. patients (PD, SZ), $\chi^2(1) = 0.796$, $P = 0.372$. Likewise, regarding the COMT genotype, no significant differences between the subsamples, $\chi^2(8) = 8.149$, $P = 0.419$, or between healthy subjects and patients, $\chi^2(2) = 4.953$, $P = 0.084$, were observed. Table 2 describes genotype frequencies and main demographic information of each sample stratified by genotype.

Each participant submitted a signed informed consent notification and received course credits or financial reimbursement for participation. The studies were approved by the local ethics committee and were performed following the Declaration of Helsinki.

Procedure and task

Although the general study procedure including various additional assessments differed between the

Table 1. Demographic and clinical data of study subsamples ($n = 89$).

Characteristic	Mean (±SD) per subsample per study				
	I	II		III	
	HY ($n = 21$)	HC_1 ($n = 18$)	PD ($n = 19$)	HC_2 ($n = 16$)	SZ ($n = 15$)
Age (yrs.)	23.53 (2.02)	60.78 (9.89)	58.81 (9.89)	43.88 (11.73)	33.37 (8.02)
BIS-11 Sum	62.67 (8.63)	70.06 (5.75)	71.19 (4.84)	58.56 (6.88)	64.07 (7.27)
Attentional	16.48 (3.50)	16.61 (1.94)	17.10 (2.79)	14.94 (3.38)	17.36 (3.62)
Motor	22.19 (3.93)	31.44 (3.24)	29.90 (4.09)	21.38 (1.96)	22.36 (4.85)
Non-Planning	24.00 (4.16)	22.00 (3.22)	24.20 (3.25)	21.63 (3.38)	23.63 (3.99)
BDI-II	-	6.00 (5.05)	7.81 (4.69)	2.94 (4.01)	10.94 (7.86)
PANDA	-	27.56 (2.09)	27.43 (3.04)	-	-
UPDRS III	-	5.33 (2.74)	19.62 (7.48)	-	-
BACS		-	-	0.40 (1.03)	−1.24 (1.16)
NSS	-	-	-	6.19 (4.15)	15.22 (9.56)
DOI	-	-	4.29 (3.33)	-	12.81 (10.91)
LEDD/CPZ	-	-	511.38 (290.33)	-	559.52 (440.62)

SD, standard deviation; HY, healthy young participants; HC, healthy control participants; PD, patients with Parkinson's disease; SZ, patients with schizophrenia; BIS, Barrett Impulsiveness Scale; BDI, Beck's Depression Inventory; PANDA, Parkinson Neuropsychometric Dementia Assessment; UPDRS, Unified Parkinson's Disease Rating Scale; BACS, Brief Assessment of Cognition in Schizophrenia; NSS, Neurological Soft Signs; DOI, Duration of Illness; LEDD, Levodopa equivalent daily dose, CPZ, Chlorpromazine equivalent dose.

Table 2. Demographic data stratified by the genotype of each polymorphism and subsample.

Genotype	Subsample				
	I	II		III	
	HY	HC_1	PD	HC_2	SZ
DRD2					
Frequency					
A1−	12	13	8	7	9
A1+	9	5	11	9	7
Age (yrs.)					
A1−	22.92 (1.89)	60.77 (10.67)	56.38 (9.16)	43.57 (11.84)	32.33 (9.86)
A1+	24.35 (1.99)	60.80 (8.59)	63.09 (8.29)	44.11 (12.35)	35.67 (4.08)
Gender (m/f)					
A1−	4/8	9/4	5/3	7/0	7/2
A1+	3/6	3/2	8/3	5/4	4/2
COMT					
Frequency					
ValVal	5	3	2	5	3
ValMet	12	9	9	9	5
MetMet	4	5	6	2	8
Age (yrs.)					
ValVal	22.18 (1.81)	51.67 (14.01)	59.00 (18.39)	52.60 (8.39)	27.00 (3.61)
ValMet	24.08 (2.21)	62.11 (8.99)	57.80 (9.10)	40.89 (12.03)	33.20 (7.73)
MetMet	23.58 (0.85)	63.20 (8.90)	63.00 (7.18)	35.50 (4.95)	36.86 (8.47)
Gender (m/f)					
ValVal	1/4	2/1	1/1	3/2	2/1
ValMet	5/7	5/4	8/2	8/1	3/2
MetMet	1/3	4/1	2/3	1/1	6/1

HY, healthy younger participants; HC, healthy control participants; PD, patients with Parkinson's disease; SZ, patients with schizophrenia.

samples, all participants performed the serial switch-drift paradigm with only minor differences in the task design. The stimulus used in the serial switch-drift paradigm consists of two constantly repeating digit sequences, one ascending (1-2-3-4) and one descending (4-3-2-1) (Fig. 1a). Digits were presented for 900 ms in study I and 1000 ms in study II and III to reduce task difficulty for the elderly participants and patients, and each separated by an interstimulus interval of 100 ms. Occasionally, either "switches," that is, a switch from the ascending to the descending sequence or vice versa, or "drifts," i.e. single digit omissions

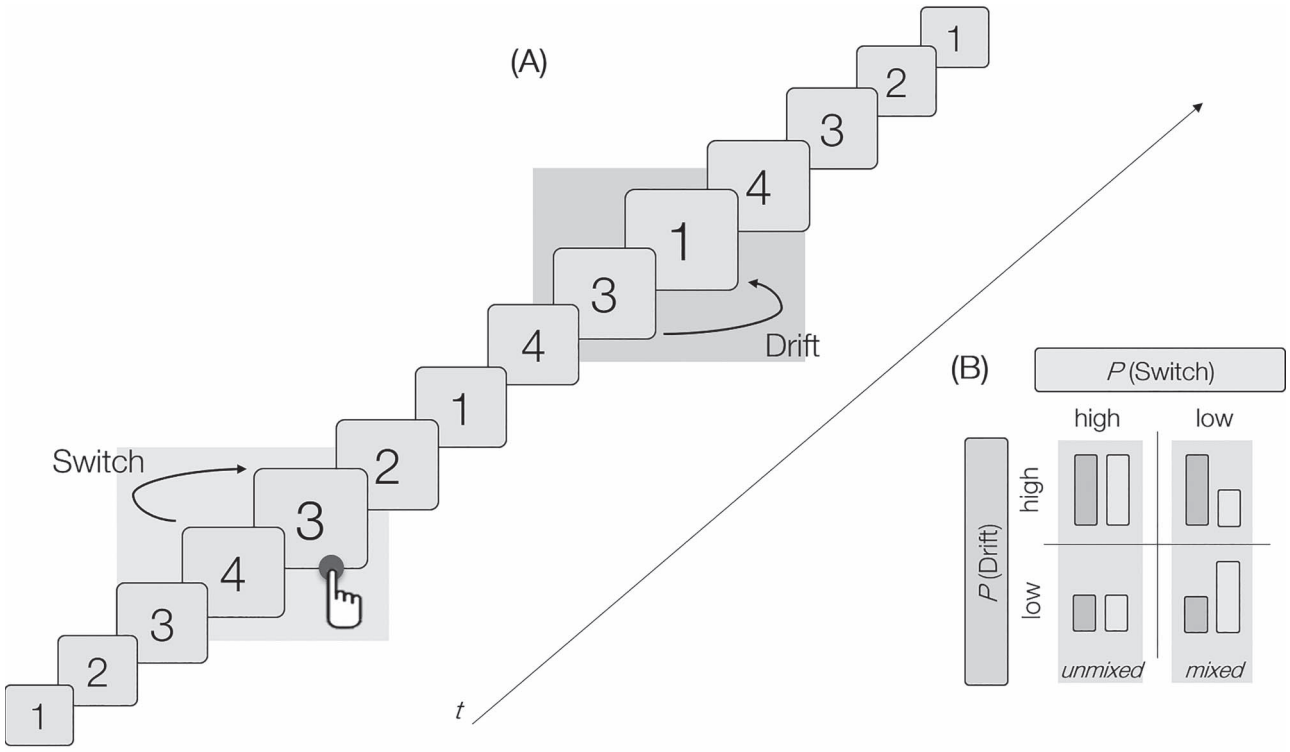

Fig. 1. Schematic diagram of the task. a) Participants were asked to indicate a directional change ("switch") within a simple 4-digit sequence via button press but to ignore the omission of a single digit ("drift"). b) The probabilities of switches and drifts varied block-wise across the experiment in a 2 × 2 design, resulting in mixed and unmixed blocks with unequal and equal probabilities of the two event types, respectively.

without a temporal gap, occurred at pseudorandom ordinal positions within the sequence. The occurrence of switches and drifts was unambiguous, meaning that the two events never appeared simultaneously. The participant's task was to signal the switches via button press as fast and accurately as possible ("switch detection") and ignore sequential omissions ("drift rejection"). To control for general motor slowing in patients and elderly controls, participants of study II and III also performed "motor control" trials ($n = 25$) that were randomly interleaved across the experiment. In these motor control trials, single digits were repeated up to 8 times until the participant responded by button press. In study I, participants received individual performance feedback in 3 breaks of 14 s, whereas in study II and III, more frequent breaks ($n = 20$) were provided by a 6-s presentation of a fixation cross and no feedback was given that could have demotivated the elderly controls and patients.

The experiment was subdivided into 12 blocks of an average number of 125 digits (160 in study I) combining high and low probabilities of switches and drifts in a two-by-two full-factorial design with the factors probability (high vs. low) and event type (switch vs. drift). This resulted in 4 different block types: high- or low-probability switch and drift blocks (unmixed blocks), and high-probability switch and low-probability drift (or vice versa) blocks (mixed blocks) (see Fig. 1b). Transitions between these block types were balanced across the experiment. In study I, probabilities varied between the participants as we used a staircase procedure to establish the maximum probability of switches and drifts per block (see Trempler et al. 2017). Staircasing resulted in a maximum mean probability of 24.5% ($SD = 1.7$) in unmixed blocks of high probability, while the probability in low probability unmixed blocks was set to approximately one-third of the individual maximum probability. In order to be able to compare controls and patients in studies II and III, probabilities were fixed, with a maximum probability of 16% and a minimum probability of 8%. The difference between the maximum and the minimum probability of the unmixed blocks served as the maximum probability in mixed blocks. In contrast, minimum probability remained equal so that the difficulty level in terms of the overall event probability was kept constant across the experiment (except for unmixed low-probability blocks). Stimulus presentation was pseudorandomized using the stochastic universal sampling method (Baker 1987), which ensured a balanced distribution of switches and drifts across the blocks. The randomization was programmed using MATLAB R2012b (The MathWorks Inc., Natick, MA, USA), and stimuli were presented using Presentation (Neurobehavioral Systems, San Francisco, CA, USA).

To ensure task comprehension, participants completed an instructed training either directly or, in the case of the patients, on an additional screening day before

the MRI session on which additional neuropsychological tests were performed (see Table 1). In the latter case, participants performed a further short training as a reminder before the fMRI session. Moreover, the PD patients were tested twice, i.e. once with their regular medication ("ON"-state) and once without medication ("OFF"-state; after overnight withdrawal of dopaminergic medication, corresponding to at least 10 h after the last dose). Session order (OFF–ON and ON–OFF) was counterbalanced across the participants. Here, only results of patients in the ON-state are reported. Saliva or blood samples of all participants were collected after the scanning session for DNA collection.

Genotyping

In the present study, we assessed an SNP in the gene that encodes for the Catechol-O-methyl-transferase (COMT, rs4680) enzyme as well as the TaqIA restriction fragment length polymorphism (ANKK1, rs1800497). DNA of the subsample I (YH) and healthy control participants of subsample II (HC_1) were extracted from buccal cells and conducted as described elsewhere (Reuter et al. 2006). Purification of genomic DNA was performed with a standard commercial extraction kit (High Pure Polymerase Chain Reaction (PCR) Template Preparation Kit; Roche Diagnostics, Mannheim, Germany). Genotyping of the SNPs was performed by real-time PCR using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). For genotyping the PD patients of subsample II, 20 mL of blood were collected in tubes containing ethylenediaminetetraacetic as anticoagulant, centrifuged at 10°C for 10 min at 3000 xg to separate the buffy coat and finally stored at −80 °C until analysis. Specifically, DNA was isolated from the buffy coat using the QIAamp DNA Blood Mini Kit (Cat No. 51106, Qiagen GmbH, Hilden, Germany) according to manufacturer's protocol. Concentration and quality of the DNA were assessed with a UV/Vis-spectrophotometer (ND-1000, Peqlab GmbH, Erlangen, Germany). Then, 20 ng of DNA was analyzed in triplicates using allelic discrimination assays (TaqMan SNP Genotyping Assays, Applied Biosystems by Thermo Fisher Scientific Inc., Waltham, MA, USA). Genotyping PCR was performed on a 7900HT Fast Real-Time PCR system (Applied Biosystems) and the data analyzed with Sequence Detection Software 2.3 (Applied Biosystems). DNA isolation and SNP-genotyping were performed by the Max Planck Institute for Metabolism Research in Cologne. Sample III including patients with schizophrenia (SZ) and healthy control participants (HC_2) was part of the larger FOR2107-cohort (see Kircher et al. 2019 for details). Genotyping procedures of the FOR2107-sample have been described elsewhere (Goltermann et al. 2019, 2020). Briefly, DNA of each participant was extracted from peripheral blood using standard procedures. Genome-wide genotyping was performed using the Infinium PsychArray BeadChip (Illumina, San Diego, CA, USA). The GenomeStudio software (v.2011.1, Illumina, San Diego, CA, USA) and the Genotyping Module (v.1.9.4) were used to conduct clustering and initial quality control. The subsequent quality control procedures were performed using PLINK (Chang et al. 2015). Samples with low genotype call rates (<95%), sex inconsistencies (X-chromosome heterozygosity), and genetically related individuals were excluded from the present analysis. Furthermore, we excluded SNPs that had a poor genotyping call rate (<95%), a minor allele frequency <1%, strand ambiguity (C/G and A/T SNPs), or that showed deviation from the Hardy–Weinberg Equilibrium ($P < 10^{-6}$). The quality-controlled genotype data were imputed using minimac and the Haplotype Reference Consortium reference panel (v3.20101123, http://www.haplotype-reference-consortium.org/home) (McCarthy et al. 2016). For the present study, genotype information for the two variants rs4680 and rs1800497 was extracted from the imputed data.

FMRI data acquisition

Imaging was performed at different study sites and with slightly different scanning protocols reported in Table 3.

Behavioral data analysis

We assessed successful task performance by the rate of correct detection of switches, i.e. the hit rate (H) and the rate of correct rejections of drifts (CR). Correspondingly, errors were reflected by the inverse measures, that is the rate of switch misses (M) and false alarms to drifts (FA). To control for general motor slowing in patients and elderly controls in study II and III, the motor control trials were used to determine the 90%-quantile of each participant's reaction times, which then served as an individual time window, in which button presses in response to switches and drifts were acknowledged as hits and false alarms, respectively. In study I, the time window was set to 2 trials for all participants. Outliers across the whole sample were determined by computing the 1.5 interquartile ranges (IQR) for the two performance measures (i.e. H and CR) and any behavioral performance that fell below the IQR was considered as outlier leading to the exclusion of two participants from the SZ sample (both female, A1, and ValMet carriers).

We tested whether information-theoretic quantities, i.e. Shannon's surprise $I(x_i)$ and entropy $H(X)$ (Shannon 1948), reflecting the inverse probability and predictability of a single stimulus, respectively, could predict error rate variance on a trial-by-trial level. To determine Shannon's surprise, we first calculated each stimulus' probability based on the frequency of a trial type x_i normalized by the sum of all past trials in the block

$$p(x_i) = \frac{n(x_i) + 1}{\sum x_t + 1}.$$

Table 3. FMRI data acquisition parameters for the three studies.

Parameters	Study		
	I	II	III
Location	University Hospital Muenster, Germany	Research Centre Juelich, Germany	University Hospital Muenster, Germany
MR tomograph	3 Tesla Siemens Magnetom Prisma	3 Tesla Siemens Magnetom Prisma	3 Tesla Siemens Magnetom Prisma
Head coil	20 channel	TRTX	20 channel
EPI sequence	T_2*-weighted	T_2*-weighted	T_2*-weighted
Resolution	64 × 64 pixel	64 × 64 pixel	64 × 64 pixel
Field of view	192 mm	192 mm	210 mm
Flip angle	90°	90°	90°
TR	2,000 ms	2,000 ms	2,000 ms
TE	30 ms	30 ms	30 ms
Number of slices	30	30	33
Slice thickness	4 mm	4 mm	3 mm
Gap	1 mm	1 mm	1 mm
Slice order	ascending	ascending	ascending
MPRAGE sequence	T_1-weighted	T_1-weighted	T_1-weighted
Resolution	256 × 256 pixel	256 × 256 pixel	256 × 256 pixel
Field of view	256 mm	256 mm	256 mm
TR	2130 ms	2130 ms	2130 ms
TE	2.28 ms	2.28 ms	2.28 ms
Number of slices	192	192	192
Slice thickness	1 mm	1 mm	1 mm

MR, magnetic resonance; EPI, echo-planar imaging; TR, repetition time; TE, echo time.

The counts before observing the first trial in the block were set to one-third for each event type (hence reflecting a discrete uniform distribution) to give a weak influence of the prior. The surprise $I(x_i)$ of each stimulus given by the negative logarithm of stimulus probability quantifies the amount of information provided by the current stimulus

$$I(x_i) = -\ln p(x_i).$$

Finally, entropy $H(X)$ measures the average surprise of all possible outcomes and quantifies the expected information of a stimulus regarding its predictability

$$H(X) = \sum_i -p(x_i) \ln p_k(x_i).$$

Both surprise (or its inverse, probability) and entropy (or its inverse, predictability) quantify the statistical structure of events. While stimulus surprise quantifies the probability of an event as its proportion of the number of all events, the information entropy of a stimulus results from the number of all events and their respective probabilities. Specifically, the probability of a switch or a drift depends on the frequency of its previous occurrence and, hence, reflects how (un-)expected its occurrence was and how much an observer needs to adapt their previously built expectations. Predictability in turn increases when the probability of one event is high while the probabilities of the other stimuli are low; conversely, entropy is high when all possible events are (approximately) equally likely. It determines how precise an observers' expectation can be and can thus vary independently of the absolute probability (Strange et al. 2005).

Using nested generalized logistic mixed-effects models in R, version 3.6.2 (R Core Team 2018) via the package *lme4*, version 1.1.21 (Bates et al. 2015), the probability for dichotomous correct responses, i.e. switch hits and drift rejections, was predicted by Shannon's surprise in interaction with event type (switch vs. drift) and genotype and by Shannon's entropy in interaction with genotype. Two separate models were estimated according to our hypotheses. One model assessed differences between carriers of the A1 allele and noncarriers of the DRD2 polymorphism (A1+ vs. A1−). A second model predicted differences between ValVal, ValMet, and MetMet carriers of the COMT polymorphism. (Note that due to the resulting small group sizes, we refrained from investigating both polymorphisms and their interaction in one model; however, we present the results in the Supplementary Material). We used dummy coding with the A1− genotype and ValVal carriers as reference groups for the factor genotype and drift as the reference group for the factor event type. It was expected that behavioral performance would vary between individual participants on the one hand and between the five different subsamples (I–IV), which included different age groups, healthy controls, and patients with schizophrenia and Parkinson's disease, i.e. diseases associated with dopaminergic disturbances, on the other. Therefore, nested models were fitted that included the subsamples I–IV and the different subjects

within each subsample as random effects to account for this variability in the analysis of genotype differences. Shannon's surprise and entropy, the interaction between surprise, genotype and event type, and the interaction between entropy and genotype were included as fixed effects of interest. Moreover, we controlled for age and gender by including these factors as further fixed effects. We compared different models with different factors as random slopes to ensure that the variance that could be explained by the subsamples and subjects per subsample would not overestimate the fixed effects (Heisig and Schaeffer 2019). We found the best fit for the model including event type and genotype as well as their interaction as random slopes (i.e. formula: correct_response ~ (surprise * event * genotype) + (entropy * genotype) + (event * genotype | subsample/subject), see Supplementary Material for the results of the model comparison). Statistical significance for each fixed effect was calculated via *lmerTest*, version 3.1.1 (Kuznetsova et al. 2017), using the Satterthwaite's approximation to denominator degrees of freedom. Random effects quantifying the variation of the regression intercept and slopes among subsamples and subjects per subsample are presented in the (Supplementary Table S1 and S2). Note that since we included all predictor variables and their interactions in the respective model, the results for the individual groups are not given. However, these can be read from the Figures where we present regression estimates and 95% confidence intervals (CIs) for the individual groups.

FMRI data analysis

Brain image preprocessing and basic statistical analyses were conducted using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; see: http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Individual functional MR (EPI) images were slice-timed to the middle slice and realigned to the mean EPI image. The results of motion correction were checked visually. In addition to the two participants already excluded from the behavioral data analysis, 5 more participants (2 female; 2 A1−; 3 MetMet, 2 ValMet, all from the PD group) were excluded from further analyses because of exceeding a maximum extent of 3-mm head movement between two scans in any degree of freedom. Anatomical scans were coregistered by rigid body transformation to the mean functional image and then segmented into native space tissue components to normalize the subject's functional scans to the MNI template brain. The normalized images were spatially smoothed using a Gaussian kernel of 6-mm^3 full width at half-maximum. Finally, a 128-s temporal high-pass filter was applied.

The statistical analysis was based on a least-squares estimation using the general linear model (GLM) for serially autocorrelated observations (Worsley and Friston 1995). The GLM included three regressors coding for onsets and durations of the specific event types, i.e. standard digits, switches, and drifts, which were then convolved with the canonical hemodynamic response function and regressed against the observed fMRI data. To model variability in the BOLD amplitude as a function of surprise and entropy, two parametric modulators each were added to the switch and the drift regressor, i.e. one for surprise and one for entropy. We mean-centered each of these modulators before entering the GLM. Whenever two trials were separated by less than 2 s (i.e. less than one TR), only the first one was included in the GLM, whereas the second was not modeled and treated as part of the implicit baseline. Likewise, motor control trials and resting periods were not modeled and served as an implicit baseline (Pernet 2014). The subject-specific 6 rigid-body transformations obtained from residual motion correction were included as covariates of no interest.

For each participant, we generated 4 individual statistical maps for variations of BOLD amplitudes with (i) switch surprise, (ii) switch entropy, (iii) drift surprise, and (iv) drift entropy. We performed region of interest (ROI) analyses to test for BOLD activation differences between the groups in the caudate nucleus and the dlPFC. For the ROIs, we identified significant caudate nucleus and dlPFC clusters by calculating a second-level one-sample *t*-test for the main effects of switches and drifts vs. standard digits across all participants at a threshold of $P < 0.05$ FWE-corrected for the caudate nucleus [left: $x = -12$, $y = 5$, $z = 8$, $k = 31$; right: $x = 15$, $y = 5$, $z = 11$, $k = 57$; note that the region was initially masked with an anatomical ROI provided by the AAL atlas (Tzourio-Mazoyer et al. 2002) to separate it from a large activation cluster] and $P < 0.001$ FWE-corrected for the dlPFC [left: $x = -45$, $y = 29$, $z = 32$, $k = 246$; right: $x = 48$, $y = 29$, $z = 23$, $k = 359$]. These clusters were used for further external analyses of genotype differences (see Fallon et al. 2013, performing a similar analysis procedure). A visualization of the ROIs as overlays of the whole-brain results of switch and drift main effects is provided in the (Supplementary Fig. S1). We extracted the surprise and entropy beta scores at switches and drifts per voxel and participant from these ROIs using customized MATLAB scripts. Two linear multilevel models were fit in R via the package *lme4*, one for a prediction of beta estimates of surprise and one for a prediction of beta estimates of entropy. Beta scores of surprise were predicted by event type, genotype, and region as well as their interaction as fixed effects, region, and event type and their interaction as random slopes varying across voxels, and event type and genotype and their interaction as random slopes varying across each subject nested within the subsamples (i.e. formula: betas ~ event type * genotype * region + [event type * region | voxel] + [event type * genotype | subsample/subject]). Beta scores of entropy were predicted by corresponding models, with event type removed as a predictor. Models for each polymorphism (i.e. DRD2 and COMT) were calculated separately. (Results of a model including both polymorphisms can be found in the Supplementary Figs S4 and S5). Statistical significance for each fixed

effect was calculated via *lmerTest* with the Satterthwaite's approximation to denominator degrees of freedom. Random effects of all models are presented in the Supplementary Material. To assess the specificity of our results, we calculated the same analyses using the putamen and supplementary motor area as ROIs (see Supplementary Figs S2 and S3).

Results

DRD2 polymorphism

Behavioral results

Generalized logistic mixed-effects models were used to test whether Shannon's surprise in interaction with event type (i.e. switch vs. drift) and genotype (i.e. A1− vs. A1+) was predictive of the probability of correct responses. Statistics of all main and interaction effects included in the model are provided in Table 4a. No significant main effect of genotype and no interaction between genotype and event type was observed. Crucially, a significant interaction between surprise and event type was found: a higher probability of switch hits accompanied increasing switch surprise (H1), whereas, as opposed to our hypothesis H2, increasing probability for drift rejections did not accompany increasing drift probability. Moreover, we observed a significant interaction between surprise, event type, and genotype (Fig. 2a). In line with H3, the correlation between switch hits and switch surprise was more pronounced in noncarriers (A1−) than in carriers of the A1 allele (A1+). Low surprise (i.e. high probability) of switches came with an increased probability of missing switches in both groups; however, the performance of A1 carriers did not decline to the same extent as for noncarriers, resulting in a comparable performance at low switch surprise. In contrast, contrary to our hypothesis H4, high surprise at drifts led to a higher probability of drift rejection in A1 carriers and a higher probability for false alarms in noncarriers than low surprise. A main effect of entropy was observed, with increasing entropy being accompanied by a higher probability of false responses (i.e. both misses and false alarms), while no interaction between entropy and genotype was found (Fig. 2b).

FMRI results

Linear multilevel models were employed to test the hypothesis that Shannon's surprise at switches and drifts modulated the BOLD response in the caudate nucleus and dlPFC differently in noncarriers (A1−) vs. carriers (A1+) (Table 4b). We found a significant interaction between event type and region, which, however, did only partly correspond with our hypotheses. In line with H1, we found a positive correlation between switch surprise and caudate nucleus, which was, however, not specific to this region. Rather, a positive correlation with dlPFC activity could also be observed. For drifts, there was only a weak nonsignificant correlation of dlPFC activity with drift probability as indicated in H2.

Although we found a significant 3-way interaction between genotype, event type, and region, the differences between the genotypes only partly corresponded to our hypotheses (Fig. 2c). Increasing switch surprise came with increased caudate activity in both A1 carriers and noncarriers; thus, contrary to H3, the correlation was not stronger in noncarriers. Interestingly, noncarriers showed significant increased dlPFC response for increased switch surprise, whereas A1 carriers showed a negative correlation of dlPFC activity with switch surprise (and thus, a positive correlation with switch probability).

As for drifts, the probability did not correlate more with dlPFC activity in neither group, as assumed in H4. BOLD responses were less pronounced and only small differences between the groups were observed, with a more positive correlation of caudate activity with drift surprise in A1 noncarriers vs. carriers and a more positive correlation of dlPFC activity with drift probability in A1 carriers vs. noncarriers.

Regarding a modulation of activity by entropy independent of event type, we did not find a significant interaction between genotype and region (Fig. 2d).

COMT polymorphism

Behavioral results

The results of the generalized logistic mixed-effects model, which was used to test whether Shannon's surprise in interaction with event type (switch, drift) and COMT genotype (MetMet, ValMet, and ValVal) was predictive of the probability of correct responses, are displayed in Table 5a. We found a significant 3-way interaction between event type, surprise, and genotype (Fig. 3a). While in all three groups the probability for switch hits increased as a function of surprise, this effect was strongest for ValMet subjects and weakest for MetMet subjects (H3). Furthermore, ValMet subjects showed the expected behavior about drifts: the probability for drift rejections increased with increasing drift probability, while the other two groups showed the opposite pattern, i.e. an increasing drift rejection rate as a function of surprise (H4). No interaction effect with entropy was observed (Fig. 3b).

FMRI results

Linear multilevel models were employed to test the hypothesis that Shannon's surprise at switches and drifts differentially modulated the BOLD response in the caudate nucleus and dlPFC in the three COMT groups. We found a significant interaction between genotype, event type, and region, which only partially corresponds to the hypothesized activity pattern (Table 5b, Fig. 3c). As expected, a stronger positive correlation of switch surprise with activity in the caudate nucleus was observed in ValVal vs. MetMet carriers (H3), which was, however,

Table 4. Behavioral and fMRI results: DRD2 polymorphism.

Regression Coefficients	*b*	SE	l-95% CI	u-95% CI	z	P
a) Logistic multilevel model predicting probability of correct responses						
Age	-0.02	0.00	-0.03	-0.01	-3.42	<0.001
Gender: Female	-0.07	0.10	-0.27	0.14	-0.65	0.514
Surprise	-0.09	0.09	-0.26	0.08	-1.02	0.312
DRD2: A1+	-0.89	0.50	-1.87	0.10	-1.77	0.077
Event: Switch	-1.84	0.26	-2.35	-1.33	-7.07	<0.001
Entropy	-1.71	0.27	-2.23	-1.19	-6.42	<0.001
Surprise × DRD2: A1+	0.17	0.13	-0.08	0.42	1.32	0.187
Surprise × Event: Switch	0.40	0.10	0.20	0.59	4.01	<0.001
DRD2: A1+ × Event: Switch	-0.64	0.37	-0.09	1.36	1.72	0.085
DRD2: A1+ × Entropy	0.58	0.39	-0.18	1.34	1.49	0.135
Surprise × Event: Switch × DRD2: A1+	-0.32	0.14	-0.60	-0.04	-2.25	0.024
b) Linear multilevel model predicting neural activity modulated by Shannon's surprise						
Age	0.00	0.00	-0.01	0.01	-0.51	0.614
Gender: Female	-1.76	0.17	-0.51	0.16	-1.03	0.305
DRD2: A1+	-0.08	0.35	-0.77	0.60	-0.24	0.811
Event: Switch	0.19	0.43	-0.65	1.04	0.45	0.663
Region: dlPFC	-0.23	0.03	-0.28	-0.17	-8.17	<0.001
DRD2: A1+ × Event: Switch	0.17	0.61	-1.01	1.36	0.29	0.777
DRD2: A1+ × Region: dlPFC	-0.04	0.04	-0.13	0.04	-1.00	0.317
Event: Switch × Region: dlPFC	0.19	0.04	0.11	0.27	4.80	<0.001
DRD2: A1+ × Event: Switch × Region: dlPFC	-0.67	0.06	-0.78	-0.55	-11.27	<0.001
c) Linear multilevel model predicting neural activity modulated by Shannon's entropy						
Age	-0.01	0.03	-0.07	0.04	-0.46	0.649
Gender: Female	0.02	0.91	-1.76	1.80	0.02	0.982
DRD2: A1+	0.33	1.16	-1.94	2.60	0.29	0.786
Region: dlPFC	2.10	0.09	1.91	2.29	22.21	<0.001
DRD2: A1+ × Region: dlPFC	-0.40	0.14	-0.68	0.12	-2.83	0.062

also found for the dlPFC: here, the positive correlation with switch surprise in Val homozygotes differed from a rather negative correlation with dlPFC activity in Met homozygotes. Unexpectedly, a positive (vs. zero to negative) correlation of drift surprise with caudate activity was observed in MetMet vs. ValVal carriers. In comparisons between ValVal carriers and ValMet carriers, there was a higher correlation of switch surprise with caudate activity in ValMet carriers, which was significantly different from a higher correlation of switch surprise with dlPFC activity in ValVal carriers, whereas no differences between the groups were observed at drifts.

With respect to a modulation of activity by entropy independent of event type, significant interactions between region and genotype were observed in comparisons of ValMet with ValVal and of MetMet with ValVal carriers. As Fig. 3d shows, these effects were driven by a positive correlation of dlPFC activity with entropy in ValVal carriers (compared with no correlation in Met carriers), while negative correlations of entropy and caudate activity were observed in all three groups that were highest in ValMet and lowest in MetMet subjects.

Discussion

In the present study, we examined the influence of the COMT and the DRD2 polymorphisms on flexibility and stability, testing the former in terms of flexible detection of switches between predictive models and the latter in terms of successful ignoring of model-uncritical drifts in predictable digit sequences. As a premise, we assumed that flexibility reflects a high precision-weighting of prediction errors signaling changes, which should be associated with increased hit rate and caudate response to surprising switches (H1), whereas stability implies a high weighting of predictions against distraction, which should be reflected in increasing drift rejection rate and dlPFC activity with increasing drift probability (H2).

Our results show that unexpected events that differ both in the level of surprise and in their behavioral implications lead to different behavioral and neural activity patterns. While drift surprise only weakly modulated behavior and neuronal responses, switch surprise showed a differential effect on caudate and dlPFC activity. Specifically, a positive correlation of switch surprise with caudate activity differed significantly from a negative correlation of switch surprise with dlPFC activity. These data do not support the assumption of a neuroanatomical double dissociation of switch surprise and drift probability contributing to flexibility and stability, respectively. Rather, the regional specificity of the dlPFC and caudate nucleus arises from their different functional roles in weighting predictions or prediction errors, but only if the latter are longer term and behaviorally relevant.

A similarly mixed picture emerged regarding differences between the dopamine-relevant genotypes we considered. Our sample included different populations

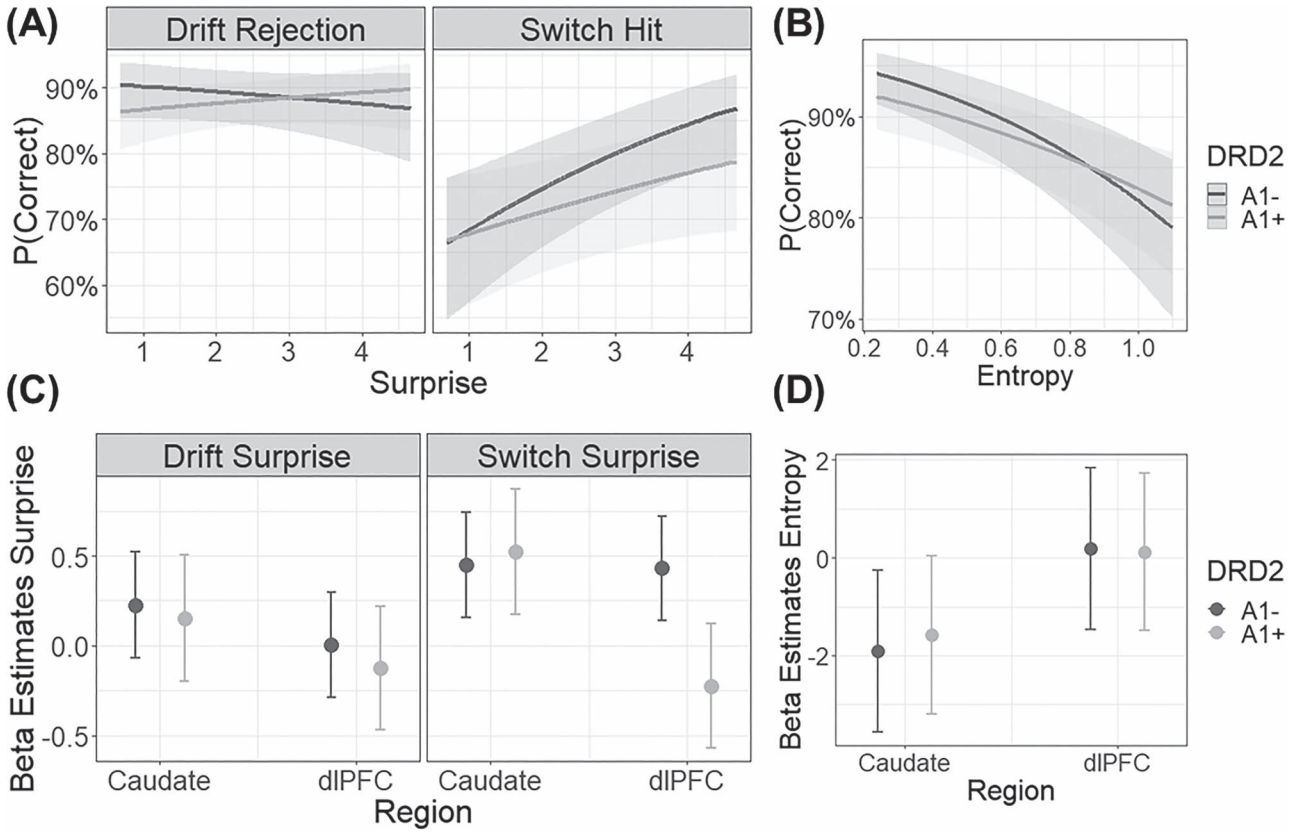

Fig. 2. Behavioral (top panel) and fMRI effects (lower panel) of the DRD2 polymorphism. The lines and shaded areas represent regression estimates and 95% CIs for the probability that participants of the two genotypes (A1− vs. A1+) make a) a correct rejection (left) and a hit (right) as a function of Shannon's surprise at drifts and switches, respectively, and b) make a correct response independent of the event type as a function of Shannon's entropy. The lower panel represents mean beta estimates and 95% CIs for the two genotypes reflecting BOLD response in the caudate nucleus and dlPFC as a function of c) Shannon's surprise at drifts (left) and switches (right) and d) of Shannon's entropy independent of event type.

with different ages and likely different disease-specific baseline dopamine levels. Still, we found that the respective genotypes significantly differed in behavior and BOLD responses to the different probability (inverse "surprise") and predictability (inverse "entropy") of the stimuli when we controlled for the variation among the different samples. With respect to the DRD2 of polymorphism, we found that the performance A1 noncarriers differed from that of A1 carriers at both switches and drifts as a function of surprise. In line with our assumption that noncarriers show a higher flexibility (H3), they detected significantly more switches when switch surprise was high but—contrary to our hypothesis H4—also made more false alarms when drift surprise was high. Thus, for A1 noncarriers, increasing surprise was associated with a higher response rate to unexpected events, whether these were required (as for switches) or not (as for drifts). A1 carriers missed more switches when switch surprise was high but performed comparably to noncarriers when switch surprise was low. In contrast, they correctly rejected more drifts when drift surprise was high vs. low and thus showed a relatively higher response threshold at high surprise of event occurrence. Interestingly, the lower response threshold of A1 noncarriers was accompanied by a surprise-related increase in the activity of the caudate nucleus (H3) but, unexpectedly, also of the dlPFC. Crucially, a positive correlation of switch surprise with caudate activity, but a rather negative correlation of switch surprise with dlPFC activity, was found in A1 subjects, whereas the expected positive correlation with drift probability (H4) was not found within this group.

Our findings contribute to a series of heterogenous results on differences between the two genotypes in many cognitive processes. On the one hand, studies found that noncarriers of the A1 allele perform better on reversal learning (Jocham et al. 2009), working memory updating (Berryhill et al. 2013; Persson et al. 2015), and probabilistic learning from errors (Klein et al. 2007). On the other hand, A1 carriers have been shown to outperform noncarriers on goal maintenance (Persson and Stenfors 2018) and task switching, a standard measure of cognitive flexibility (Stelzel et al. 2010; Furman et al. 2020). This latter finding is explained by the possibility that the reduced D2R density in A1 carriers leads to enhanced dopamine synthesis due to strengthened dopamine transmission via D1Rs (Laakso et al. 2005). So far, however, it remains unclear whether the reduced density is associated with higher or lower dopamine availability. Consistent with these conflicting findings, a recent meta-analysis by Klaus et al. (2019) found no significant results for the

Table 5. Behavioral and fMRI results: COMT polymorphism.

Regression Coefficients	*b*	SE	l-95% CI	u-95% CI	z	P
a) Logistic multilevel model predicting probability of correct responses						
Age	-0.02	0.00	-0.03	-0.00	-3.46	<0.001
Gender: Female	-0.02	0.11	-0.23	0.18	-0.23	0.821
Surprise	0.13	0.15	-0.16	0.42	0.86	0.392
COMT: ValMet	0.78	0.67	-0.53	2.09	1.71	0.242
COMT: MetMet	-0.83	0.72	-2.25	0.59	-1.15	0.251
Event: Switch	-1.16	0.42	-1.98	-0.35	-2.80	0.005
Entropy	-1.67	0.44	-2.54	-0.81	-3.79	<0.001
Surprise × COMT: ValMet	-0.28	0.18	-0.63	0.06	-1.63	0.104
Surprise × COMT: MetMet	0.03	0.19	-0.35	0.41	0.15	0.880
Surprise × Event: Switch	0.08	0.16	-0.24	0.39	0.46	0.643
COMT: ValMet × Event: Switch	-0.85	0.51	-1.84	0.14	-1.68	0.093
COMT: MetMet × Event: Switch	0.19	0.54	-0.88	1.25	0.34	0.731
Entropy × COMT: ValMet	0.18	0.52	-1.20	0.85	-0.34	0.736
Entropy × COMT: MetMet	0.93	0.57	-0.20	2.05	1.61	0.107
Surprise × Event: Switch × COMT: ValMet	0.39	0.19	0.01	0.79	2.02	0.043
Surprise × Event: Switch × COMT: MetMet	-0.12	0.21	-0.53	0.29	-0.58	0.561
b) Linear multilevel model predicting neural activity modulated by Shannon's surprise						
Age	-0.00	0.00	-0.01	0.01	-0.47	0.641
Gender: Female	0.06	0.14	-0.21	0.34	0.43	0.668
COMT: ValMet	0.30	0.67	-1.02	1.61	0.44	0.676
COMT: MetMet	1.01	0.56	0.00	2.20	1.96	0.065
Event: Switch	0.75	0.75	-0.71	2.22	1.01	0.347
Region: dlPFC	-0.10	0.05	-0.19	-0.01	-2.25	0.025
COMT: ValMet × Event: Switch	0.09	0.09	-1.80	1.63	-0.10	0.924
COMT: MetMet × Event: Switch	-1.49	0.10	-3.43	0.45	-1.51	0.151
COMT: ValMet × Region: dlPFC	0.16	0.05	0.05	0.27	2.94	0.003
COMT: MetMet × Region: dlPFC	-0.88	0.06	-1.00	-0.76	-14.39	<0.001
Event: Switch × Region: dlPFC	0.35	0.06	0.22	0.47	5.48	<0.001
COMT: ValMet × Event: Switch × Region: dlPFC	-0.85	0.08	-1.00	-0.70	-11.23	<0.001
COMT: MetMet × Event: Switch × Region: dlPFC	-1.76	0.09	-0.34	-0.01	-2.05	0.040
c) Linear multilevel model predicting neural activity modulated by Shannon's entropy						
Age	-0.01	0.03	-0.06	0.04	-0.54	0.610
Gender: Female	-0.27	0.81	-1.86	1.33	-0.33	0.742
COMT: ValMet	-0.73	1.02	-2.72	1.27	-0.72	0.494
COMT: MetMet	0.74	1.51	-2.21	3.69	0.49	0.627
Region: dlPFC	2.97	0.15	2.67	3.27	19.47	<0.001
COMT: ValMet × Region: dlPFC	-1.13	0.18	-1.49	-0.78	-6.20	<0.001
COMT: MetMet × Region: dlPFC	-1.89	0.21	-2.29	-1.48	-9.12	<0.001

DRD2 gene involvement in flexible behavior (see also Zmigrod and Robbins 2021). One reason for this could be the various operationalization approaches of flexibility within the different studies. Tasks that examine cognitive flexibility typically consist of a range of subfunctions in which the genotypes can differ (Cools and D'Esposito 2011). For example, Markett et al. (2011) found that the superior performance of A1 carriers in task switching was due to a greater backward inhibition effect. They updated more efficiently because they were better able to inhibit task sets that were no longer relevant, i.e. they were more stable against distractors.

Employing the relatively simple task of either ignoring or detecting deviant stimuli in a predictable digit sequence, our study extends previous findings by showing that unexpectedness of task-critical events may explain some of the behavioral and neural response differences between A1 carriers and noncarriers. Against the background of the findings mentioned above, it is conceivable that A1 noncarriers outperform A1 carriers at highly surprising switches because these require a fast bottom-up mediated detection of salient events rather than a top-down mediated inhibition of the no-longer-valid predictive models. As the probability of switches increases, so does the requirement to switch between different models by rapidly inhibiting the previous model in order to adjust and stabilize the revised prediction as fast as possible. While A1 noncarriers may be better at the former function (i.e. detecting unexpected events), A1 carriers may be better at the latter (i.e. stabilizing the new model by inhibiting the old one). In this way, as the probability of switching increases, the performance of A1 carriers does not decline to the same extent as for noncarriers. In line with this interpretation, A1 noncarriers also reacted to irrelevant surprising events but learned to ignore them the more frequent and, thus, the less salient they became. In contrast, when disruptive stimuli become more frequent, A1 carriers tended to have more difficulty maintaining the currently valid model.

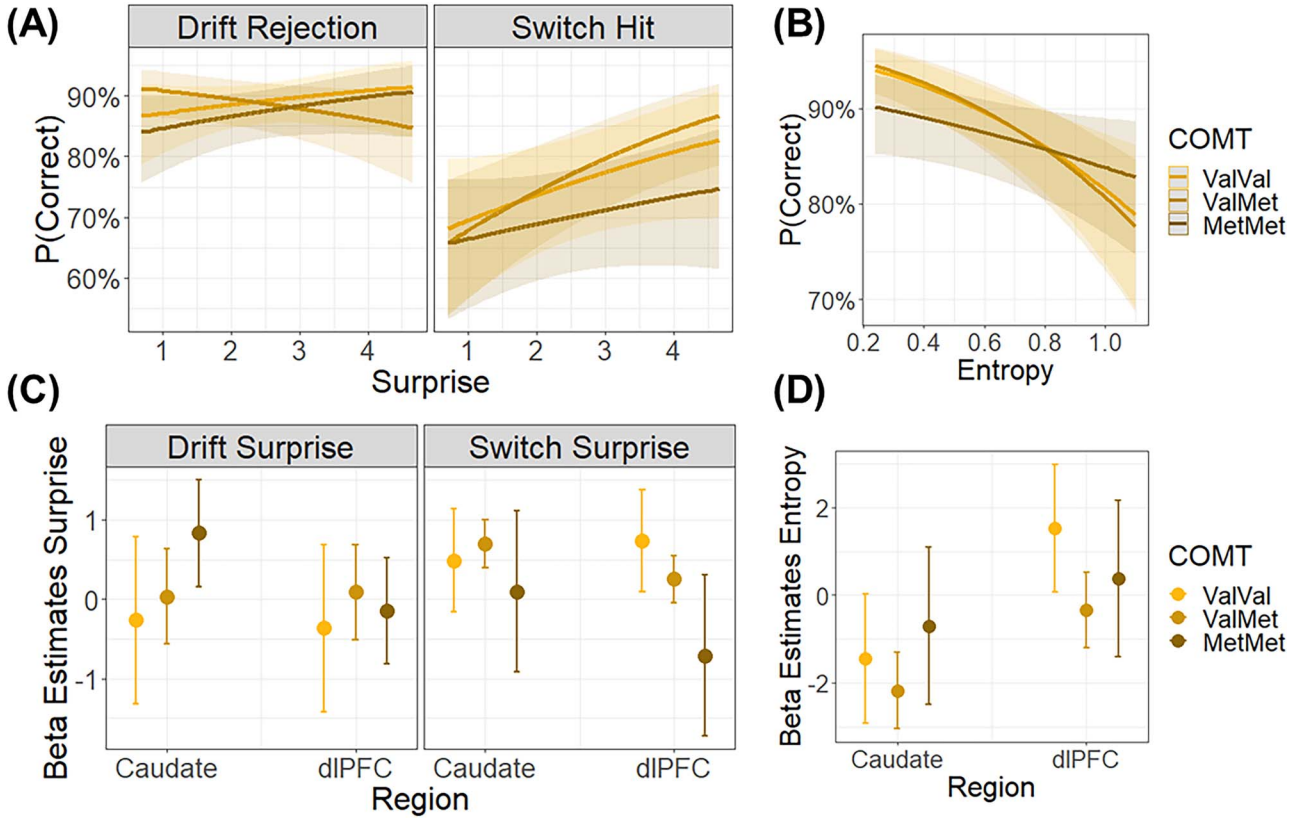

Fig. 3. Behavioral (top panel) and fMRI effects (lower panel) of the COMT polymorphism. The lines and shaded areas represent regression estimates and 95% CIs for the probability that participants of the two genotypes (ValVal vs. ValMet vs. MetMet) make a) a correct rejection (left) and a hit (right) as a function of Shannon's surprise at drifts and switches, respectively, and b) make a correct response independent of the event type as a function of Shannon's entropy. The lower panel represents mean beta estimates and 95% CIs for the two genotypes reflecting BOLD response in the caudate nucleus and dlPFC as a function of c) Shannon's surprise at drifts (left) and switches (right) and d) of Shannon's entropy independent of event type.

The neural activation pattern partially supports this interpretation. We found that in A1 noncarriers, detection of unexpected events (whether switches or drifts) was accompanied by activation in the caudate nucleus, but there was an additional increase in dlPFC activity only for switches. In A1 carriers compared with noncarriers, there was a comparable positive correlation of switch surprise with the caudate nucleus but a negative correlation with the dlPFC, meaning that activation increased as the event became more probable.

Our finding supports the view that A1 carriers and noncarriers use different strategies for switching between tasks or internal models (Stelzel et al. 2010). Dorsolateral PFC activity that increases as a function of switch probability might reflect a state during which A1 carriers keep multiple internal models (or precise predictions) in an activated state to be able to switch between them. In contrast, surprise-related dlPFC activity in A1 noncarriers reflects highly precise prediction errors that provide gating signals to update internal models. We can only speculate that these strategies correspond with tonic D1R vs. phasic D2R activation states and that A1 carriers tend to be in the D1R state (probably due to compensatory dopamine transmission via D1Rs), whereas noncarriers are more likely to be in the D2R state.

With a view to the COMT polymorphism, we found in line with hypothesis H3 that Val carriers, especially Val-Met heterozygotes, outperformed MetMet homozygotes at high switch surprise. MetMet carriers showed a higher miss rate than the other groups at highly surprising switches, but as the switch probability increased, their performance matched that of Val carriers. In contrast to what was expected in H4, not the MetMet carriers but the ValMet carriers showed a higher drift rejection, i.e. higher stabilization, with increasing drift probability, whereas homozygotes showed a higher rejection rate with increasing drift surprise. Just as for the DRD2 genotype, previous studies regarding the contribution of the COMT gene to different cognitive functions provide a mosaic of findings, with higher cognitive performance either for the Val homozygotes or for the Met homozygotes, depending on the process under study. Overall, it appears that Met allele carriers show better stabilization of working memory in delay or inhibition tasks (Rosa et al. 2010; Farrell et al. 2012; Mione et al. 2015). Instead, Val allele carriers are better at tasks requiring updating and learning (Krugel et al. 2009; Bellander et al. 2015). Crucially, Bonetti et al. (2021) noticed that the ValMet carriers were sometimes assigned to the Val and sometimes to the Met homozygotes, and apparently the group to which they were assigned usually showed the better

performance in the end. In their own MEG study, the authors found a significant amplitude enhancement of prediction error responses in ValMet carriers compared with homozygotes. Our results further suggest that a more robust surprise signal of the ValMet heterozygotes goes along with a decreased response threshold to both to-be-detected and to-be-ignored stimuli.

These findings can be interpreted against the background of the inverted U-shape hypothesis, by which both deficient and excessive levels of dopamine in the PFC predict poor performance on working memory tasks (Cools and D'Esposito 2011). It is suggested that an optimal dopamine availability in the PFC may result from the moderate COMT enzyme activity of the ValMet genotype so that heterozygotes are near the apex of the inverted U-shaped response curve, while ValVal and MetMet are at the bottom and top of the curve, due to high and low dopaminergic metabolism, respectively. Notably, in our study, the modulation of dlPFC activity by surprise was actually lowest in ValMet subjects (i.e. correlations were close to zero), while a robust switch-specific surprise signal was found in the caudate nucleus within this group, as expected in H3. ValVal homozygotes, however, showed lower positive correlations in the caudate but an unexpected high switch-surprise response in the dlPFC, likely reflecting bottom-up gating and updating in response to highly unpredictable sequential changes. In contrast, just like A1 carriers, MetMet homozygotes appeared to be successful in switch detection by maintaining and switching between the different internal models, which was reflected by increased activity in dlPFC as a function of increasing switch probability (while no correlation with caudate activity could be observed). Thus, our findings provide evidence for different strategies in dealing with sensory input that requires prediction adaptation in ValVal and MetMet homozygotes, as also neuronally reflected in a different activity pattern in the dlPFC.

In contrast, H4 could not be confirmed insofar as for drifts, the modulation of activation by surprise was overall low. Here, a nonhypothesized positive correlation of caudate activation with drift surprise was particularly striking in MetMet subjects. Previous studies found that, in addition to beneficial PFC performance, the Met allele is associated with higher activity in limbic regions in response to unpleasant stimuli (Drabant et al. 2006) and with stronger anxiety and pain states (Enoch et al. 2003; Zubieta et al. 2003). It is therefore possible that the increased caudate activity to surprising drifts represents a heightened responsivity to aversive disruptive stimuli.

As the COMT enzyme has a primary influence on dopamine availability in the PFC and not in the striatum, caudate responses to surprising events could reflect prefrontal modulation of the striatum during anticipatory action and learning. Recent models suggest that the striatum does not only contribute to input-gating of relevant information to update PFC representations but also to output-gating, that is selecting one out of various representations for top-down processing (e.g. for attention modulation or motor response selection) (Chatham and Badre 2015; Rac-Lubashevsky and Frank 2020; see also Cools 2019, for a thorough review). Evidence for output-gating comes from a series of fMRI studies using a face-scene discrimination task requiring attentional switching between the two stimulus dimensions (van Schouwenburg et al. 2010, 2015). Here, the striatal activity appeared to control whether the PFC selectively enhanced stimulus-specific processing of either faces or places in posterior areas. Moreover, the COMT polymorphism was found to modulate striatal responses and changes in effective connectivity between the striatum and the PFC as a function of learning from prediction errors (Krugel et al. 2009). The present results suggest that differential dopamine levels in the PFC may lead to differences in striatal signaling in response to unexpected events that require either updating or stabilizing of internal models, and initiation or suppression of a motor response. This interpretation is supported by our additional finding of an activation pattern in the putamen and the SMA, i.e. regions typically associated with overt behavior, that was similar to the pattern observed in the caudate nucleus (see Supplementary Material).

Finally, we explored the modulation of behavioral and neural responses by stimulus entropy. Here, we found that behavioral performance in all groups decreased as a function of increasing entropy. Effects of differences between genotypes were found for the COMT polymorphism, but only on BOLD responses, not on behavior. While in all groups a rather negative correlation of entropy with caudate activity was observed (which was highest in ValMet carriers and lowest in MetMet carriers), there was a positive correlation of entropy with dlPFC activity (which was highest in ValVal carriers). Hence, dissociable effects of dopaminergic polymorphisms on frontal and striatal activity also became evident with changing environmental volatility.

Learning strategies are adjusted to the volatility of the environment, whereby learning rates typically increase in volatile environments (Behrens et al. 2007). It is suggested that higher learning rates are based on short time-scale information stored in working memory associated with activity in a dorsal frontoparietal network. In contrast, a lower learning rate based on longer time-scale information is associated with frontostriatal activity (Summerfield et al. 2011). In our experiment, switches and drifts occurred both equally frequently and very frequently in blocks with the highest entropy and required a particularly increased need for control and a memory-based strategy that can be assigned to increased dlPFC activity (Jiang et al. 2015). We suggest that in our study, Val homozygotes could achieve the same level of performance in a volatile situation, but only by compensating for its disadvantage with higher prefrontal engagement. Previous studies found a comparable performance between the COMT genotypes on working memory tasks

but increased prefrontal activity of Val vs. Met carriers (Caldú et al. 2007). Accordingly, increased entropy-related dlPFC activity in Val homozygotes as found in the present study could reflect increased costs for frequent and unexpectable alternating between ignoring drifts and detecting switches. In contrast, the increasing activity of the caudate with increasing predictability, which was highest in ValMet and lowest in MetMet carriers, may reflect the attempt to apply a higher order learning strategy as the environment becomes more predictable and stable. Thus, since dopamine has been found to play a role in such meta-learning (Cook et al. 2019), future studies could explicitly address the question of whether and how genetic polymorphisms associated with dopaminergic signaling in the striatum and the PFC contribute to differential learning strategies in stable vs. volatile environments.

Lastly, it should be noted that our sample was highly heterogenous, including participants from different age groups and patients with Parkinson's disease and schizophrenia. Due to the critical role of dopamine in the aging process and especially in the pathogenesis of the two diseases, the polymorphisms were found to have a different influence in older vs. younger subjects and patients vs. healthy controls (Ceaser et al. 2013; Fallon et al. 2013; Li et al. 2019). Accordingly, in our previous works with the same subsamples but without considering genotype effects, we found that healthy controls differed from patients with Parkinson's disease (Trempler et al. 2018; 2019) and patients with schizophrenia (Standke et al. 2021) when performing the switch-drift paradigm on the behavioral as well as neural level. Consistent with the assumption that several neuropsychiatric disorders are accompanied by impaired precision-weighting of prediction errors (Friston 2017), both groups showed difficulties in discriminating switches and drifts and this deficit was associated with a striatal hypoactivation. In the present study, we modeled the specific genotype effects that vary between samples and individuals, so that it can be assumed that our sampling resulted in relatively high external validity of the resulting fixed effects of genotypes. However, we cannot rule out that it is conceivable that effects other than those reported here may be observed in the respective subpopulations meaning that there might be interaction effects of genotype and disease (Fallon et al. 2013). Also, given the complex analyses including 3-way interaction effects that only partially corresponded to our hypotheses, the current findings need to be validated in future studies with a greater and more homogenous sample.

In summary, the present study provides first evidence that dopaminergic polymorphisms significantly influence how effective individuals update and stabilize internal models in response to stimuli of variable probability in volatile situations. Our findings deepen the understanding of behavioral costs and benefits of genetic variations influencing the dopamine system in the PFC and the striatum. Our results highlight the role of dopamine in adaptive learning, where statistical regularities can determine the precision of sensory input. Given the mixed evidence on the contribution of dopamine-associated genotypes to different cognitive functions, our results indicate that this role should be taken into account when interpreting relevant findings.

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Supplementary material

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