



Cerebral and behavioral signs of impaired cognitive flexibility and stability in schizophrenia spectrum disorders

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ABSTRACT

Background: Manifold cognitive deficits have been reported in schizophrenia spectrum disorders, including disturbances in flexible updating to altered circumstances as well as stabilization deficits in the face of distractors. In this functional magnetic resonance imaging study, we examined the neural correlates of these deficits as two complementary components of predictive processing.

Methods: In 22 patients with schizophrenia spectrum disorders and 22 healthy matched control participants, we applied a serial predictive switch-drift task to assess flexibility as successful detection of prediction-rule switches, and stability as successfully ignoring distractors (“drifts”).

Results: Patients compared with controls less reliably detected rule switches and also less efficiently inhibited drifts. A reduced striatal response to switches or drifts correlated with weaker switch-drift-discrimination in patients, suggesting impaired gating of prediction errors. The increase in activity in anterior cingulate cortex and hippocampus for detected vs. undetected switches was reduced in patients compared to controls, which may reflect impaired behavioral adaptation following prediction errors. The comparison between shielding against distractions and undetected switches showed increased activity in the inferior frontal cortex and posterior insula in controls but not in patients.

Conclusion: Our results suggest new insights into the specific disruption of predictive flexibility and stability in schizophrenia spectrum disorders, which is characterized by impaired striatal gating and inadequate cortical encoding of predictive errors.

1. Introduction

Cognitive deficits are considered a core feature of schizophrenia spectrum disorders, and many of them are associated with impaired behavioral and cognitive control (Boudewyn et al. 2012; Lesh et al. 2011; Ragland et al. 2009; Cohen et al. 1999; Barch and Ceaser 2012). This capability is expressed in an effective balance between two components: *cognitive flexibility*, which enables behavioral and attentional

adjustments, and *cognitive stability*, top-down inhibition of distraction (Cools 2016; Duncan 2001). The balance between flexibility and stability, i.e. the rapid discrimination between stimuli that should attract our attention and those that should be ignored, is a complex mechanism that is subject of ongoing research.

One candidate for cerebral implementation of this balance is the dopaminergic regulation of excitation and inhibition within fronto-striatal loops. It is assumed that these loops have a gating function,

Abbreviations: NSS, Heidelberg Scale for Neurological Soft Signs (Schröder et al., 1991); BACS, Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004); BIS, Barratt Impulsiveness Scale (Patton et al., 1995); BDI-II, Becks Depression Inventory-II (Beck et al., 1996); SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984a); SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1984b); CPZ, chlorpromazine equivalents (Andreasen et al., 2010); RT, reaction time; MC, motor control; Swi, switches; Dri, drifts; H, hits at switches; CR, correct rejections of drifts; M, misses of switches; FA, false alarms at drifts; P_d , discrimination index; B_r , response bias; SD, standard deviation.

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due to which only the currently relevant information is passed on to the frontal lobes (Miller and Cohen 2001; Badre 2012; Chatham et al. 2014; Chatham and Badre 2015; Frank et al. 2001; Gruber et al. 2006). The concept of predictive coding (Clark 2013) explains the regulation of this gating by means of so-called precision (or neural amplification), which flexibly determines the respective influence of sensory prediction (top down) and prediction error (bottom up). Correspondingly, the failure of gating regulation is considered an aberrant precision in various psychiatric diseases (Friston, 2017), including schizophrenia spectrum disorders (Friston et al., 2016). Consequently, impaired attribution of precision could account for deficits in both areas: the flexible updating of predictions associated with the frontomedian cortex (Floresco et al. 2009; Krawitz et al. 2011; Reinhart et al. 2015) and the stability against distraction relying on the lateral prefrontal cortex (Ceaser and Barch 2016; Kim et al. 2015; Anticevic et al. 2012; Kaladjian et al. 2011). Both frontal regions are informed by striatal gating of prediction errors (Chatham and Badre, 2015; Haber, 2016; Trempler et al., 2017). During the ensuing output gating, frontal areas project back to the striatum, mediating whether or not the behavior is adapted (Badre, 2012). Flexibility and stability of prediction thus share some processes, while they differ in others (Hedden and Gabrieli, 2015; Armbruster et al. 2012). Still, it remains to be clarified how unexpected events that require behavioral adaption are discriminated from those that require stabilization of the predictive model, and how exactly cognitive flexibility and stability are coordinated and implemented in the brain. Moreover, the two functions have not yet been directly compared in the same group of patients with schizophrenia spectrum disorders, but only in separate studies unrelated to predictive processing.

The fMRI study reported here aimed to investigate the extent of altered cognitive flexibility and stability in schizophrenia spectrum disorders and its associations with key brain systems known to be involved in dopaminergic transmission. We used a newly designed serial switch-drift paradigm, which we recently used to demonstrate impaired flexibility and stability in patients with Parkinson's disease (Trempler et al. 2018). In this task, participants track sequences of digits to indicate the occurrence of sequential rule switches that provoke an adjustment of current predictions, while at the same time omissions of single digits ("drifts") must be ignored. This two-dimensional operationalization allows flexibility and stability of prediction to be measured as potentially independent functions. Here, one dimension ranges from highly flexible to inflexible behavior, reflected by the rate of switch hits and misses, respectively. The other dimension ranges from highly stable to unstable behavior towards distractors, reflected by the rate of drift rejections and false alarms, respectively. Studies in healthy participants indicate that these functions represent two separable and not functionally opposed processes, with flexibility of prediction reflected in medial prefrontal activity, and stability of prediction in lateral prefrontal activity (Trempler et al. 2017).

In the study of patients with schizophrenia spectrum disorders and healthy controls using the serial switch-drift paradigm mentioned above, we tested the following hypotheses.

First, patients are impaired in flexibility and stability of prediction, so that they show lower rates of switch detection (Everett et al. 2001; Prentice et al. 2008) and drift rejection (Westerhausen et al. 2011; Lipszyc and Schacher 2010) than healthy controls (H1).

Second, in comparison to healthy controls, patients show a reduced activation of the striatum in response to both switches and drifts, and this reduction is systematically related to poorer discrimination between switches and drifts, reflecting a gating failure in patients (Gradin et al. 2011; Maia and Frank 2017) (H2).

Third, in comparison to healthy controls, patients show a decreased medial prefrontal activity for switches (Floresco et al. 2009; Krawitz et al. 2011; Reinhart et al. 2015) and a decreased lateral prefrontal cortex activity in response to drifts (Ceaser and Barch 2016; Kim et al. 2015; Anticevic et al. 2012; Kaladjian et al. 2011) (H3).

2. Materials and methods

2.1. Participants

Twenty-five patients (8 females) diagnosed with schizophrenia or a schizoaffective disorder were recruited at the Department of Mental Health at the University Hospital Muenster. Diagnoses were determined at consensus conferences using all available clinical data including assessments on the Structured Clinical Interview I (SCID-I) for DSM-IV (American Psychological Association, 1994). Moreover, 23 healthy controls (9 females) were recruited after exclusion of any psychiatric disorder using a short-form SCID-I interview and any known history of psychotic disorders in first-degree relatives. In total, four participants (3 patients (1 female) and 1 healthy control (male)) were excluded because of either structural aberrancies or excessive head motion throughout the experiment. Thus, a total number of twenty-two patients and twenty-two healthy controls entered further analyses. The local ethics committee of the University of Muenster accorded to the study procedures conforming with the Helsinki Declaration. All participants provided signed informed consent and were compensated for their participation in form of reimbursement or course credits.

2.2. Stimuli and task

We used a serial switch-drift paradigm (Trempler et al. 2017), which consists of a predictable sequence of four consecutive digits (see Fig. 1). The digits were presented for 1 s separated by a 100 ms inter-stimulus interval. At variable positions in the sequence, the following three unexpected events could occur that disrupted the predicted succession of digits: First, there could be a reversal of direction, so that an ascending sequence changed to a descending sequence or vice versa. These switches required a flexible adjustment of the internal prediction model, which was to be indicated by a key press. Second, a digit could be skipped without changing the (ascending or descending) direction of the sequence. These omissions, called drifts, required the shielding of the currently valid internal prediction model and should not be indicated by keystroke. Third, a single digit could be presented repeatedly. Participants were instructed to respond with a key press as soon as there was a repetition. The digit was repeated until the participants answered or, in case they did not, up to eight times. These motor control trials ($n = 25$) were needed to calculate individual reaction time windows (RT) to decide whether a subject's key press was a reaction to an expected or an unexpected event (switches or drifts).

The task was subdivided into 12 blocks of 125 digits each on average combining high and low probabilities of switches and drifts in a 2x2 full-factorial design. The stochastic universal sampling method allowed a balanced distribution of the different types of events throughout the experiment (Baker 1987). The six-second presentation of a fixation cross between the blocks served as the baseline (resting) trial. The randomization was programmed using MATLAB R2012b (The MathWorks Inc., Natick, MA, USA) and stimuli were presented using Presentation 18.1 (Neurobehavioral Systems, San Francisco, CA, USA).

To ensure task comprehension, participants completed an instructed practice of ten blocks of 80 trials each the day before the fMRI session and an additional short practice consisting of three blocks immediately before the fMRI session. During the training, the task was explained in detail and participants were asked to explain the task in their own words afterwards. The training was then monitored by the experimenter to ensure that the task was truly understood.

2.3. fMRI data acquisition and fMRI data analysis

Imaging was performed on a 3 Tesla Siemens Magnetom Prisma MR equipped with a 20-channel head coil. T2*-weighted single-shot, blood-oxygen-level-dependent (BOLD), echo-planar-imaging (EPI) sequences were recorded for functional imaging (64 × 64 pixel, 210 mm field of

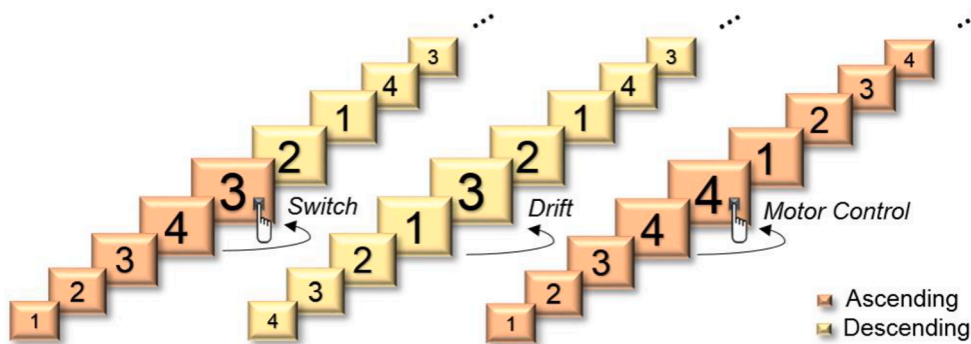


Fig. 1. Schema of the task according to (Trempler et al. 2018). Three types of unexpected events during a counter-rotating, predictable four-digit-sequence were presented at variable positions throughout the task: first, direction reversals termed *switches* requiring flexible adaption of the internal prediction model had to be indicated by a button press. Second, single-digit omissions termed *drifts* should be ignored reflecting shielding of current predictions against distractors. Third, motor control trials during which single digits were repeated until the participant responded or, in case they did not, up to eight times had to be indicated by a button-press as quickly as possible and served for the calculation of individual re-

action time windows at switches and drifts.

view, 90° flip angle, repetition time = 2000 ms, echo time = 30 ms). Each volume consisted of 33 axial slices with a slice thickness of 3 mm and a gap of 1 mm. Images were orientated along the AC-PC plane. High resolution structural images were recorded by a standard Siemens T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence for detailed reconstruction of anatomy with isotropic voxels (1x1x1mm) in a 256 mm field of view (256x265 pixels, 192 slices, repetition time = 2130, echo time = 2.28).

Preprocessing of the imaging data was performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). We slice-timed data slices to the middle slice. Individual functional MR (EPI) images were realigned to the mean EPI image. Motion correction estimates were inspected visually to verify that head movements were <3 mm between two scans in x, y and z dimensions and <5° rotation. The results of motion correction were checked visually. Anatomical scans were co-registered 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. Normalized images were spatially smoothed using a Gaussian kernel of 8 mm3 full width at half-maximum (FWHM). Finally, a 128 s temporal high-pass filter was applied.

2.4. Behavioral data analysis

IBM SPSS Statistics 25 was used for statistical analyses. The rate of correct detection of switches, i.e., the hit-rate (H), was defined as indicator of flexibility, whereas the rate of correct rejections of drifts (CR) was defined as indicator of stability. Furthermore, the miss rate of switches (M), reflecting inflexibility, and the rate of false alarms to drifts (FA), reflecting instability, were determined. A discrimination index [$P_r = H - FA$] was calculated to quantify participants' ability to specifically select the correct response to either switches or drifts (Snodgrass and Corwin 1988). Moreover, the response bias index [$B_r = FA / (1 - P_r)$] was calculated to reflect an individual's tendency to respond rather than not to a stimulus (Snodgrass and Corwin 1988). The average individual RT in motor control trials plus one standard deviation was used to calculate the individual RT windows for classifying key presses as hits and false alarms. This approach ensured a correct assignment of responses to unexpected events even in participants with generally slower RTs. Patients had significantly prolonged reaction times due to general motor slowing; thus, we measured a mean individual RT window of $Mean(SD) = 3104 (162)$ ms for them compared to a RT window of $Mean(SD) = 2241 (129)$ ms for controls. As only those unexpected events that had a minimum distance of the respective RT window length to the next event were considered in the analysis, fewer trials per condition were included in the analysis of patients than of controls (group-average number of switches: $Mean(SD)_P = 53(22)$ vs. $Mean(SD)_C = 74(23)$, $p = 0.003$;

number of drifts: $Mean(SD)_P = 52(21)$ vs. $Mean(SD)_C = 74(23)$, $p = 0.002$). Finally, key presses to standard digits were analyzed to ensure that the patients understood the task sufficiently well and did not simply press the key randomly across the experiment.

Group differences in task performance were tested using independent t -tests. The raw p -values of the t -statistics were Bonferroni-corrected by multiplying them with the total number of t -tests of the behavioral data analysis (i.e., p^*6) and compared to the α -level of 0.05. To control for the inter-individually differing response biases regarding the performance at switches and drifts, we further calculated an analysis of covariance (ANCOVA) with the B_r -index as covariate when comparing hit- and correct-rejection-rates between groups (Snodgrass and Corwin 1988). Pearson's correlation coefficients were calculated for associations between task performance and clinical parameters to rule out a possible dependence of performance on disease state and antipsychotic medication. We also analyzed differences in the performance at switches and drifts depending on whether they occurred within or between the sequences (see Supplementary Material, Table S5).

2.5. Design specification

For the fMRI data analysis, we defined two general linear models (GLM) on the first level (Friston, et al. 1994; Worsley and Friston 1995) each with a regressor for predictable standard digits (Std), motor control trials, and resting trials, plus six rigid body transformations obtained from the residual motion correction. The first GLM was set up to study the effects of switches and drifts, i.e., prediction error gating. In addition to the nine regressors just mentioned, the design included one regressor for switches (Swi) and one for drifts (Dri). We generated the two contrasts between respective unexpected event (switch, drift) and standard digits, i.e. $Swi > Std$ and $Dri > Std$. The second GLM additionally included the performance measures, i.e. hits (for flexibility), misses (for inflexibility), correct rejections (for stability) and false alarms (for instability). We hereby tested whether patients differed from controls with respect to the neural correlates of successful vs. failed updating or stabilization on the one hand ($H > M$, $CR > FA$) and correct vs. failed classification of prediction errors on the other ($H > FA$, $CR > M$). As the number of the four response categories differed between groups, we carried out an additional control analysis adjusting the events included in the analysis (see Supplementary Material, see Table S2b and S3b).

2.6. Group analysis

The resulting contrast images of all participants related to the first model, $Swi > Std$ and $Dri > Std$, entered the second level random effects analyses using two-sample t -tests comparing controls and patients. Contrast images were furthermore subjected to a two-way ANOVA to perform a conjunction analysis of the two contrasts and test against the

conjunction null hypothesis. We performed a region of interest (ROI) based small-volume correction (SVC) on the striatum to test for group differences, with an initial voxel threshold at $p < 0.001$ and a FDR corrected cluster threshold at $p < 0.05$. The striatum ROI was derived from the probabilistic atlas of the basal ganglia (Keuken et al., 2014). The averages of the parameter estimates of both contrasts extracted from the significant voxels were externally correlated with discrimination index P_r (Snodgrass and Corwin 1988).

Four contrast images revealed by the second model, $H > M$, $CR > FA$, $H > FA$, and $CR > M$, were submitted to second-level random-effects analyses, including the B_r -index as a covariate in ANCOVAs paralleling the behavioral data analysis. We set the minimum cluster extent to $k \geq 20$ and corrected for multiple comparisons using a threshold of $p < 0.05$, FDR-corrected.

3. Results

3.1. Behavioral results

Compared to healthy controls, patients were worse in their overall discrimination performance, as measured by the P_r index (see Table 1). Consistent with hypothesis H1, the controls revealed a significantly higher hit rate compared to the patients, but no difference was observed

Table 1

Demographical and clinical characteristics and task performance in patients with schizophrenia spectrum disorders and healthy controls.

Characteristics	Schizophrenia Spectrum Disorders Patients (n = 22, 7 females)	Healthy Controls (n = 22, 9 females)	t- value ^a	p-value
	Mean (\pm SD)			
Age [years]	36.41 (\pm 10.28)	38.23 (\pm 12.26)	0.53	0.597
Years of Education	14.19 (\pm 2.62)	15.35 (\pm 3.22)	1.23	0.227
NSS	14.50 (\pm 8.57)	5.91 (\pm 3.82)	-4.30	<0.001
BACS	-1.29 (\pm 1.09)	0.64 (\pm 1.02)	6.09	<0.001
BIS-11	63.55 (\pm 7.49)	58.00 (\pm 7.11)	-2.52	0.016
BDI-II	10.91 (\pm 8.57)	2.36 (\pm 3.47)	-4.31	<0.001
SAPS	15.14 (\pm 17.02)	0.00 (\pm 0.00)	-4.17	<0.001
SANS	22.09 (\pm 18.33)	0.046 (\pm 0.21)	-5.64	<0.001
CPZ [mg]	642.72 (\pm 422.80)	-	-	-
Years since diagnosis	12.67 (\pm 10.11)	-	-	-
Task performance	Adjusted Mean ^b (Mean \pm SD)		F- value ^c	p-value
Hit rate of switches	0.57 (0.54 \pm 0.23)	0.78 (0.81 \pm 0.13)	16.32	<0.006
Correct rejection rate of drifts	0.87 (0.89 \pm 0.10)	0.93 (0.90 \pm 0.09)	11.78	0.006
	Mean (SD)		t- value ^a	p-value
RT _{Hits} (ms)	1561 (\pm 584)	1114 (\pm 265)	-3.27	0.018
RT _{FAs} (ms)	1496 (\pm 656)	995 (\pm 407)	-3.04	0.024
P_r	0.44 (\pm 0.22)	0.71 (\pm 0.19)	4.54	<0.006
B_r	0.20 (\pm 0.18)	0.31 (\pm 0.17)	2.04	0.288

^a from independent *t*-test

^b corrected for the B_r -index

^c from ANCOVA including the B_r -index

between the groups in terms of drift rejection ($p = 0.718$). However, when controlling for the response probability B_r , the healthy controls outperformed the patients in both switch hits and drift rejections, indicating less flexibility and stability in the patients. The subgroups of patients diagnosed with schizophrenia and patients diagnosed with schizoaffective disorder did not differ significantly regarding depressive symptom expression, cognitive performance on the BACS and task performance (see Supplementary Material, Table S4).

A *post-hoc* power analysis with the software G*Power (Faul et al. 2007), assuming a type I error of $\alpha = 0.05$, yielded a power of 98% to detect a difference in the hit rate with an effect size of Cohen's $f = 0.631$, and a power of 93% to detect a difference in the correct rejection rate with an effect size $f = 0.536$. Remarkably, hit rate and correct rejection rate were not significantly correlated in either group ($p > 0.56$).

A higher *hit* rate, but not *correct rejection* rate ($p > 0.347$), correlated in patients with lower NSS scores ($r = -0.751$, $p < 0.001$) and higher BACS scores ($r = 0.641$, $p = 0.001$). There were no such correlations in healthy controls ($p > 0.268$). CPZ were related to neither task performance measures, NSS nor BACS scores in patients (all $p > 0.478$).

Results on hit and CR rate depending on their sequential position and on false alarms to standard digits can be found in the Supplementary Material (Table S5).

3.2. Imaging results

Whole-brain level group comparison regarding processing of switches versus standard digits [Controls(Swi > Std) > Patients(Swi > Std)] revealed higher activations for controls compared to patients in a network involving the middle frontal gyrus (left(L): $k = 91$, $x = -27$, $y = 41$, $z = 23$, $t = 3.48$; right(R): $k = 116$, $x = 51$, $y = 17$, $z = 41$, $t = 3.63$) and a cluster ($k = 2858$) including the left thalamus ($x = -15$, $y = -10$, $z = 2$, $t = 5.55$), the caudate nucleus ($x = -15$, $y = 8$, $z = 8$, $t = 5.06$) and the anterior cingulate cortex inferior to BA 6/8 ($k = 24$, $x = 6$, $y = 20$, $z = 32$, $t = 5.05$) which extended into the supplementary motor area (see Fig. 2a). The reverse contrast [Patients(Swi > Std) > Controls(Swi > Std)] showed no significant activation. One-sample *t*-tests revealed that whole-brain responses were similar for both groups, but weaker in patients compared to controls (Figure S1). In contrast, no group differences were observed in activation during drifts, neither for [Controls(Dri > Std) > Patients(Dri > Std)] nor for [Patients(Dri > Std) > Controls(Dri > Std)].

However, consistent with H2, a small-volume corrected conjunction of the two contrasts [Controls(Swi > Std) > Patients(Swi > Std) \cap Controls(Dri > Std) > Patients(Dri > Std)] revealed significantly reduced bilateral striatal activations in patients compared with controls (L: $k = 22$, $x = -15$, $y = 8$, $z = 8$, $t = 3.74$; R: $k = 14$, $x = 18$, $y = 5$, $z = 11$, $t = 3.69$). Mean activation during switches and drifts in the striatum correlated with the discrimination index P_r across the whole group (L: $r = 0.403$, $p = 0.008$; R: $r = 0.514$, $p = 0.001$), controlled for age and gender, Fig. 2b. Partial correlation analyses considering patients only including disease duration and SAPS and SANS as control variables still revealed a significant correlation with right but not with left striatal activation (L: $r = 0.390$, $p = 0.109$; R: $r = 0.481$, $p = 0.04$).

Using the second model, we tested hypothesis H3 by analyzing group differences in terms of participants' performance. Comparing flexibility measures with inflexibility measures [Controls(H > M) > Patients(H > M)] revealed higher activation in the right pregenual anterior cingulate cortex ($k = 405$, $x = 12$, $y = 50$, $z = -7$, $t = 4.28$), the retrosplenial cortex ($k = 874$, $x = 3$, $y = -61$, $z = 29$, $t = 5.13$), and the hippocampus proper ($k = 148$, $x = 21$, $y = -13$, $z = -19$, $t = 5.43$) in controls compared to patients (Fig. 3a). Considering the two groups separately, we found activation in a network of bilateral putamen ($k = 2131$, $x = -30$, $y = -4$, $z = -7$, $t = 6.54$), right middle frontal gyrus ($k = 75$, $x = -27$, $y = 17$, $z = 32$, $t = 5.51$), right inferior frontal gyrus ($k = 117$, $x = 48$, $y = 47$, $z = -1$, $t = 4.47$), and right middle cingulate gyrus ($k = 66$, $x = 12$, $y = 2$, $z = 38$,

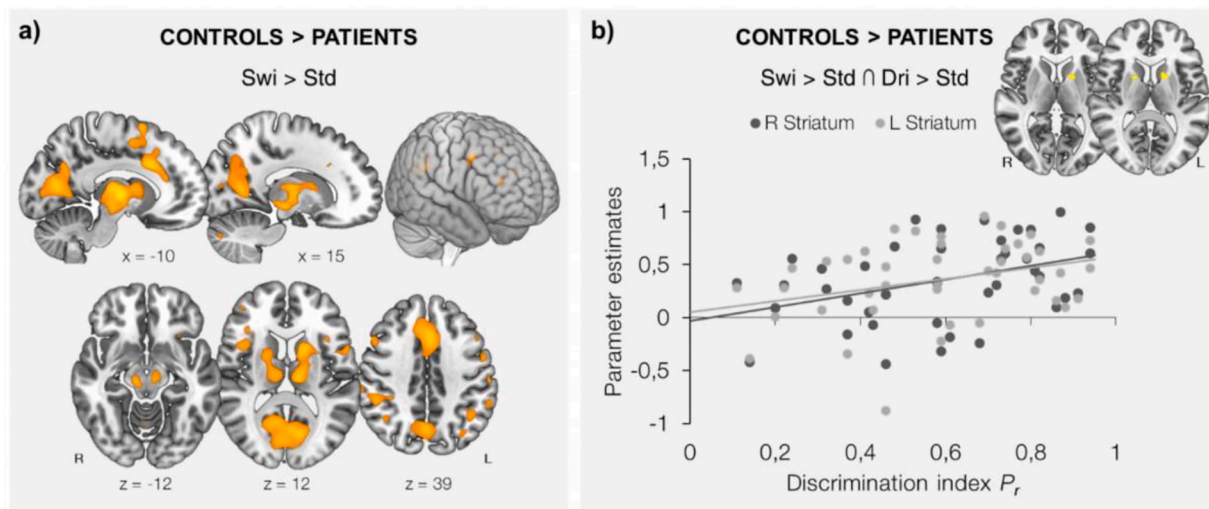


Fig. 2. a) Results of the whole-brain analysis of BOLD activation differences between groups at switches (Swi) versus standard digits (Std), FDR-corrected, $p < 0.05$, $k > 20$. For more details regarding activated areas, [Table S1](#). b) Results of small-volume corrections in bilateral striatum for the conjunction analysis of switches and drift (Dri) versus standard digits in controls versus patients. The scatter plot illustrates the relationship between striatal activation (averaged parameter estimates from the significant clusters) and discrimination index P_r across the whole sample.

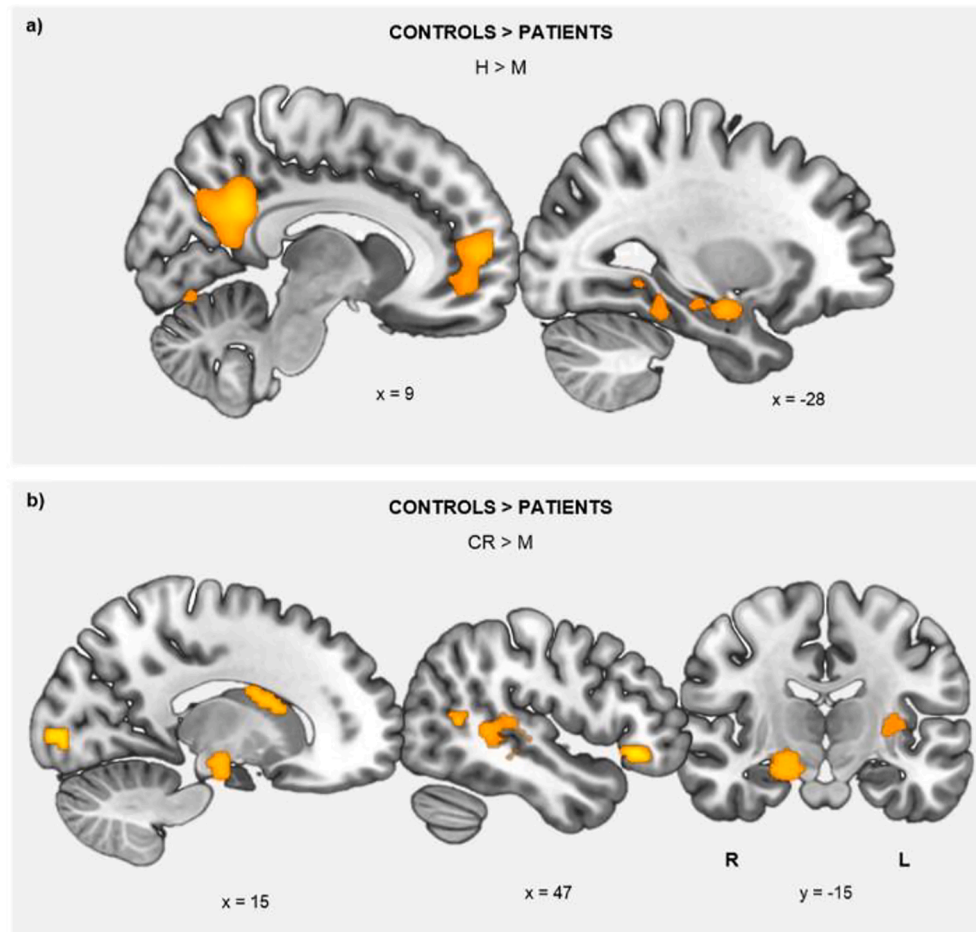


Fig. 3. Results of the whole-brain analysis of BOLD activation differences between groups at a) switch hits (H) versus switch misses (M) reflecting flexibility and inflexibility, respectively, and b) correct rejections of drifts (CR) versus switch misses (M) reflecting stability and inflexibility, respectively, FDR-corrected, $p < 0.05$, $k > 20$. For more details regarding activated areas, [Table S2a](#) and [S3a](#).

$t = 4.42$) in controls, while there were no differences between the conditions in patients ([Figure S2](#)). Comparing flexibility measures with instability measures [Controls(H > FA) > Patients(H > FA)] revealed no

group differences.

No group differences were found for stability vs. instability [Controls(CR > FA) > Patients(CR > FA)]. Stability vs. inflexibility [Controls(CR

> M) > Patients(CR > M)] revealed a significant BOLD effect in a network including the orbital part of the right inferior frontal gyrus ($k = 47$, $x = 48$, $y = 26$, $z = -7$, $t = 4.12$), the caudate nucleus extending into the putamen ($k = 87$, $x = 21$, $y = 11$, $z = 14$, $t = 5.41$) and the left posterior insula ($k = 48$, $x = -33$, $y = -19$, $z = 8$, $t = 4.90$) in controls compared to patients (Fig. 3b). There was no difference between conditions in patients, but significantly increased activation in an extensive cluster ($k = 5569$) incorporating bilateral putamen ($x = -27$, $y = 5$, $z = 8$, $t = 4.97$) and right caudate nucleus ($x = 21$, $y = 11$, $z = 14$, $t = 4.67$) in controls (Figure S3).

4. Discussion

The main findings from our study suggest that patients with schizophrenia spectrum disorders are impaired regarding the two components *cognitive flexibility* and *cognitive stability*. Patients had significant problems with responding to rule switches flexibly, but were also less stable with ignoring irritating, but rule-uncritical drifts. The latter observation was only revealed when controlling for the participants' overall response bias, which compensates for the general tendency to be more likely to not respond. Remarkably, our measures of flexible updating and stabilization against distractors were not statistically correlated. Correct responses to switches, but not correct rejections of drifts, systematically covaried with patients' general motor and cognitive (dys)function, but neither of these characteristics covaried with antipsychotic medication.

The fMRI results showed that patients' striatum was hypoactive when they encountered either switches or drifts, and this insufficient engagement was statistically related to deficits in discriminating the two event types. Finally, patients showed significantly weaker anterior cingulate signaling for processing correct versus erroneous switches, and likewise hypoactivation in the inferior frontal cortex for shielding against drifts versus missed switches.

Taken together, our findings suggest deficient prediction error processing in schizophrenia spectrum disorders, which impairs flexible updating but also stability of predictions, and is associated with aberrant functionality of fronto-striatal circuits.

4.1. Impaired regulation of striatal prediction error gating

Using a novel serial switch-drift paradigm (Trempler et al. 2017), we observed reduced striatal activation for processing both switches and drifts in patients compared to healthy controls when patients' task performance was not taken into account. Computational models support the idea that alterations in fronto-striatal gating play a crucial role in the pathogenesis of schizophrenia spectrum disorders (Braver et al. 1999; Frank et al. 2001; Maia and Frank 2017). According to these computational models, striatal dopaminergic neurons cancel the tonic inhibition of thalamic neurons, which in turn are connected to frontal neurons (Frank et al. 2001). In this way, contextually important information can update prefrontal predictive models. Furthermore, the same models suggest a poorer signal-to-noise ratio in schizophrenia spectrum disorders due to increased intrinsic spontaneous activity of dopaminergic neurons and a concomitant reduced phasic dopamine response to external stimuli. Accordingly, it is assumed that impaired cognitive flexibility in schizophrenia spectrum disorders results from such reduced striatal gating (Braver et al. 1999). However, we recently found that striatal activation in healthy subjects is related to both flexibility and stability demanding prediction errors (Trempler et al. 2017). In addition, fronto-striatal circuitry has been shown to contribute to response inhibition (Aron 2011; Chambers et al. 2009). Our finding of reduced striatal activation in response to switches and drifts in patients reported here supports these previous observations by suggesting that processing of prediction errors is impaired in schizophrenia spectrum disorders, whether they require updating or stabilizing current predictions. Since striatal activity positively correlated with the individual

ability to discriminate between the two types of prediction errors, we assume that corresponding selection processes rely heavily on striatal computations. This selection requires the differentiation of flexibility-requiring and stability-requiring prediction errors. The former must add new contextual information to the currently valid predictive model, while the latter must be discarded.

4.2. Inappropriate cortical encoding of prediction errors in patients

For rule switches, patients showed significantly reduced activation in a network including the dopaminergic midbrain, thalamus and caudate nucleus, as well as parts of the superior, middle, and inferior frontal gyri. This finding supports our interpretation of impaired fronto-striatal gating of relevant stimuli in schizophrenia spectrum disorders for the successful updating of top-down predictions. In addition, patients showed significantly weaker activation in the pregenual anterior cingulate cortex, in the hippocampus proper and the amygdala when switch processing was correct compared to incorrect. This finding is in line with previous research showing that activity within this network is reduced in response to commissions of errors in schizophrenia spectrum disorders (Laurens et al. 2003; Polli et al. 2008). Consistent with its presumed role in generating error signals in response to changes in current behavioral demands (Alexander and Brown 2015), reduced activation of the medial prefrontal cortex has been found in patients; this is associated with disruptions in learning from prediction errors (Reinhart et al. 2015) and corresponding evaluations of behavioral outcomes (Krawitz et al. 2011). Accordingly, reduced prefrontal activity for hits versus misses could reflect a suboptimal behavioral monitoring in response to relevant prediction errors to generate correct responses.

Besides signs of impaired predictive flexibility, we also observed impaired predictive stability in patients, confirming previous findings of impaired cognitive stability (Westerhausen et al. 2011; Lipszyc and Schacher 2010; but also Westerhausen et al. 2013). It is noteworthy that impaired stability was only found after controlling for the individual response bias. This means that a possible advantage for stability probably only results from the inflexibility of the patients. To get to the bottom of this option, we compared the neural activity of the two groups during shielding against drifts (reflecting stability) with activity during missed switches (reflecting inflexibility). Indeed, this analysis revealed increased activation in a network consisting of, amongst others, the inferior frontal gyrus pars orbitalis, the posterior long insular gyrus, and the pallidum, putamen and caudate in controls, while no differences were observed between conditions in patients. The orbital part of the inferior frontal gyrus plays a critical role as an interface between online appraisal and goal-directed processing of stimuli in the orbitofrontal and lateral prefrontal cortex. This region is thought to integrate cognitive and motivational information to translate stimuli into decisions to inhibit behavior (Sakagami et al. 2001; Sakagami and Pan 2007). Active rejection of drifts probably occurs in interaction with the posterior insula, which is involved with the integration and regulation of aversive physical and emotional states (Gehrlach et al. 2019; Uddin et al. 2017), and the pallidum and striatum, which probably mediate motor inhibition (Guo et al. 2018). The reduced activity in this network observed when comparing measures for stability versus inflexibility in patients therefore probably reflects the fact that patients do not actively reject disturbing input, but simply do not notice it. These findings therefore support the idea that beyond prediction error discrimination in patients, also deficient prediction error detection is suggested to contribute to impaired cognitive stability in schizophrenia spectrum disorders.

4.3. Associations with cognitive dysfunction and neurological soft signs

Deficits in cognitive flexibility in schizophrenia spectrum disorders have previously been associated with confounding factors such as disease state and medication (Waltz 2017). In contrast, antipsychotic dosage was not statistically associated with task performance in our

sample. However, we found an association of deficits in flexibility with general cognitive and motor symptoms. The association with cognitive function may suggest that the lack of predictive flexibility captures dysfunctions of various cognitive processes that occur in patients with schizophrenia spectrum disorders (Griffin and Fletcher 2017). Furthermore, neurological soft signs in psychotic disorder have been associated with dysfunction in cortical-subcortical-cerebellar circuits including the striatum (Zhao et al. 2013) and hippocampus (Kong et al. 2019). For example, it has been suggested that cerebellar dysfunction in neurological patients reflects the recognition of sequence violations, hence switches (Leggio and Molinari 2015; Molinari and Masciullo 2019). However, the correlation with motor symptoms could also be partly explained by the motor response to switches as opposed to drifts required in our task.

5. Limitations

As this was the first time the switch-drift-paradigm was applied to a relatively small sample of patients with schizophrenia spectrum disorders, further studies with larger samples are needed to confirm our results. The behavioral effects revealing differences between controls and patients were quite strong, as suggested by a post-hoc power analysis. Regarding the interpretation of the fMRI results of our second model, it cannot be excluded that at least some differences in activation could result from the unequal signal-to-noise ratio between the groups, as fewer trials were included in the analyses of patients than in those of controls. In fact, two possible interpretations can explain our findings of impaired flexibility and stability in patients. One possibility is that patients struggle to differentiate between flexibility-demanding and stability-demanding prediction errors, whereas another possible interpretation is that rather prediction error detection is impaired in patients, which may both lead to poorer task performance. Our finding of an impaired ability to discriminate both event types in patients related to reduced striatal signaling supports the hypothesis that patients' impaired cognitive flexibility and stability may stem from aberrant prediction error discrimination in patients. This is also supported by an increased false alarm rate to standard digits in patients vs. controls (see [Supplementary Material](#)). However, the significant inflexibility, which also makes patients more resistant to distraction, suggests that already the detection of prediction errors is impaired in schizophrenia spectrum disorders. Thus, in this study we could not specify to which extent exactly deficient prediction error detection or discrimination contribute to cognitive control deficits in patients. Further studies are needed to assess this question.

6. Conclusion

Our results support the notion that distinct aspects of prediction error processing are impaired in schizophrenia spectrum disorders: First, there is impaired striatal gating of prediction errors that require both flexibility and stability; and second, there is deficient cortical coding of prediction errors for updating and shielding based on the integrity of different networks, including anterior cingulate and inferior frontal cortex. Our findings support the usefulness of specific treatment approaches for schizophrenia spectrum disorders that promote cognitive flexibility and improve shielding against distractors.

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CRediT authorship contribution statement

Isabel Standke: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Ima Trempler:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Udo Dannowski:** Funding acquisition, Writing – review & editing. **Ricarda I. Schubotz:** Conceptualization, Investigation, Methodology, Resources, Project administration, Software, Supervision, Validation, Writing – review & editing. **Rebekka Lencer:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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