doi:10.1093/brain/awy203 BRAIN 2018: 141; 2806–2819 | 2806

BRAIN
A JOURNAL OF NEUROLOGY

Deficits in context-dependent adaptive coding in early psychosis and healthy individuals with schizotypal personality traits

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Adaptive coding of information is a fundamental principle of brain functioning. It allows for efficient representation over a large range of inputs and thereby alleviates the limited coding range of neurons. In the present study, we investigated for the first time potential alterations in context-dependent reward adaptation and its association with symptom dimensions in the schizophrenia spectrum. We studied 27 patients with first-episode psychosis, 26 individuals with schizotypal personality traits and 25 healthy controls. We used functional MRI in combination with a variant of the monetary incentive delay task and assessed adaptive reward coding in two reward conditions with different reward ranges. Compared to healthy controls, patients with first-episode psychosis and healthy individuals with schizotypal personality traits showed a deficit in increasing the blood oxygen level-dependent response slope in the right caudate for the low reward range compared to the high reward range. In other words, the two groups showed inefficient neural adaptation to the current reward context. In addition, we found impaired adaptive coding of reward in the caudate nucleus and putamen to be associated with total symptom severity across the schizophrenia spectrum. Symptom severity was more strongly associated with neural deficits in adaptive coding than with the neural coding of absolute reward outcomes. Deficits in adaptive coding were prominent across the schizophrenia spectrum and even detectable in unmedicated (healthy) individuals with schizotypal personality traits. Furthermore, the association between total symptom severity and impaired adaptive coding in the right caudate and putamen suggests a dimensional mechanism underlying imprecise neural adaptation. Our findings support the idea that impaired adaptive coding may be a general information-processing deficit explaining disturbances within the schizophrenia spectrum over and above a simple model of blunted absolute reward signals.

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Received January 4, 2018. Revised June 13, 2018. Accepted June 18, 2018

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Keywords: adaptive coding; information-processing; functional magnetic resonance imaging; reward outcome; schizophrenia spectrum

Abbreviations: FEP = first-episode psychosis; PANSS = Positive and Negative Syndrome Scale; SPT = schizotypal personality trait; SPQ = Schizotypal Personality Questionnaire

Introduction

How can neurons, with their limited firing rate, accurately represent a theoretically infinite range of inputs in the natural environment? To efficiently solve this problem the firing rate of neurons dynamically adjusts to inputs that are most common in the current context. This core mechanism of information processing, also known as adaptive coding, has been described in detail for sensory systems, including the retina and visual cortex (Smirnakis *et al.*, 1997; Smith and Lewicki, 2006; Wark *et al.*, 2009). In line with the notion that adaptive coding is a fundamental principle of brain functioning, it has also been shown for the processing of reward magnitude and range by single neurons (Tremblay and Schultz, 1999; Tobler *et al.*, 2005; Padoa-Schioppa, 2009; Kobayashi *et al.*, 2010). For example, dopaminergic midbrain neurons code received rewards relative to the range of likely rewards rather than simply coding absolute reward magnitude (Tobler *et al.*, 2005). Thus, dopamine neurons discriminate reward values with higher sensitivity when the variability of possible rewards is smaller (small reward range) than when it is larger. This adaptation process allows for efficient use of the neural coding range given the predicted or experienced reward range. In recent years, functional MRI studies started to elucidate this general principle of adaptive reward coding in humans. It has been shown that reward outcome and reward prediction error signals of the striatum and other regions throughout the reward system adapt to the current reward context (Park *et al.*, 2012; Cox and Kable, 2014; Burke *et al.*, 2016; Diederen *et al.*, 2016). Moreover, the relevance of intact dopamine function for efficient adaptive coding has been highlighted by disrupted adaptive coding after administration of a dopamine D2-receptor antagonist in healthy human volunteers (Diederen *et al.*, 2017).

Given the fundamental role of adaptive coding in reward processing and its tight relation to dopamine transmission, it is crucial to understand how potential deficits in adaptive coding may contribute to the pathophysiology of disorders with a dopamine dysfunction such as schizophrenia, addiction and Parkinson's disease (Dagher and Robbins, 2009; Howes *et al.*, 2012; van der Vegt *et al.*, 2013; Volkow and Morales, 2015; Maia and Frank, 2017). Indeed, proof-of-principle work suggests that chronic schizophrenia and psychotic symptoms are associated with deficits in adaptive coding, particularly in the dorsal striatum and the insula (Kirschner *et al.*, 2016). By extension, inefficient neural adaptation to the current reward context may contribute to the complex nature of reward and salience processing deficits in schizophrenia (Schlagenhauf *et al.*, 2014; Winton-Brown *et al.*, 2014; Kirschner *et al.*, 2015; Mucci *et al.*, 2015; Radua *et al.*, 2015; Dowd *et al.*, 2016) and its precursor states.

In line with the notion that schizophrenia corresponds to the extreme end of a spectrum disorder (Supplementary Fig. 1) (van Os *et al.*, 2009; Nelson *et al.*, 2013; Barrantes-Vidal *et al.*, 2015; van Os and Reininghaus, 2016) striatal reward and salience processing deficits have been observed also in healthy individuals with schizotypal personality traits (SPTs), ultra-high risk states and early psychosis (Nielsen *et al.*, 2012; de Leeuw *et al.*, 2015; Simon *et al.*, 2015; Kirschner *et al.*, 2016; Winton-Brown *et al.*, 2017). However, one major challenge is to integrate the accumulating evidence of striatal dysfunction as core deficit for both negative symptoms (related to impaired reward learning) and positive symptoms (related to aberrant discrimination between relevant and irrelevant information) in the schizophrenia spectrum (Howes *et al.*, 2009; Kegeles *et al.*, 2010; Winton-Brown *et al.*, 2014; Maia and Frank, 2017). While there is evidence for reduced absolute coding of reward values and prediction error signals in the schizophrenia spectrum (Corlett *et al.*, 2007; Murray *et al.*, 2008; Ermakova *et al.*, 2018), a conclusive association with symptom expression integrating negative and positive symptoms is still missing (Radua *et al.*, 2015; Ermakova *et al.*, 2018). An alternative organizing principle could be that symptoms relate to relative and context-adaptive rather than absolute and context-independent coding of reward. Therefore, the aim of the present study was to focus on this unexplored mechanism in the schizophrenia spectrum. In particular, we tested whether an impaired capacity to relate reward magnitudes to the context of currently likely reward outcomes explains symptom severity better than a blunted absolute reward magnitude signal.

The present study investigates healthy non-medicated individuals with SPTs as well as patients with early psychosis. Specifically, we test whether imprecise neural reward adaptation already occurs in relation to non-clinical variations in personality traits in the general population (SPT) and first-episode psychosis (FEP). Moreover, including all symptom dimensions of the schizophrenia spectrum (Supplementary Fig. 1) allows us to investigate how adaptive coding is associated with symptom severity across both groups of the schizophrenia spectrum. We used a modified

version of the monetary incentive delay task that enabled us to investigate adaptive coding of reward magnitude during the outcome phase (Simon *et al.*, 2015; Kirschner *et al.*, 2016). Based on our previous proof-of-principle findings in patients with chronic schizophrenia, we focused our main analysis on adaptive reward coding deficits in the caudate nucleus and insula.

Materials and methods

The present analysis of adaptive coding during reward outcomes uses the functional MRI dataset of Kirschner *et al.* (2016). The previous analysis focused exclusively on classical binary reward 'anticipation' by comparing activity induced by the presentation of stimuli that predict future reward versus stimuli that predict no reward. In contrast, here, we focus on reward 'outcome' in the context of small or large reward ranges and present an entirely different analytical approach, which we have so far used only in patients with chronic schizophrenia (Kirschner *et al.*, 2016). Specifically, we take advantage of a task design that enables us to investigate adaptive coding of reward amounts at the outcome phase using parametric contrasts. The investigation of adaptive reward signals is orthogonal to the previous approach of investigating reward anticipation signals. In addition, we fully control for stimulus presentation effects in the present analysis.

Participants

We acquired data from 28 patients with first episode non-affective psychosis (FEP), 27 healthy individuals with high SPTs and 26 healthy control participants. The ethics committee of the Canton of Zurich approved the study, and all participants gave written informed consent.

Individuals with FEP were recruited during their first psychiatric admission in outpatient ($n = 6$) and inpatient ($n = 22$) units of the Psychiatric Hospital of the University of Zurich. All FEP patients received a stable dose of second-generation antipsychotics. Inclusion criteria were a clinical diagnosis of brief psychotic disorder, schizophreniform disorder or schizophrenia confirmed in a structured Mini-International Neuropsychiatric Interview for DSM-IV (M.I.N.I) (Lecrubier *et al.*, 1999). We used the same exclusion criteria as in our previous study in chronic schizophrenia patients (Kirschner *et al.*, 2016). We excluded participants with any other current DSM-IV axis I disorder (in particular current substance use disorder and substance-induced psychotic disorder), lorazepam more than 1 mg/day, florid psychotic symptoms, i.e. any positive subscale item score of five or higher as measured with the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1989), or extrapyramidal side effects (Simpson and Angus, 1970). As patients took part in a larger study protocol, those with higher psychotic symptom levels had to be excluded to ensure adequate task performance. Fifteen patients fulfilled the criteria of a first episode schizophrenia and 13 patients were diagnosed with a brief psychotic disorder. Individuals with schizotypal traits were recruited using an online form of the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). Nine hundred and fifty-six participants completed the questionnaire [mean score 16.66 (standard deviation, SD 11.34)]. Individuals with the highest SPQ total scores (upper 10% of the SPQ total score) were invited to participate in the study. Exclusion criteria were any current or past Axis I disorder confirmed with the M.I.N.I. as well as use of psychopharmacological drugs. For further details on SPT participants and inclusion criteria of healthy control subjects see the Supplementary material. All study participants underwent an extensive psychopathological and neuropsychological assessment (Supplementary material). Severity of positive and negative symptoms was assessed with the PANSS.

Experimental design and task

We used a variant of the Monetary Incentive Delay Task (Knutson *et al.*, 2000) with stimuli based on the Cued-Reinforcement Reaction Time Task (Cools *et al.*, 2005). This modified version was originally developed by Simon *et al.* (2015) (Fig. 2). In each correct trial, participants received a reward, which was determined directly by the individual response time (for further details see the Supplementary material and Supplementary Fig. 1). Thus, in contrast to most versions of the Monetary Incentive Delay Task, there was no dichotomy of reward versus no-reward in the outcome phase, but a continuous distribution of rewards, which allowed us to study reward amount processing separately from reward anticipation. Importantly, our task included two different reward contexts, a low context, ranging from Swiss Franc (CHF) 0 to 0.40, and a high context, ranging from CHF 0 to 2.00 (in addition to a neutral control condition without reward). The differential reward range of the low and high reward context allowed us to investigate the dynamic adaptation of reward-induced activation to the current reward context. In particular, adaptation would correspond to a steeper slope of the mapping between output (response strength) and input (reward amount) for the low reward context compared to the high reward context (Fig. 1A and below).

Before the start of the experiment, we informed all participants that they would receive the accumulated amount of money they would win during the two experimental sessions. The maximum amount of money to be won was CHF 50. Every participant performed two training runs, one outside and one inside the scanner. Excluding the training runs, the experiment contained two sessions with 36 trials each, resulting in 24 trials per reward condition, with every trial lasting ~10 s. The intertrial interval was jittered from 1 to 9 s with a mean of 3.5 s. In total, one session lasted ~6 min. The task was implemented using the MATLAB toolboxes Cogent 2000 and Cogent Graphics. For acquisition parameters please see the Supplementary material.

Data analysis

All demographic, clinical, neuropsychological and behavioural data were analysed and correlations performed using IBM SPSS Statistics Version 22. We analysed functional MRI data with SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK).

Behavioural data analysis

The main behavioural outcome measure was response time, defined as time between target presentation and pressing the

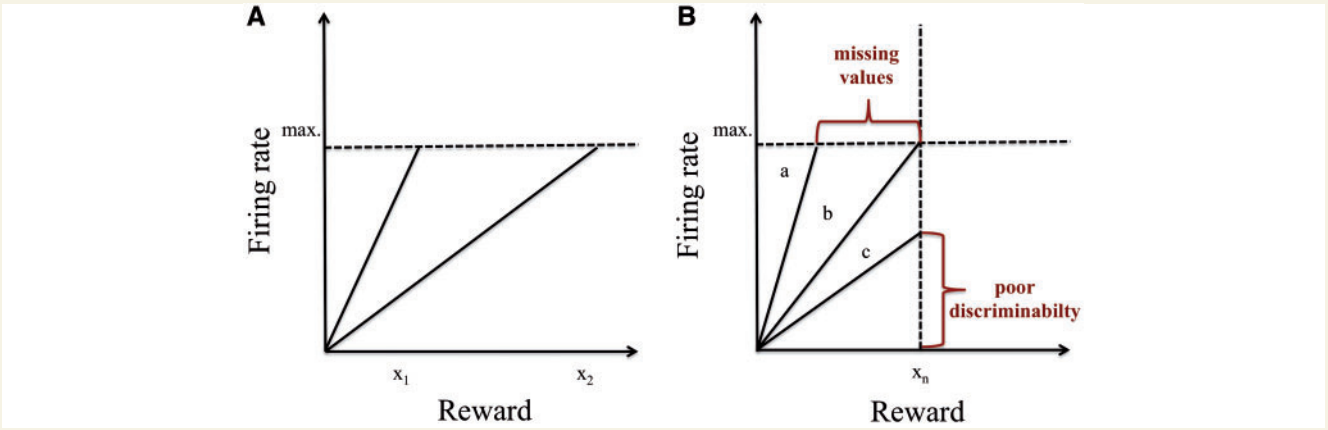

Figure 1 A simple model of efficient and inefficient adaptive coding. (**A**) A simple model of adaptive coding of reward. To efficiently encode all possible reward amounts with a limited coding range, reward adaptation corresponds to dynamically adjusting the response sensitivity to the currently available rewards. This relative coding mechanism allows for optimal discrimination between different amounts of reward in any given context, enabling efficient processing of reward information. (**B**) Contrast of optimal and inefficient adaptive coding. This plot illustrates two potential consequences of inefficient adaptation to the range of possible rewards. With too much adaptation, the response function is too steep (a), leading to a miscoding/incomplete representation of reward information. With too little adaptation, the response function is too shallow (c), which leads to poor discriminability of reward amount due to restricted coding range. Response function (b) shows optimal adaptive reward coding, where the slope of the response function adapts so as to efficiently represent the full range of reward. Figure adapted from Kirschner *et al.* (2016).

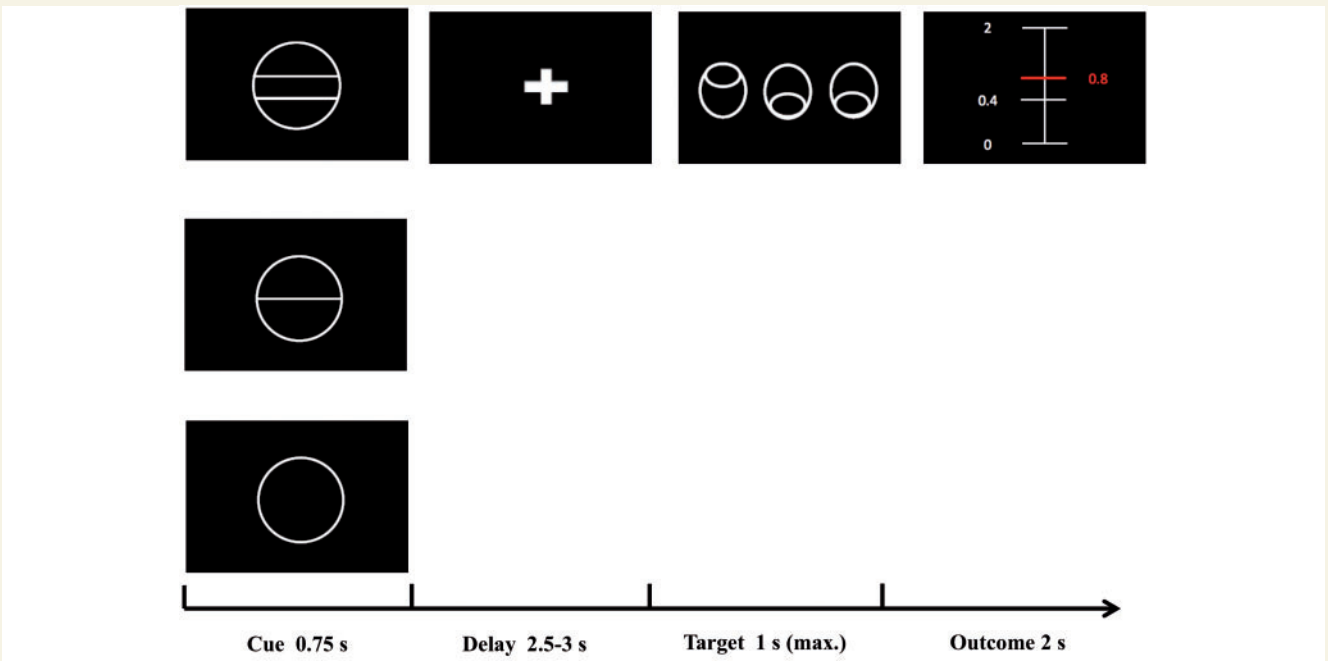

Figure 2 Task design of the adapted monetary incentive delay task. Adapted monetary incentive delay task: At the beginning of each trial, one of three different cues was presented for 0.75 s. The cue indicated the reward context, specifically the range of possible amounts participants could gain in that trial, i.e. CHF 0 to 2 (circle with two lines), CHF 0 to 0.40 (circle with one line), or CHF 0 (circle only) (1 CHF = 1.08 US$ at the time of the experiment). After a delay, varying from 2.5 to 3 s, participants identified an outlier from three presented circles and pressed a button (either left or right) as fast as possible. In case of a correct response, participants were immediately notified of the amount of money they had won, which was proportional to their individual performance (duration of feedback 2 s). The monetary amount won in a correct trial was calculated based on the response times of the previous 15 individual trials. Error trials were defined as trials with a wrong response or late response (> 1 s) and participants did not receive any monetary reward.

correct answer button. We performed a two-way repeated measures analysis of variance (ANOVA) with group as between-subject factor and reward context (low, high) as within-subject factor. In addition, we performed a group comparison of reward-related speeding, defined as the difference in response times between low and high rewards. Potential group

differences in all other behavioural data were investigated using two-sample *t*-tests. For non-normally distributed data (as assessed by the Kolmogorov-Smirnov test), Mann-Whitney U-tests were applied.

Image preprocessing

For acquisition parameters see the online Supplementary material. Functional images were corrected for differences in the time of slice acquisition. The Realign and Unwarp functions of SPM8 were used to correct our data for head motion, with an allowed translational head motion limited to ±4 mm. A voxel displacement map, calculated from double phase and magnitude field map data, was used to correct for combined static and dynamic distortions. We performed segmentation, bias correction, and spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width at half-maximum. We evaluated the quality of functional MRI data by manual inspection and excluded data with poor quality due to significant signal dropout in EPI sequences. Three participants (one FEP, one SPT and one healthy control subject) were excluded because of excessive head movement, leaving a total sample of 27 FEP, 26 SPT and 25 healthy controls for final functional MRI analyses.

First level image analyses

We computed a general linear model (GLM) with a parametric design to identify brain regions that encode reward amount in an adaptive fashion at the outcome phase. In particular, we modelled each reward outcome condition separately (no/low/high reward outcome). Please note that these three regressors accounted for potential effects of group on mean activation for the low (CHF 0–0.40) and the high reward outcomes (CHF 0–2.00). In addition, the low and high reward outcome regressors were parametrically modulated (pmod) by the actual outcome received in each trial (pmod low reward, pmod high reward). Thereby we followed the standard rationale of parametric modulation (Wood *et al.*, 2008) as implemented in SPM (Büchel *et al.*, 1998). Specifically, the two parametric modulators capture linear deviations of reward amount from the mean and are orthogonal to the mean regressors; pmod low ranged from CHF 0 to 0.40, whereas pmod high ranged from CHF 0 to 2.00. Regressors of no interest consisted of one regressor for the stimulus-induced anticipation phase (duration 3.25–3.75 s), one regressor for target presentation, and one regressor for error trials (modelled at target presentation). In total, the first level model included eight regressors. The canonical haemodynamic response function was used for convolving all explanatory variables. Please note that by design in this model the two parametrically modulated reward regressors of interest are not correlated with the anticipation regressor, which serves to account for unspecific visual activations due to stimulus presentation.

Second level image analyses

Identification of reward sensitive regions

At the second (i.e. group) level of analysis, we included the individual contrast images obtained with the parametric modulators at the first level for all participants in a random-effects model. To identify brain regions coding reward amount, we used a contrast including both parametric modulators (pmod low reward + pmod high reward), which we applied in a voxel-wise whole brain analysis across all participants. The statistical threshold was set to $P < 0.05$, whole-brain voxel-level family-wise error (FWE) rate corrected for multiple comparisons.

Adaptive coding of reward

In a second step, we tested adaptive coding of reward. Efficient neural coding of inputs implies that the responses dynamically adjust to the range of possible inputs. Specifically, the slope of the response function should be steeper with a smaller range of possible inputs compared to a larger range (Fig. 1A). Consequently, in case of adaptive coding in our task, the slope of the response function in the low reward context should be steeper than the slope in the high reward context. We therefore subtracted the contrast estimates of the high reward parametric regressor from those of the low reward parametric regressor (pmod low reward – pmod high reward), which we refer to as 'adaptive coding contrast'. We interrogated this contrast within the reward-sensitive regions (identified with the pmod low + pmod high contrast; for alternative regions of interest, see Supplementary material) of the right caudate and insula, in which we have recently demonstrated deficits in adaptive coding in patients with schizophrenia (Kirschner *et al.*, 2016). Please note that the adaptive coding contrast (pmod low reward – pmod high reward) differs from the one used to identify the reward sensitive regions (pmod low reward + pmod high reward).

We first investigated adaptive coding in the reward sensitive regions across the complete sample. Next, we extracted the mean contrast estimate of the adaptive coding contrast (pmod low reward – pmod high reward) from the identified reward sensitive regions (pmod low reward + pmod high reward) in the right caudate and insula using the REX toolbox for SPM8. To test for significant group differences between healthy controls and both groups of the schizophrenia spectrum (first aim of the study), we then performed one-way ANOVAs with the adaptive coding contrast as dependent variable. The second aim of the study was to test the association between symptom severity and adaptive coding deficits. Therefore, we performed two-tailed Spearman rank correlation analyses (r_s) between the adaptive coding contrast estimates and symptom severity ratings measured with the PANSS total score across the complete schizophrenia spectrum. The group comparison of adaptive coding and the main correlations analysis were controlled for multiple comparisons across the four identified reward sensitive regions using Bonferroni correction.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary material. Additional data queries may be directed to the corresponding author.

Results

Demographic and clinical data

Demographic and clinical data of the study sample are summarized in Table 1. Please note that individuals with FEP and

Table 1 Demographic, psychopathological and clinical data

	Healthy controls ($n = 25$)	SPT ($n = 26$)	FEP ($n = 27$)	Test statistic (U/F/χ^2)
Age	28.8 (6.7)	29.5 (10.3)	24.1 (6.9)	$\chi^2 = 8.08$*
Gender, female/male	6/19	9/17	5/22	$\chi^2 = 1.67$
Education, years	13.9 (2.4)	15.3 (2.6)	12.1 (2.5)	$\chi^2 = 16.7$***
Duration of illness, months			5.4 (6.2)	
Duration of antipsychotic treatment, days			41 (30)	
Chlorpromazine equivalents, mg/day			268.8 (244.5)	
PANSS Total		40.9 (8.7)	44.5 (10.6)	U = 261.5
PANSS Positive		9.2 (2.8)	9.6 (1.9)	U = 265.5
PANSS Negative		10.1 (2.9)	12.9 (5.2)	U = 231*
PANSS General		21.6 (5.3)	22.0 (5.1)	U = 325.5
GAF		71.2 (11.1)	63.6 (10.3)	U = 199.5*
Cognition[a]				
Cognition score	0 (0.48)	0.64 (.64)	−0.27 (.62)	$F = 16.28$***
MWT IQ	28.2 (3.8)	27.7 (3.4)	23.2 (5.8)	$F = 1.2$***
Response time, ms				
No reward	505.2 (68.2)	491.8 (81.5)	513.9 (91.0)	$F = 0.49$
Low reward	471.2 (71.1)	447.5 (60.7)	488.0 (80.1)	$F = 2.14$
High reward	449.5 (71.3)	431.8 (59.4)	463.6 (81.3)	$F = 1.19$

Data are presented as mean (SD). GAF = Global Assessment of Functioning; MWT IQ = Multiple Word Test Intelligence Quotient.
[a]Cognition data were z-transformed based on the data of the healthy control group for each test separately. The composite cognition score was computed as the mean of the z-transformed test scores on the subject level. Duration of illness included the duration of untreated psychosis and the time period since initiation of treatment.
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

SPT did not differ significantly in total symptom severity (PANSS total score). In contrast, patients with FEP had stronger impairments in global functioning (GAF) than SPT. With respect to the differences in global functioning between individuals with FEP and SPT it is relevant to note that patients with FEP showed higher negative symptoms compared to individuals with SPT and no differences in positive or general symptoms. Although speculative, the lack of difference in positive or general symptoms might be an effect of successful antipsychotic treatment of patients with FEP.

Reward decreases response times irrespective of group

Response times showed a significant main effect of reward [$F(1.78,133.48) = 105.128$, $P < 0.0001$], but no significant effect of group [$F(2,75) = 1.49$, $P = 0.23$] or group × reward interaction [$F(3.56,133.48) = 1.062$, $P = 0.37$]. Bonferroni *post hoc* pairwise comparison of response times revealed significant differences between all reward conditions with participants responding more quickly in high-reward than low-reward contexts or no-reward contexts (all P's < 0.001). These results indicate that participants adapted their behaviour to the different reward contexts. In other words, the distinction between the contexts was equally good—and significantly present—in each of the groups individually. Furthermore, we did not observe any significant group differences in reward-related speeding [$F(2,75) = 0.388$, $P = 0.68$], error rates [$\chi^2(2) = 1.89$, $P = 0.39$], and total gain [$F(2,75) = 1.79$, $P = 0.17$]. These findings suggest intact and similar task performance across all groups and indicate that reduced reward adaptation at the neural level (see below) is not due to reduced differentiation in reward anticipation.

Significant activation of reward network during reward processing

To assess reward adaptation on the neural level, we first identified brain regions coding reward amount. Voxel-wise whole brain analysis of parametrically increasing responses across all participants during the reward outcome (pmod low reward + pmod high reward) revealed several brain regions sensitive for reward amount (peak-level FWE-corrected, $P \leqslant 0.05$), such as the right caudate, the left and right putamen and the insula (Fig. 3 and Supplementary Table 1). In other words, activation in these regions increased with reward amount at the time of outcome. Importantly, these regions are the same as those processing reward amounts in our previous study (Kirschner *et al.*, 2016).

Significant group differences in adaptive coding of reward

In our paradigm, adaptive coding corresponds to a steeper response slope in the low reward condition than in the high reward condition (Fig. 1A and 'Experimental design and task' section). Accordingly, the main analysis investigated adaptive coding with the contrast (pmod low reward – pmod high reward). Based on our previous findings

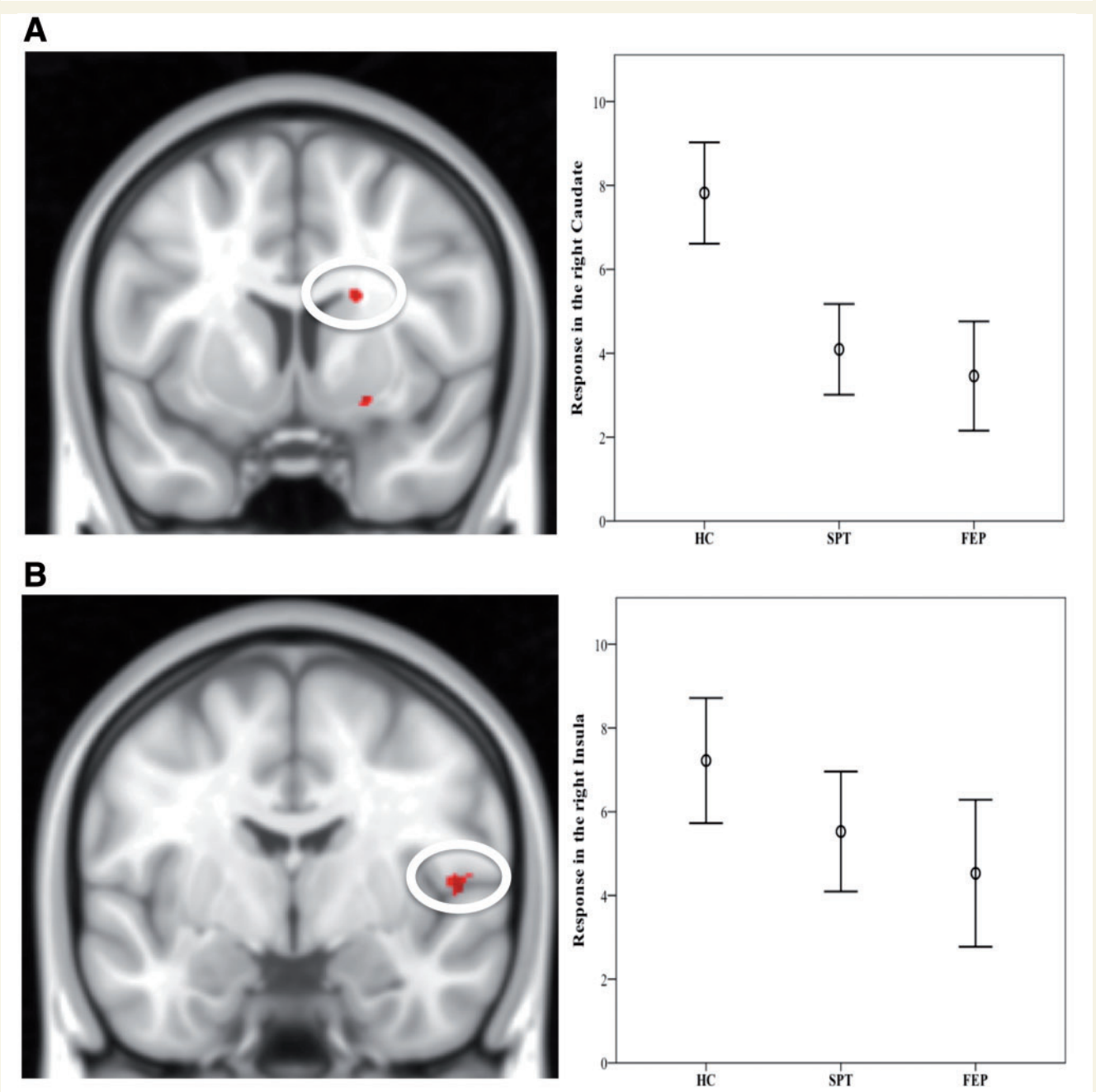

Figure 3 Reward sensitive regions. Neural activity coding reward amount. The contrast (pmod low + pmod high) identified (**A**) the right caudate (circle) and right putamen as well as (**B**) the right insula ($P < 0.05$, whole brain peak level corrected). Plots display the response during low and high reward (**A**) in the right caudate and (**B**) right insula for each group separately.

(Kirschner, *et al.*, 2016), we interrogated this contrast within the reward sensitive regions (identified with the pmod low + pmod high contrast) in the right caudate and insula. Thus, the adaptive coding contrast (pmod low - pmod high) differs from the one used to identify the reward sensitive regions. In a first step, we performed a one sample *t*-test with the adaptive coding contrast for the right caudate and insula separately. In both regions, we observed significant adaptive coding across the complete sample [right caudate: $t(75) = 4.19$, $P < 0.0001$, right insula: $t(75) = 4.23$, $P < 0.0001$]. These data confirm that the caudate and insula code reward in an adaptive fashion. Please note that the observed adaptive coding effects were not related to potential differences in activation induced by the mean of the low and high reward condition (Supplementary material).

In a second step, we aimed to identify group differences between healthy controls and individuals within the

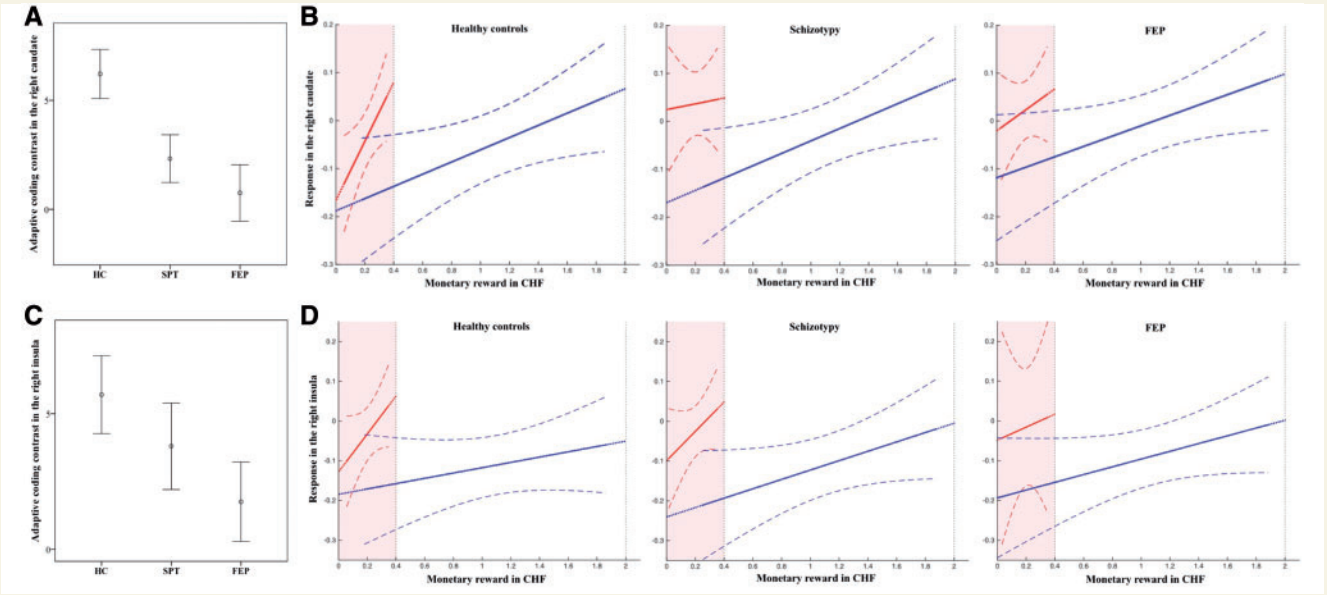

Figure 4 Group differences in adaptive reward coding in the right caudate and insula. (**A** and **C**) Mean adaptive coding contrast signal in the right caudate and right insula, separately for each group. Error bars depict one standard error of the mean. (**A**) In the right caudate, healthy controls showed stronger adaptive coding than the other groups, healthy control > SPT ($P = 0.024$), healthy control > FEP ($P = 0.002$). (**B** and **D**) Response functions illustrating neural adaptation in the right caudate and right insula, plotted separately for the low-reward (red) and the high-reward (blue) context. For visualization purposes, each reward context was divided into two levels of reward amount received (low reward: CHF 0–0.2, CHF 0.2–0.4; high reward: CHF 0–1, CHF 1–2), which is represented by the *x*-axis. The *y*-axis represents the pmod low reward contrast estimate and the pmod high reward contrast estimate. (**B**) In the right caudate, healthy controls optimally adapt the neural coding range to the current range of rewards, resulting in a steeper slope of neural responses in the low reward context than in the high reward context. In contrast, individuals from the schizophrenia spectrum show significant deficits in adaptive coding. In particular, both patients with FEP and individuals with SPT showed blunted slope increases in the low reward context compared to the high reward context. (**C**) Mean adaptive coding contrast signal in the right insula, separately for each group. Only FEP showed impaired adaptive coding compared to healthy controls at trend-level. ($P = 0.067$). (**D**) Response functions illustrating neural adaptation in the right insula. Healthy controls and individuals with SPT adapt the neural coding range to the current range of rewards, resulting in a steeper slope of neural responses in the low reward context than in the high reward context. In FEP patients, we observed blunted slope increase in the low-reward context, reflecting adaptive coding deficits in the right insula.

schizophrenia spectrum. Therefore, we performed an ANOVA on the adaptive coding contrast using group as fixed factor (healthy controls, SPT, FEP). In the right caudate, we observed a highly significant effect of group [$F(2,75) = 5.59$, $P = 0.005$, Bonferroni adjusted $P = 0.020$] (Fig. 4A). *Post hoc* analysis revealed significant differences between healthy control and both groups of the schizophrenia spectrum (healthy control > SPT $P = 0.027$; healthy control > FEP $P = 0.002$). In contrast, we found no group differences between individuals with SPT and patients with FEP ($P = 0.345$). Importantly, the main effect of group remained significant when controlling for age and cognition as potential confounding variables [$F(2,67) = 5.07$, $P = 0.009$, Bonferroni adjusted $P = 0.045$]. To visualize the differences in the adaptive coding of reward, we plotted the response functions of the neural activity in the low- and high-reward context separately for healthy control, SPT and FEP (Fig. 4B). Compared to individuals with SPT and patients with FEP, healthy control subjects show a steeper slope in the low reward context. Moreover, the more pronounced slope difference in the response function between low and high reward contexts indicates more effective adaptive coding in healthy controls than in the other two groups. Please note that the adaptive coding differences were similar when using a fully *a priori* defined region of interest based on our previous study (Kirschner *et al.*, 2016) or a region of interest based on the pmod high reward condition alone. The region of interest based on pmod high reward alone controls for potentially confounding group differences within the pmod low reward condition while retaining the basic requirement of reward coding (Supplementary material).

In the right insula we did not observe significant group differences in adaptive coding [$F(2,75) = 1.73$, $P = 0.184$] (Fig. 4C). However, explorative *post hoc* analysis revealed a trend-level difference between healthy controls and patients with FEP ($P = 0.067$) (Fig. 4D). Together, the observed categorical group differences provide strong evidence for impaired adaptation of reward coding in the caudate in both groups of the schizophrenia spectrum. In the insula, differences in adaptive coding were only observed at a trend level between healthy controls and patients having already developed a first psychotic episode.

Explorative analysis of adaptive coding in the putamen

In addition to our main analysis, we tested whether the reward sensitive clusters in the right and left putamen code reward values in an adaptive fashion. One-sample *t*-tests confirmed significant adaptive coding of rewards across the complete sample [right putamen: $t(75) = 4.67$, $P < 0.0001$, left putamen: $t(75) = 3.83$, $P < 0.0001$]. In a second step, we aimed to identify group differences in adaptive coding using the same ANOVA as in our main analysis. However, we did not observe any group differences in the left putamen [$F(2,75) = 1.42$, $P = 0.247$] or in the right putamen [$F(2,75) = 0.03$, $P = 0.974$]. These data suggest that neural adaptation to the current reward context remained relatively intact when viewed from a categorical perspective (see next section for a dimensional perspective). In keeping with this notion, we observed a trend-level group × region interaction, comparing the adaptive coding difference in the right caudate and right putamen [$F(2,75) = 2.68$, $P = 0.075$]. Thus, individuals from the schizophrenia spectrum appear to show stronger deficits in adaptive reward coding in the caudate than in the putamen.

Deficits of adaptive coding correlate with total symptom severity

Next, we addressed the second aim of the study, i.e. the association between symptom severity and adaptive coding deficits. To do so, we calculated Spearman rank correlations between contrast estimates of the adaptive coding contrast and symptom severity across the complete schizophrenia spectrum (SPT and FEP). Impaired adaptive coding in both the right caudate ($r_s = -0.313$, $P = 0.023$, Bonferroni adjusted $P = 0.092$) and right putamen ($r_s = -0.455$, $P = 0.001$, Bonferroni adjusted $P = 0.004$) correlated significantly with global symptom severity as determined with the PANSS Total score (Table 2 and Fig. 5). These correlations did not differ significantly ($z = 0.562$, $P = 0.574$). In contrast, in the right insula and left putamen individual symptom severity was not associated with adaptive coding (Table 2). Taken together, we observed an association between total symptom severity and adaptive coding deficits in the right striatum including the caudate and putamen.

In addition, we performed an explorative analysis to investigate potentially specific associations between adaptive coding deficits and positive, negative and general symptoms across the schizophrenia spectrum, including individuals with SPT and FEP. We found that adaptive coding deficits in the right caudate and right putamen were significantly correlated with negative and general symptoms but not with positive symptoms (Supplementary Table 3). However, direct comparisons using Steiger z-tests (Steiger, 1980) revealed no significant differences between the correlations with positive symptoms and the correlations with negative symptoms (right caudate: $z = 1.54$; right putamen, $z = 1.48$, both P's > 0.1) or between the correlations with positive symptoms and the correlations with general symptoms (right caudate: $z = 1.04$; right putamen, $z = 1.27$, both P's > 0.2). These findings suggest that adaptive coding deficits were primarily associated with negative and general symptoms in the current sample. Furthermore, we performed a correlation analysis in our subsample of healthy individuals with SPT between adaptive coding deficits and non-clinical psychotic symptoms assessed with the SPQ. We found that adaptive coding deficits in the right putamen correlated with the SPQ Disorganized Factor (Supplementary Table 4).

Finally, we tested whether symptom severity may be better explained by a deficit of adaptation as captured by deficient relative coding of reward magnitudes rather than by adaptation-independent deficits in absolute coding of reward magnitudes. Specifically, we investigated potential associations between the mean reward signal during the different reward conditions (low and high reward) and symptom severity. We did not find any association of total symptom severity, negative symptoms, or positive symptoms with individual coding of the mean reward signal (Supplementary Table 5). Moreover, direct comparison showed that total symptom severity correlated significantly more strongly with deficits in adaptive coding than with mean reward signals in the right caudate and putamen (Supplementary Table 6). Thus, impaired relative coding of reward magnitude appears to explain symptom severity better than absolute reward coding.

No association between medication dose and adaptive coding deficits

In our subsample of patients with FEP we investigated potential effects of antipsychotic medication on adaptive coding. Please note that all patients were on second-

Table 2 Correlation analysis of adaptive coding contrast

Complete schizophrenia spectrum (SPT and FEP) $n = 53$				
Adaptive coding contrast	**Right caudate**	**Right insula**	**Right putamen**	**Left putamen**
PANSS total score	−0.313*	−0.134	−0.455**	−0.082
Chlorpromazine equivalents, mg/day (FEP, $n = 27$)	−0.057	0.026	0.035	0.252

Spearman rank correlations (r_s). *$P < 0.05$, **$P < 0.01$.

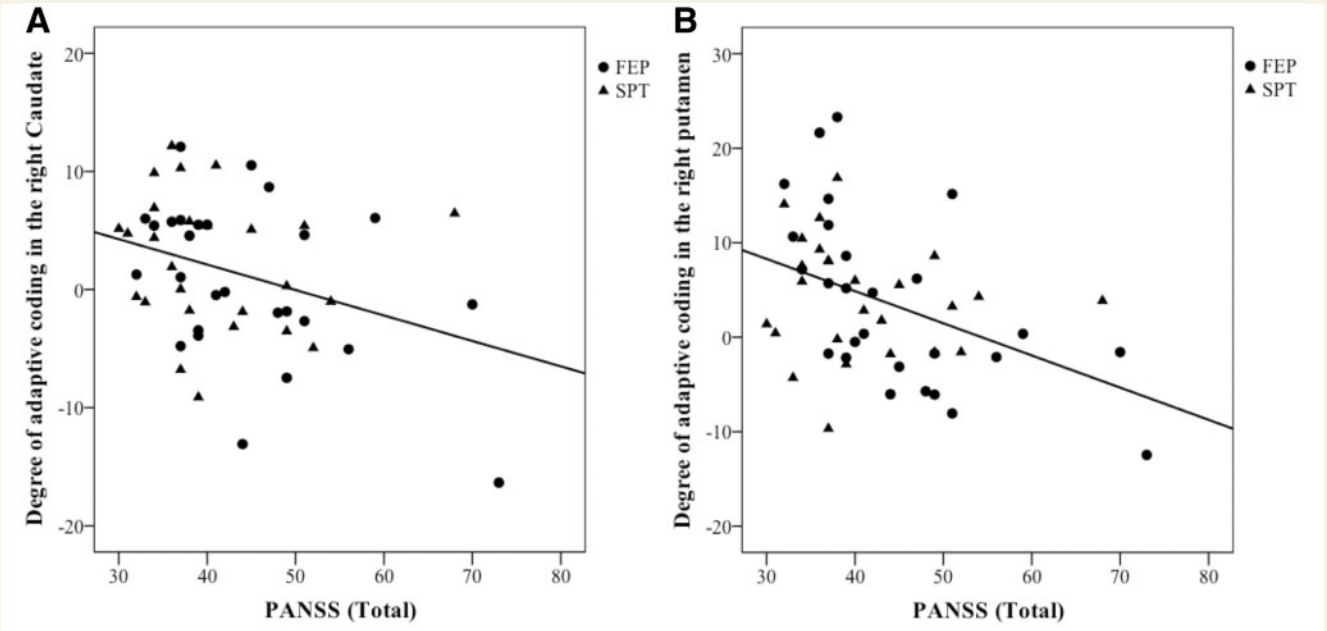

Figure 5 Adaptive coding deficits in striatum correlate with symptom severity. Correlation plots of the adaptive coding contrast estimates (pmod low reward – pmod high reward) with the PANSS total score across the complete sample of the schizophrenia spectrum. Adaptive coding deficits correlated significantly with total symptom severity (**A**) in the right caudate ($r = -0.338$, $P = 0.013$) and (**B**) right putamen ($r = -0.426$, $P = 0.001$).

generation antipsychotics. We did not find any association between current antipsychotic dose and adaptive reward coding (Table 2).

Discussion

We found that individuals from the schizophrenia spectrum show inefficient neural adaptation to the current reward context. The adaptive coding deficits were most prominent in the right caudate and even detectable in unmedicated healthy individuals with SPTs. These findings suggest that across the schizophrenia spectrum, individuals fail to take advantage of contextual information to adjust their sensitivity to more likely amounts, which would normally allow for an efficient representation of reward information. As indicated by intact behavioural sensitivity to contexts, inefficient neural reward adaptation was not due to reduced context sensitivity in general. The association between symptom severity and impaired adaptive coding in the right caudate and putamen suggests a dimensional mechanism, which relates adaptive coding to the pathophysiology of schizophrenia spectrum disorders.

Our findings in non-medicated individuals with SPTs show for the first time that subtle mental symptoms are linked to impaired adaptive coding irrespective of antidopaminergic medication. This is of high relevance given that previous work in healthy controls suggests that adaptive coding is critical for efficient behavioural adaptation (Diederen *et al.*, 2016) and linked to normal dopamine function (Diederen *et al.*, 2017). Furthermore, the observed adaptive coding deficits in non-clinical states (individuals with SPTs) and early psychosis (FEP patients) suggest that impaired adaptive coding may contribute to the development of reward and information processing deficits in disorders with dopamine dysfunction. Crucially, symptom severity within the schizophrenia spectrum was better explained by impaired context-dependent adaptation to relative reward magnitude rather than by an absolute reward signal. Taken together, these findings substantially extend the current literature on reward processing deficits in the schizophrenia spectrum and support the idea that inefficient adaptive coding may be a general deficit in the schizophrenia spectrum, with early onset within the course of the disease.

Implications for dysfunctional reward and salience processing

Our modified version of the Monetary Incentive Delay Task paradigm revealed a robust adaptive coding signal in several regions of the reward network including the striatum (both caudate and putamen) and the insula. These findings converge with previous reports of adaptive reward coding in the human brain (Park *et al.*, 2012; Burke *et al.*, 2016; Diederen *et al.*, 2016, 2017). In our sample, individuals from the schizophrenia spectrum showed the strongest impairments of adaptive coding in the caudate. From a functional perspective, the dorsal

striatum is involved in reward-guided action selection and in learning about actions and their reward consequences (Tricomi *et al.*, 2004; Balleine *et al.*, 2007; Delgado, 2007). However in the schizophrenia spectrum, the role of the dorsal striatum in the complex picture of disturbed neural reward coding just starts to emerge. There is increasing evidence suggesting that dorsal striatal dysfunction is related to widespread impairments in reward processes, including value representations (as assessed by devaluation of food rewards) guiding choice behaviour (Morris *et al.*, 2015), reward anticipation (Mucci *et al.*, 2015) as well as prediction error signalling (Waltz *et al.*, 2008; Dowd *et al.*, 2016). Our findings suggest that impaired adaptive coding could be an important pathophysiological mechanism, because precise representation of reward information can be considered a prerequisite for all further reward-related processes.

FEP patients showed imprecise neural adaptation to the current reward context in the insula, comparable to patients with chronic schizophrenia (Kirschner *et al.*, 2016) but unlike individuals with SPT. These divergent findings suggest that the deficits in adaptive coding may be partly stage-dependent and increase after the onset of first psychosis. However, further studies are needed to determine whether deficient adaptive coding in the insula could be a marker of disease progression.

At a more general level, the impaired neural reward adaptation in the striatum and insula is in line with a general deficit in basic information processing and with studies showing aberrant salience processing in individuals at risk for psychosis and early disease stages (Manoliu *et al.*, 2014; Smieskova *et al.*, 2015; Walter *et al.*, 2016; Winton-Brown *et al.*, 2017). Specifically, the imprecise neural representation of reward information could lead to increased uncertainty about external stimuli or internal values. This in turn may alter the processing of what is important in the current context and subsequently lead to inefficient dopamine firing and context-insensitive attribution of salience (Heinz and Schlagenhauf, 2010; Winton-Brown *et al.*, 2014).

Relationship to symptom severity

Across the schizophrenia spectrum, total symptom severity was associated with adaptive coding deficits in the dorsal striatum including the caudate and putamen. Moreover, our findings point towards an association of negative symptoms with a reduction in context-dependent discrimination of reward magnitudes in the striatum, which is in line with our previous findings in patients with chronic schizophrenia (Kirschner *et al.*, 2016). This imprecise representation and insufficient adaptation is likely to affect reward learning, motivation and cost-benefit computation (Barch and Dowd, 2010; Strauss *et al.*, 2014; Gold *et al.*, 2015; Hartmann-Riemer *et al.*, 2018). Indeed, the presently observed impairment in adaptation corresponds to impaired processing of rewards that are at the extreme ends of small reward ranges, which may impair daily functioning where small rewards and small reward ranges are the norm. The well-documented reductions in goal-directed behaviour shown by individuals of the schizophrenia spectrum (Barch and Dowd, 2010) could thus find a natural explanation in these forms of adaptive coding deficits.

With respect to positive symptoms, the link to impaired adaptive coding in the striatum was limited to the subsample of individuals with SPTs and non-clinical forms of disorganization (Raine *et al.*, 1994). This observation should be considered in the context of the previously described association of adaptive coding deficits with positive symptoms in chronic schizophrenia (Kirschner *et al.*, 2016). Imprecise representation and reduced differentiation of rewards (and information more generally) arising from a failure to adapt to different reward ranges likely results in reduced differentiation of relevant from non-relevant outcomes. This might lead to positive symptoms such as paranoid ideation, thought disorders and disorganized symptoms, either directly or via impaired learning about which information is important in the current context. The apparent lack of a relation between adaptive coding deficits and clinically relevant positive symptoms across the complete sample may reflect the fact that due to successful antipsychotic treatment the subsample of individuals with first episode psychosis had only mild levels of positive symptoms.

Taken together, the strong association between total symptom severity and reward adaptation deficits in the present and the previous study (Kirschner *et al.*, 2016) suggests a more general dysfunction of context-dependent adaptation relating to a broad range of symptoms instead of a specific neural correlate of positive, disorganized, or negative symptoms. Furthermore, given that context dependent adaptation of neural activity does not solely apply to the encoding of reward information, but also to sensory information processing, i.e. the processing of auditory and visual information (Smith and Lewicki, 2006; Wark *et al.*, 2009; Kastner and Baccus, 2014), one might speculate that imprecise adaptive coding may at least partly contribute to the general information processing deficit underlying the pathophysiology of the schizophrenia spectrum (Cohen and Servan-Schreiber, 1992; Hemsley, 2005; Fletcher and Frith, 2009).

Role of dopamine for adaptive reward coding

Our previous findings in chronic schizophrenia patients, the present study, and insights from healthy volunteers speak to the role of dopamine in adaptive reward coding. Recent findings from Diederen and colleagues (2017) suggest that dopamine perturbation (dopamine antagonism) prevents precise adaptive prediction error coding in healthy individuals. Specifically, acute single doses of a selective dopamine D2-receptor antagonist reduced adaptive prediction error coding (Diederen *et al.*, 2017). In contrast, we found that

stable atypical antipsychotic medication in our dose range was not associated with adaptive coding, neither in chronic schizophrenia patients (Kirschner *et al.*, 2016) nor in individuals with FEP (here). These results may be related to the differences between acute effects of single administration of a strong dopamine antagonist in healthy individuals (Diederen *et al.*, 2017) compared to continuous medication and antipsychotics with varying dopamine receptor blocking properties in a clinical sample (Kirschner *et al.*, 2016 and the present study). More generally, the combined findings support the idea that dopamine antagonism may have different effects on individuals with normal dopamine function and individuals with altered dopamine transmission.

Together with previous work (Park *et al.*, 2012; Burke *et al.*, 2016; Diederen *et al.*, 2016, 2017) our proposed model (Fig. 1) highlights the relevance of investigating the role of adaptive reward coding in the pathophysiology of disorders with dopamine dysfunction and can be extended to disorders such as Parkinson's disease and addiction. In Parkinson's disease one might speculate that the loss of dopamine neurons may lead to insufficient adaptation with poor discriminability of reward amount due to a restricted coding range (Supplementary Fig. 3). In addiction, the exposure to drugs may critically expand the range of rewards to which the system adapts and as a consequence result in insufficient adaptation to, and poor discriminability of, natural rewards (Supplementary Fig. 3). In summary, future research should test adaptive reward coding from a transdiagnostic perspective.

Limitations and future directions

Some limitations of our study need to be considered. Our sample showed only mild levels of positive symptoms, which did not differ between patients and individuals with SPT. This limits the representativeness of our study sample and the possibility to draw conclusions about patients with high levels of positive symptom expression. While our findings provide first evidence of adaptive coding deficits across individuals with non-clinical psychotic symptoms and early psychosis, future studies should focus on different groups to cover the full range of the schizophrenia spectrum, including individuals with ultra-high risk states, unmedicated patients with schizophrenia, patients with higher psychotic symptom levels and chronic patients with treatment-resistant symptoms. In addition, the PANSS has limitations in detecting non-clinical positive symptoms, while the SPQ factors do not fully map on the symptom structure of the clinical disease entities within the schizophrenia spectrum. Future studies focusing on non-clinical psychotic symptoms in at-risk groups and the general population should therefore use other rating scales such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al.*, 2005) or the Structured Interview for Prodromal Syndromes (SIPS) (Miller *et al.*, 2003) to specify our explorative findings of an association between adaptive coding deficits and non-clinical psychotic symptoms in healthy individuals with SPT. Furthermore, although dosage of second-generation antipsychotics were not related to impairments in adaptive coding, studies with unmedicated patients would be valuable to further elucidate the effects of medication on adaptive coding. An alternative approach may be the application of combined PET/functional MRI studies to clarify the role of dopamine for adaptive coding deficits in the schizophrenia spectrum. While we observed deficits in adaptive coding of reward, future studies should focus on adaptive coding in sensory and cognitive processes to test whether imprecise neural adaptation reflects a generalized deficit of information processing in the schizophrenia spectrum.

Conclusion

In summary, the present findings provide new evidence that insufficient adaption to reward contexts constitutes a deficit that characterizes both subclinical and clinical forms of the schizophrenia spectrum. Diminished discriminability of different reward amounts causes imprecise representation of reward information and may affect subsequent reward-related processes. Finally, the association between symptom severity and impaired adaptive coding suggests that adaptive coding may index a pathophysiological mechanism explaining disturbances within the schizophrenia spectrum over and above a simple model of absolute reward processing deficits.

Acknowledgements

We are grateful to Dr. Philipp Staempfli for his excellent technical support. Furthermore, we would like to thank all participants for their time and interest in our study.

Funding

This study was supported by the Swiss National Science Foundation (Grant No. 105314_140351 to Stefan Kaiser). P.N.T. was supported by the Swiss National Science Foundation (PP00P1_128574, PP00P1_150739, and 100014_165884).

Competing interests

S.K. has received speaker honoraria from Roche, Lundbeck, Janssen and Takeda. He receives royalties for cognitive test and training software from Schuhfried. P.N.T. has received grant support from Pfizer. E.S. has received grant support from H. Lundbeck and has served as a consultant and/or speaker for AstraZeneca, Otsuka, Takeda, Eli Lilly, Janssen, Lundbeck, Novartis, Pfizer, Roche, and Servier. None of these activities are related to

the present study. All other authors declare no biomedical financial interests or potential conflicts of interest.

Supplementary material

Supplementary information is available at *Brain* online.

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