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Reward disturbances in antipsychotic-naïve patients with first-episode psychosis and their association to glutamate levels

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Original Article

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Abstract

Background. Aberrant anticipation of motivational salient events and processing of outcome evaluation in striatal and prefrontal regions have been suggested to underlie psychosis. Altered glutamate levels have likewise been linked to schizophrenia. Glutamatergic abnormalities may affect the processing of motivational salience and outcome evaluation. It remains unresolved, whether glutamatergic dysfunction is associated with the coding of motivational salience and outcome evaluation in antipsychotic-naïve patients with first-episode psychosis.

Methods. Fifty-one antipsychotic-naïve patients with first-episode psychosis (22 ± 5.2 years, female/male: 31/20) and 52 healthy controls (HC) matched on age, sex, and parental education underwent functional magnetic resonance imaging and magnetic resonance spectroscopy (3T) in one session. Brain responses to motivational salience and negative outcome evaluation (NOE) were examined using a monetary incentive delay task. Glutamate levels were estimated in the left thalamus and anterior cingulate cortex using LCModel.

Results. Patients displayed a positive signal change to NOE in the caudate ($p = 0.001$) and dorsolateral prefrontal cortex (DLPFC; $p = 0.003$) compared to HC. No group difference was observed in motivational salience or in levels of glutamate. There was a different association between NOE signal in the caudate and DLPFC and thalamic glutamate levels in patients and HC due to a negative correlation in patients (caudate: $p = 0.004$, DLPFC: $p = 0.005$) that was not seen in HC.

Conclusions. Our findings confirm prior findings of abnormal outcome evaluation as a part of the pathophysiology of schizophrenia. The results also suggest a possible link between thalamic glutamate and NOE signaling in patients with first-episode psychosis.

Introduction

Reward processing is a complex but important feature in humans, and alterations in the brain reward system have been documented in medicated and in antipsychotic-naïve schizophrenia patients (Nielsen et al., 2012; Radua et al., 2015). Several steps are involved in reward processing, e.g. the coding of motivational salient events and prediction error (PE) during outcome evaluation. Coding of motivational salience indicates the importance of stimuli that attract attention and behavioral resources (Zink, Pagnoni, Martin-skurski, Chappelow, & Berns, 2004). PE, which is the coding of a mismatch between expected and obtained outcome, forms the basis for learning (Schultz & Dickinson, 2000). If PE coding is absent, learning does not occur, and the stimuli may not be assigned salience which subsequently may diminish the anticipation of a reward value (Diederen & Fletcher, 2020). Abnormalities in the coding of motivational salience and outcome evaluation may add to an impaired ability to distinguish between relevant and irrelevant sensory information. This is hypothesized to misallocate attention and salience to otherwise neutral stimuli, resulting in false associations and development of psychotic symptoms (Fletcher & Frith, 2009; Heinz, 2002; Heinz et al., 2019; Kapur, 2003).

In healthy individuals, the anticipation of both reward and punishment activates the caudate (Knutson, Adams, Fong, & Hommer, 2001), whereas an attenuated blood oxygen level-dependent (BOLD) response during anticipation of motivational salient events has been reported in striatal regions in patients with psychosis (Nielsen et al., 2012; Radua et al., 2015). Likewise, an aberrant signal during outcome evaluation has been found in the midbrain, striatum, thalamus, prefrontal cortex, including the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Ermakova et al., 2018; Radua et al., 2015; White,

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Kraguljac, Reid, & Lahti, 2015). An exaggerated BOLD response in the prefrontal cortex during negative PE, i.e. when the outcome is worse than expected, has been reported in unmedicated patients with schizophrenia (Schlagenhauf et al., 2009). However, studies on medicated patients with schizophrenia report mixed findings of intact or exaggerated negative PE signal (Walter, Kammerer, Frasch, Spitzer, & Abler, 2009; Waltz et al., 2018) which stresses the importance of examining antipsychotic-naïve patients to exclude confounding effect of medication.

The use of N-methyl-D-aspartate antagonists (NMDA-A), which act upon the glutamatergic system (Weckmann et al., 2019), produces delusional beliefs and modulates PE-dependent associative learning signals in the prefrontal cortex in healthy controls (HC) (Corlett et al., 2006). Likewise, NMDA-A have been suggested to disrupt prior expectations and the signaling of violated expectations (Corlett, Honey, Krystal, & Fletcher, 2010). Moreover, in preclinical studies, infusion of NMDA into the thalamus enhances dopamine neuron activity in the ventral tegmental area (Zimmerman & Grace, 2016), an area involved in reward processing (Robison, Thakkar, & Diwadkar, 2020). The association between glutamate and reward activity has only been investigated *in vivo* in a few studies, which report mixed findings depending on brain regions (Bossong, Wilson, Appiah-Kusi, McGuire, & Bhattacharyya, 2018; Gleich et al., 2015; Jocham, Hunt, Near, & Behrens, 2014; White et al., 2015). Reports of a positive association between ACC glutamate and BOLD response during cognitive task exist in schizophrenia patients (Cadena et al., 2018; Falkenberg et al., 2014). In another study, a correlation between glutamate levels in substantia nigra and PE was found in HC but not in schizophrenia patients (White et al., 2015).

Glutamatergic abnormalities are believed to be involved in schizophrenia (Egerton & Stone, 2012; Moghaddam & Javitt, 2012; Olney & Farber, 1995) and have been found in ACC (Bustillo et al., 2010; Kegeles et al., 2012) and the thalamus (Bojesen et al., 2019; Théberge et al., 2002, 2007), which are parts of major cortico-striato-thalamo-cortical networks believed to be disrupted in psychosis (Dandash, Pantelis, & Fornito, 2017). Glutamatergic projections from the prefrontal cortex and thalamus may modulate striatal output (Carlsson, Waters, & Carlsson, 1999; Dandash et al., 2017) including responses to stimuli associated with a motivational value (Matsumoto, Minamimoto, Graybiel, & Kimura, 2001). Therefore, it seems likely that glutamatergic activity in ACC and thalamus may modulate the processing of motivational salience and outcome evaluation.

In the present study, we primarily compared signaling of motivational salience and negative outcome evaluation (NOE) between a large group of HC and antipsychotic-naïve patients with first-episode psychosis using a region of interest (ROI) approach. For ROIs with significant group differences, we further examined the relationship with glutamate levels in ACC and left thalamus. Explorative analyses of relationships were also performed for ROI without group differences in motivational salience or NOE signal, and for ROIs in the right hemisphere and on positive outcome (PO) signaling.

We hypothesized that patients would show an attenuated motivational salience signal and an altered NOE signal, as well as an abnormal association between these signaling and glutamate levels.

Methods

The study, approved by the Danish National Committee on Biomedical Research Ethics (H-3-2013-149), was carried out in accordance with Helsinki Declaration II. Participants received thorough information about the study before providing written informed consent.

Participants

Antipsychotic-naive patients with FEP were recruited from in and out-patient clinics in the Capital Region of Denmark Mental Health Services (2014–2019) as part of a larger study previously described (Bojesen et al., 2019). Patients were included if they were 18–45 years of age, lifetime antipsychotic-naïve, had no prior use of central nervous system stimulants (verified by medical records), and no substance abuse in the preceding 3 months. HC were recruited from the local community through advertisement (forsøgsperson.dk). HC were matched to FEP according to age, sex, and parental educational background. Inclusion and exclusion criteria are further specified in the online Supplementary material.

Spectroscopy data from the study partially overlap with data included in two other papers [$N_{FEP} = 34$, $N_{HC} = 34$ (Bojesen et al., 2019); $N_{FEP} = 51$, $N_{HC} = 51$ (Bojesen et al., 2020)].

Clinical assessment

For patients, symptom severity was assessed by trained raters with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) in the same week as magnetic resonance imaging (MRI) was performed. Prior to the MRI, participants were asked about the use of drugs and performed a drug urine test (Rapid Response, Jepsen Healthcare, Tune, Denmark).

MRI data acquisition

Participants underwent structural MRI and proton magnetic resonance spectroscopy (1H-MRS) followed by functional MRI (fMRI) in one session in a 3.0 Tesla scanner (Achieva, Phillips Healthcare, Eindhoven, The Netherlands), using a 32-channel head coil (Invivo, Orlando, Florida, USA). Initially, a whole-brain 3D T1-weighted structural scan (TR 10 ms, TE 4.6 ms, flip angle = 8°, voxel size $0.79 \times 0.79 \times 0.80$ mm^3) was acquired for anatomical reference, spectroscopic voxel placement, and tissue classification of gray and white matter. Glutamate was measured using single voxel 1H-MRS [point-resolved spectroscopy sequence (PRESS): TR 3000 ms, TE 30 ms, 128 averages with multiply optimized insensitive suppression train (MOIST) water suppression] in a $2.0 \times 1.5 \times 2.0$ cm^3 voxel in the left thalamus and in a $2.0 \times 2.0 \times 2.0$ cm^3 voxel prescribed in ACC prior to the functional sequence. Mean voxel placement and spectra are shown in online Supplementary Fig. S1. The MRS voxels were prescribed in the ACC and left thalamus based on the previous findings of abnormalities in glutamatergic measures (Bustillo et al., 2010; Théberge et al., 2002) and because these regions are part of cortico-striato-thalamo-cortical networks believed to be dysregulated in psychotic disorders and implicated in reward processing.

For the fMRI, 336 echo-planar images were acquired (TR 2000 ms, TE 25 ms, flip angle = 75°, 38 slices and voxel size of $2.8 \times 2.97 \times 2.4$ mm^3). To minimize motion artifacts, patients were instructed not to move their heads during scans.

fMRI task

Brain reward activity was examined with fMRI while participants played a variant of the MID task (Knutson, Westdorp, Kaiser, &

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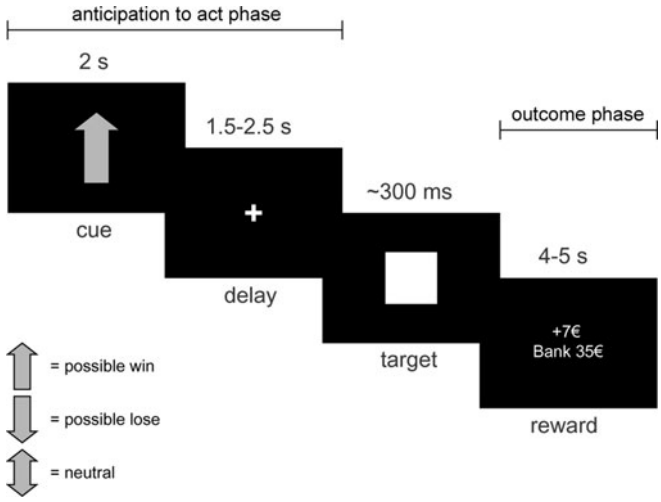

Fig. 1. The modified monetary incentive delay task used in the present study. First, a cue was presented on the screen representing a trial with possible win, possible loss, or a neutral condition. This was followed by a waiting phase (cross) and a target cue (white box), where participants pressed a button as fast as possible, expecting to win or avoid losses. Afterwards, the trial outcome appeared on the screen. In possible win trials, participants gained Euro 7 on a hit and Euro 0 on a miss. In possible loss trials, participants earned Euro 0 on a hit and lost Euro 7 on a miss. Neutral trials resulted in Euro 0 every time.

Hommer, 2000; Uldall et al., 2020), a task widely used to probe the neural activity of anticipation and outcome. The paradigm used in the present study included trials with the possibility of winning or losing money and neutral stimuli only (Fig. 1). The task lasted 12 min and comprised 72 interactive trials that were evenly distributed between winning or losing money and neutral trials. The task adapted to the individual reaction time to provide a hit rate of 66%. Participants were instructed about the task, the meaning of the cues, the possibility of monetary gain, and practiced the task for 5 min before data acquisition. Participants were not informed about the adaptive hit rate. All participants correctly believed that they would receive money upon completion of the task. Hence, participants had expectations of monetary gain. For detailed description, see online Supplementary material.

fMRI analysis

Analyses of fMRI data were performed using tools from FMRIB (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) Software Library fmrib.ox.ac.uk/fsl. First-level analyses were carried out using the FSL fMRI Expert Analysis Tool. Functional images were corrected for slice timing and motion effects, realigned, spatially smoothed with a 5 mm full-width at half-maximum Gaussian kernel. A high pass filter was applied with a 200 s cutoff. The images were co-registered to the corresponding T1-weighted image and normalized to Montreal Neurological Institute (MNI) space (MNI, Quebec, Canada). We used a general linear model consisting of nine predictors and their temporal derivative to analyze data. Three predictors modeled each of the cues, one predictor indicated button press, and five predictors defined the different outcomes: win, lose, hit, miss, and neutral. All predictors were convolved with the hemodynamic response function. Our contrasts of interest were a contrast of joint effect of the anticipation of win and loss *v.* neutral, and a contrast of outcome miss *v.* outcome neutral, see online Supplementary Fig. S3 for task design. The former contrast is hereinafter referred to as motivational salience, and the latter contrast as NOE.

Explorative analyses were performed for PO (outcome hit *v.* neutral outcome). The mean percent signal change for the contrasts was extracted from predefined ROIs to be used for group comparison and correlations with glutamate levels. For illustrative purpose, the contrasts of interest were taken to second-level analysis for a whole-brain group comparison. The resulting *z*-statistic images were thresholded using clusters determined by $Z > 2.3$ and corrected significance threshold of $p = 0.05$ (Worsley, 2001).

MRS analysis

PRESS acquisitions were analyzed using LCModel version 6.3-1L (http://s-provencher.com/lcmodel.shtml) (Provencher, 1993) and fitted in the spectral range 0.2–4.0 ppm, as previously described (Bojesen et al., 2019). Unsuppressed water reference spectra were acquired separately as inbuild sequences in the PRESS sequences. The *in vivo* water-scaled values of metabolites reported by LCModel were corrected for partial volume cerebral spinal fluid to estimate concentration in institutional units (IU) (Stone et al., 2012). Details of 1H-MRS acquisition, quality assessment and analyses are reported in online Supplementary material, including the illustration of mean voxel placements, representative spectra (online Supplementary Fig. S1), and analyses with the correction of gray matter and with glutamate + glutamine (glx).

ROIs

Since glutamatergic measures were assessed in ACC and in the left thalamus only, we also extracted fMRI activity based on ROIs in the left hemisphere. For explorative analyses, fMRI activity was extracted from ROIs in the right hemisphere. The striatal ROIs were defined as a 6 mm radius spherical region centered in the MNI coordinates: −10, 12, 8 (caudate) and −10, 14, −6 (accumbens), in accordance with published studies (Nielsen, Rostrup, Broberg, Wulff, & Glenthøj, 2018; Nielsen, Rostrup, Wulff, Glenthøj, & Ebdrup, 2016; Zink, Pagnoni, Martin, Dhamala, & Berns, 2003). The ROIs in ACC, DLPFC, and thalamus were defined as a 5 mm radius spherical region centered in the MNI coordinates −5, 39, 20 (ACC), −46, 38, 8 (DLPFC), and −7, −17, 5 (thalamus), in accordance with the previous findings of monetary outcome processing in DLPFC area within BA 46 (Waltz et al., 2010), ACC within BA 32 (Knutson et al., 2000), and thalamus (Oldham et al., 2018) converted to MNI space using Talairach Daemon http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html.

Overlap of the fMRI ROIs and spectroscopic voxels is provided in online Supplementary Fig. S2.

Statistics

Analyses were performed using IBM SPSS Statistics 25.

Group differences in demographic, clinical variables, motivational salience, and outcome evaluation signal were analyzed using independent *t* tests and χ^2 tests. Glutamate levels were analyzed using ANOVA, with and without correction for covariates sex, age, and smoking due to previously shown impact on glutamate (Marsman et al., 2013; O'Gorman, Michels, Edden, Murdoch, & Martin, 2011). To correct for multiple comparisons, significant level of group differences in the five left fMRI ROIs was set to $p = 0.05/5 = 0.01$.

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Table 1. Demographic and clinical characteristics of participants

	FEP $N = 51$	HC $N = 52$	Statistics
Age, years mean ± S.D.	22 ± 5.2	22 ± 4.6	T(101) = 0.03[a], $p = 0.98$, CI −1.89 to 1.95
Sex, male/female	20/31	21/31	$\chi^2 = 0.015$[b], $p = 0.90$
Education, years mean ± S.D.	12.0 ± 2.1	14 ± 2.3	T(101) = −4.76[a], $p < 0.001$, CI −2.92 to −1.20
Parental education (high/moderate/low)	20/22/9	19/30/3	$\chi^2 = 4.25$[b], $p = 0.12$
Ethnicity, *N* white/Asian/African/other	47/1/1/2	52/0/0/0	Fisher's[c] $p = 0.06$
Handedness (right/left/both)	43/4/4	41/8/2	Fisher's[c] $p = 0.41$
Current substance use			
Tobacco, yes/no	18/33	11/41	$\chi^2 = 2.55$[b], $p = 0.11$
Cannabis, yes/no	2*/49	2*/50	Fisher's[c] $p = 1.0$
Benzodiazepine, daily/occasionally/no	1/5/45	0/0/52	Fisher's[c] $p = 0.01$
Diagnoses ICD-10, *N* (%)			
Schizophrenia	39 (76)		
Paranoid psychosis	2 (4)		
Schizoaffective depressive	1 (2)		
Non-organic psychosis	9 (18)		
PANSS score, mean ± S.D.			
Total score	75 ± 15		
Positive score	19 ± 4		
Negative score	20 ± 6		
General score	37 ± 8		

FEP, first-episode psychosis patients; HC, healthy controls; *N*, number of subjects; S.D., standard deviation; PANSS, Positive and Negative Syndrome Scale.
*Current use of cannabis was less than once a month, [a]independent *t* test, [b]χ^2 test, [c]Fisher's exact test.

Regression analysis was used to test the association between motivational salience or NOE signal and glutamate levels in ACC and thalamus separately for HC and FEP with and without correcting for covariates. For these regression analyses, the main outcome was analyses involving the left fMRI ROIs with significant group differences in BOLD responses, and to correct for multiple comparisons, the significance level for the association between glutamate voxels and two fMRI ROI with motivational salience signal and NOE signal was set to $p < 0.05/2 \times 2 \times 2 = 0.006$. Explorative regression analyses between three left fMRI ROIs with non-significant group differences in fMRI measures and glutamate voxels were set to $p < 0.05/2 \times 3 \times 2 = 0.004$.

Behavioral measures of hit rate and response time were analyzed using ANOVA with trial type (three levels: possible win, possible lose, neutral trial) as within-subject factor and group as between-subject factor.

Explorative analyses of correlations between PANSS scores and imaging measures were tested using spearman correlation and to correct for multiple correlations the significance level was set to $p < 0.05/(4$ PANSS subscores$\times 12$ imaging measures$) = 0.001$.

Results

A total of 103 participants were included, herein 52 HC and 51 FEP. The majority of FEP were diagnosed with schizophrenia ($n = 39$). Table 1 presents the demographic and clinical characteristics. There were no group differences in age, handedness, parental educational background, sex, and smoking status or cannabis use (all $p > 0.15$).

Patients were less educated ($p = 0.001$) and used benzodiazepine more often ($p = 0.01$).

Behavioral data

The mean monetary gain was Euro 76 with no group difference [T(101) = 0.10, mean difference 0.048, confidence interval (CI) −9.6 to 9.7; $p = 0.99$].

Analysis of hit rate showed no effect of group [$F_{(1,\ 101)} = 0.02$, $p = 0.89$] and no significant group×trial type interaction. There was a main effect of trial type [$F_{(1,\ 101)} = 64.9$, $p < 0.001$], and post hoc tests showed a difference between hit rates of neutral trials and trials with possible win ($p < 0.001$) or possible loss ($p < 0.001$), with the lowest hit rates in neutral trials.

The analysis of response time showed a main effect of group [$F_{(1,\ 101)} = 6.2$, $p = 0.015$], with FEP showing a higher response time but no effect of trial type [$F_{(1,\ 101)} = 0.84$, $p = 0.36$] and no group×trial type interaction, see online Supplementary material and Table S7.

Thus, all participants understood the importance of the cues, and no group difference in hit rate omit the confounding effect of behavioral data on the analyses in motivational salience and NOE signal.

Motivational salience and NOE signal

For the motivational salience signal, there were no group differences in any ROIs [caudate (T(101) = −0.9, $p = 0.35$, CI −0.11

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to 0.04), accumbens (T(101) = −1.3, p = 0.18, CI −0.10 to 0.02), DLPFC (T(101) = −0.08, p = 0.94, CI −0.09 to 0.08), ACC (T(101) = −0.02, p = 0.98, CI −0.06 to 0.06), and thalamus (T(101) = −0.2, p = 0.80, CI −0.9 to 0.07)], see Fig. 2.

For NOE signal, there was a group difference, with FEP showing a positive contrast signal which was not found in HC in the caudate [T(101) = 3.4, p = 0.001, CI 0.07–0.28] and in DLPFC [T(101) = 3.1, p = 0.003, CI 0.07–0.34] but not in accumbens [T(101) = 1.8, p = 0.07, CI −0.009 to 0.19], thalamus [T(101) = 1.9, p = 0.06, CI −0.006 to 0.21], or ACC [T(101) = 1.7, p = 0.09, CI −0.1 to 0.17], see Fig. 2.

Explorative analyses for NOE signal on ROIs in the right hemisphere were the same as for the left hemisphere, and analyses for PO signal showed no group difference, see online Supplementary material and Table S1.

Glutamate levels in ACC and left thalamus

Glutamate measures in ACC in three FEP were excluded, while glutamate measures in the thalamus in one FEP and three HC were excluded.

There was no group difference in glutamate levels [thalamus: $F_{(1,\ 97)}$ = 0.39, p = 0.53, CI −0.24 to 0.46; ACC: $F_{(1,\ 98)}$ = 0.98, p = 0.32, CI −0.42 to 0.14], nor when controlled for covariates (thalamus: p = 0.24, CI 0.54–0.14; ACC: p = 0.33, CI −0.14 to 0.41). The main effects of age, sex, and smoking status are reported in online Supplementary results as well as mean values, 95% CI, and glutamate measures corrected for the content of gray matter.

Association between motivational salience or NOE signal and glutamate levels

There was a different association between NOE signal in the left caudate and left DLPFC and thalamic glutamate levels in FEP and HC [significant interactions: caudate $F_{(1,\ 95)}$ = 7.2, p = 0.009; DLPFC: $F_{(1,95)}$ = 7.1, p = 0.009] due to a negative correlation in FEP (caudate: β = −0.40, p = 0.004, CI −0.62 to −0.12; DLPFC: β = −0.39, p = 0.005, CI −0.69 to −0.13), also after adjustment for covariates (caudate: β = −0.55, p = 0.001, CI −0.44 to −0.15; DLPFC: β = −0.48, p = 0.002, CI −0.82 to −0.19), but not in HC (caudate: p = 0.37, CI −0.15 to 0.40; DLPFC: p = 0.46, CI −0.12 to 0.39) (Fig. 3).

For ROIs with no group differences in fMRI measures, explorative correlations between BOLD response and glutamate levels in FEP showed an association between thalamic glutamate and NOE signal in left thalamus (r = −0.39, CI −0.65 to −0.12, p = 0.005), which did not survive Bonferroni correction. No other correlations were found between motivational salience, NOE signal or PO signal, and glutamate levels in thalamus or ACC, nor when correcting for covariates, when correcting for gray matter, or when performing analyses with glx measures, see online Supplementary material and Tables S2–S4.

Correlations between PANSS scores in patients and imaging measures

Explorative correlations showed no correlations between PANSS scores and imaging measures (all p > 0.07), see online Supplementary material and Table S6.

Whole-brain analysis of motivational salience and NOE signal

NOE

Analysis showed significant group differences in parts of several brain areas (left thalamus, left superior and inferior frontal

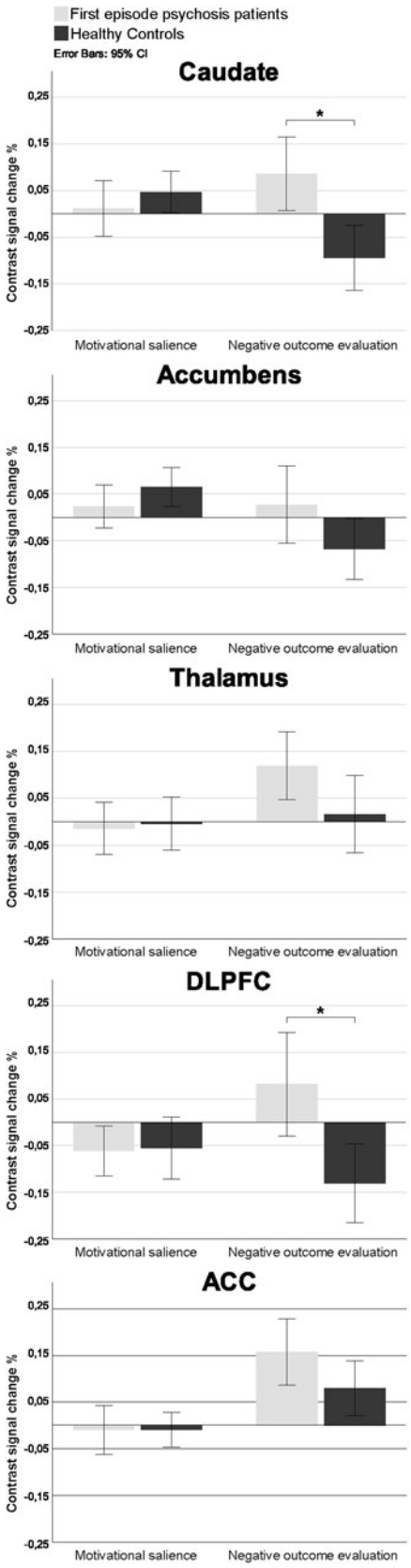

Fig. 2. Responses in predefined left regions of interest to motivational salience and negative outcome evaluation divided by groups. Extraction of parameter estimates was performed using FMRIB (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) Software Library tools. Group differences were found for negative outcome evaluation in the caudate (p = 0.001) and in the dorsolateral prefrontal cortex (p = 0.003).

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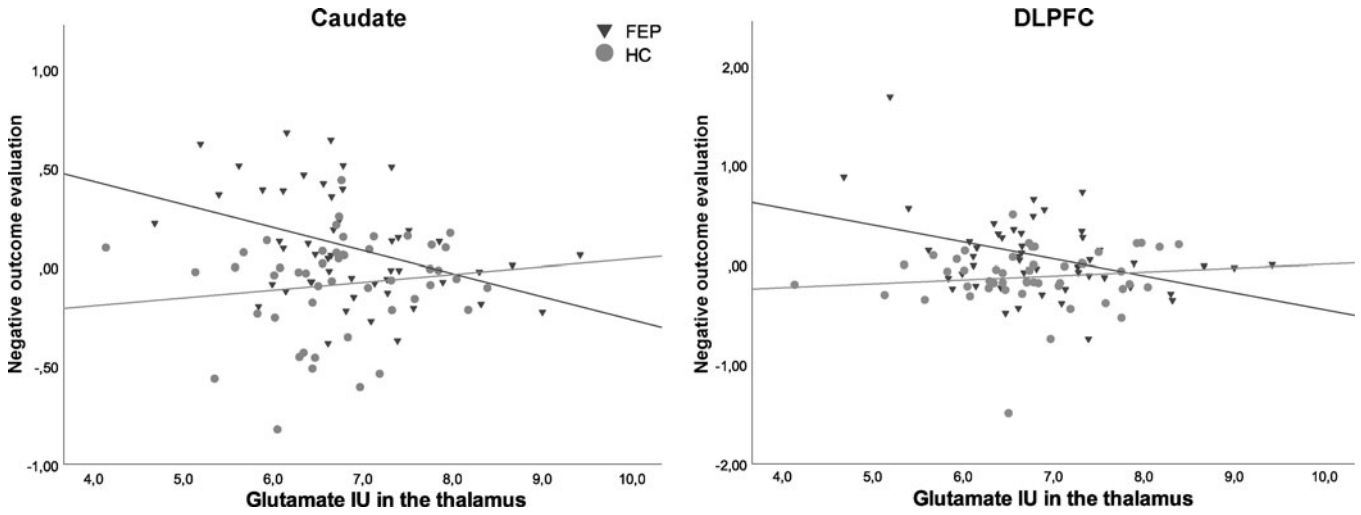

Fig. 3. Correlation between thalamic glutamate levels and negative outcome evaluation signaling in the left caudate (*a*) and left DLPFC (*b*) in antipsychotic-naïve patients with first-episode psychosis and healthy controls. Using regression analysis, a negative correlation was found in the former (caudate: $\beta = -0.44$, $p = 0.004$, DLPFC: $\beta = -0.39$, $p = 0.005$) but not in the latter ($p = 0.37$).

gyrus, left middle and superior temporal gyrus, intra-calcarine cortex, and occipital fusiform gyrus), including regions partly overlapping predefined ROIs with higher signaling in FEP. HC showed no brain areas with increased NOE signal compared to FEP (online Supplementary Fig. S3).

Motivational salience

No group difference was found, though HC displayed increased signal in areas of striatum, midbrain, and occipital regions, and FEP did not (online Supplementary Fig. S4).

Discussion

Our primary outcome examining group differences in motivational salience and NOE signal in predefined ROIs showed a positive signal change in FEP during NOE in the caudate and DLPFC compared to HC. For the motivational salience signal, no significant group differences were found. Our secondary outcome examining associations between glutamate levels and motivational salience or NOE signal showed an inverse correlation between thalamic glutamate levels and NOE signal in the caudate and DLPFC of FEP only.

To our knowledge, this is the largest study to date investigating signaling of motivational salience and NOE using a MID task in a large cohort of antipsychotic-naïve patients with FEP. In addition, this is the first study exploring associations between glutamate levels and coding of motivational salience and NOE in antipsychotic-naïve patients with FEP.

In general, fMRI studies in patients with schizophrenia report hypoactivation in the ventral striatum during anticipation of monetary reward (Radua et al., 2015). Our group has previously reported attenuated signal using a comparable contrast of motivational salience in antipsychotic-naïve schizophrenia patients (Nielsen et al., 2012). We did not replicate these findings in the present study. Importantly, the MID task used in the present study was modified to include cues with possible win or loss only, leading to higher frequency of salient trials which may have introduced habituation in HC (Avery et al., 2019). Further, an effect of uncertainty on tonic dopamine firing has been suggested (Mikhael & Bogacz, 2016), thus the presence of uncertainty in the cues involved may confound the response to motivational salience. In addition, the present study included patients with FEP and not exclusively patients with schizophrenia. Moreover, previous studies have reported associations between attenuated response to anticipation of salient events and increased level of positive (Esslinger et al., 2012; Nielsen et al., 2012) and negative symptoms in patients with schizophrenia (Radua et al., 2015). In the present study, the mean PANSS scores were lower compared to other studies of unmedicated/antipsychotic-naïve patients with schizophrenia (Esslinger et al., 2012; Nielsen et al., 2012).

We found a positive signal change during NOE in the caudate and DLPFC in FEP. Previous studies of HC report striatal activation during unexpected rewards and hypoactivation in striatal and prefrontal regions during unexpected unsuccessful outcomes, i.e. omission of rewards or loss of money (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Kim, Shimojo, & O'Doherty, 2006; Knutson, Fong, Bennett, Adams, & Hommer, 2003; Morris et al., 2012; Schlagenhauf et al., 2009). Studies of patients with schizophrenia have shown, in contrast to HC, an exaggerated response in prefrontal and striatal regions when expected rewards were not delivered (Schlagenhauf et al., 2009; Walter et al., 2009) which is in line with our results.

These findings may be explained by altered responses to neutral events in people with psychosis (Maia & Frank, 2017) or that FEP coded NOE in an unsigned fashion, which indicates surprise without valence (Haarsma et al., 2020). Our NOE contrast was defined as miss *v.* neutral outcome, however, additional exploratory analyses on neutral outcome, and on PO signaling, showed no alterations in FEP, see online Supplementary material. Hence, the NOE signal in FEP in this study may not be influenced by alterations in neutral responses or unsigned coding.

Findings in the literature, however, are not consistent since a negative signal change and no group difference have also been reported (Koch et al., 2010; Morris et al., 2012; Waltz et al., 2018). Importantly, group differences in signal during outcome evaluation may depend on the design of the contrast used to analyze brain responses, where increased activity during the evaluation of neutral outcome or expected rewards (Jensen et al.,

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2008; Murray et al., 2008) in patients with schizophrenia may affect the signal of the contrast defined in various studies. Moreover, some argue that brain responses may differ between receiving a punishment and not receiving a reward depending on individual sensitivity to punishment and reward (Boksem, Tops, Kostermans, & De Cremer, 2008) and, to some degree, may involve different neural processes (Boksem et al., 2008; Matsumoto, 2008; Matsumoto & Hikosaka, 2007).

Processing of aversive outcome in HC seems to involve DLPFC, thalamus, and ACC, where the brain responses to aversive outcomes decrease, with decreased expectation of the outcome indicating learning (Dunsmoor, Bandettini, & Knight, 2008). In contrast, patients with schizophrenia have shown impaired learning of PE, with an inverse association between learning rate and brain response activity in DLPFC and thalamus (Koch et al., 2010). Thus, impaired learning may contribute to the altered NOE signal in FEP.

Contrasting previous findings on alterations in positive PE coding in early psychosis patients (Ermakova et al., 2018), we found no group difference in PO signaling, maybe because the task involved was less suited for the evaluation of positive PE as there was a high hit rate (Waltz et al., 2010).

Our secondary outcome showed an inverse association between thalamic glutamate level and NOE signal in the caudate and DLPFC in FEP but not in HC. Patients with higher levels of glutamate displayed a less positive contrast signal during NOE, and this may suggest a possible compensatory mechanism of glutamate on NOE signaling in these patients. Suggested to be a key component in regulating the reward circuit (Haber & Knutson, 2009), the thalamus may balance disturbances in striatal NOE signaling through glutamatergic projections to inhibitory striatal GABAergic neurons (Carlsson et al., 1999; Dandash et al., 2017; Nanda, Galvan, Smith, & Wichmann, 2009) or through the ventral tegmental area (Zimmerman & Grace, 2016). In line with our findings, a study on individuals at ultra-high risk of psychosis has shown a negative correlation between thalamic glutamate levels and DLPFC functional responses, and suggests that variations in thalamic glutamate can affect cortical function (Fusar-Poli et al., 2011). However, the association between NOE signal and thalamic glutamate levels was insignificant when corrected for gray matter and when investigating the association with glx levels (see online Supplementary Tables S3 and S4).

We did not find any correlations between ACC glutamate levels and NOE signal. Other studies have reported an association between ACC glutamate and BOLD response in patients with schizophrenia (Cadena et al., 2018; Falkenberg et al., 2014), which was not present or reversed in HC (Falkenberg et al., 2014; Gleich et al., 2015). This, however, was primarily observed when examining cognitive functions with the Stroop color task and the auditory speech perception task. To some extent, the mixed results can be explained by experimental design and the ROIs examined, as well as the effects of medication and number of subjects included (Bossong et al., 2018; Cadena et al., 2018; Falkenberg et al., 2014; Jocham et al., 2014; White et al., 2015).

Thalamic glutamate levels in IU were not increased in FEP, but after adjustment for gray matter, there was a trend of higher glutamate levels in FEP compared to HC. We have previously found increased measures of thalamic glutamate levels (Bojesen et al., 2019). These variations may be explained by differences in symptom severity or diagnosis, which may affect glutamate levels (Merritt, Egerton, Kempton, Taylor, & McGuire, 2016). No group difference in ACC glutamate levels was found, which is in line with a recent meta-analysis of antipsychotic-naïve/free patients (Iwata et al., 2018). Variations in studies may be explained by prior exposure to antipsychotic medication (Bustillo et al., 2010; Kegeles et al., 2012) or examinations in more dorsal regions of ACC (Reid et al., 2019; Wang et al., 2019).

Our data did not indicate that glutamate levels in the thalamus or ACC are associated with reward processing on a more general level, since no association was found with motivational salience. Rather, glutamate levels in the thalamus were specifically related to caudate and DLPFC NOE signaling in FEP. Complex cognitive processes appear to be involved in the encoding of outcome evaluation (Heinz et al., 2019), which theoretically may be sensitive to glutamatergic activity in patients with schizophrenia (Corlett et al., 2006, 2010; Honey et al., 2005; Vinckier et al., 2016). It has been suggested that higher levels of glutamate can act as a buffer, preventing patients with schizophrenia from showing marked cognitive impairments (Falkenberg et al., 2014) which is in line with our results of a more normalized NOE signal in FEP with higher levels of thalamic glutamate.

A strength of the present study was the multimodal approach and the inclusion of antipsychotic-naïve FEP, thus excluding the possible impact of antipsychotic medication. One of the limitations is that the study cohort represented only moderately ill patients, which may affect results. In addition, the task and contrast used did not measure a learning estimate of outcome evaluation, and may not formally test a PE model, however our findings are compatible with a disturbed processing of outcome evaluation in FEP. Applying larger cortical ROIs would be preferable, as previous studies show more widespread cortical activity for reward tasks (Bartra, McGuire, & Kable, 2013; Garrison, Erdeniz, & Done, 2013).

Finally, the assessment of glutamate was limited to voxels in the thalamus and ACC, and the inclusion of MRS voxels in the striatum and DLPFC would be preferable.

In conclusion, we found an altered NOE signal in caudate and DLPFC in FEP as part of the pathophysiology of schizophrenia. In addition, our findings indicated a possible link between the levels of thalamic glutamate and signaling of NOE in patients with first-episode psychosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721003305

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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