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Increased responses of the reward circuitry to positive task feedback following acute stress in healthy controls but not in siblings of schizophrenia patients

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Abstract

Acute stress is known to affect the way we process rewards. For example, during, or directly after stress, activity within key brain areas of the reward circuitry is reduced when a reward is presented. Generally, the effects of stress on the brain are time-dependent, changing neural and cognitive processing in the aftermath of stress to aid recovery. Such a dynamic response to stress is important for resilience on the longer term. However, relatively little is known about reward processing during the recovery phase of stress and whether this is changed in individuals at increased risk for stress-related psychopathology.

Healthy male individuals (N = 40) and unaffected siblings of schizophrenia patients (N = 40) were randomized to either an acute stress task (Trier Social Stress Test) or a no-stress task. Neural responses during reward anticipation and reward feedback (monetary gain or no gain) were examined 50 min later using an fMRI monetary incentive delay task. The ventral striatum and orbitofrontal cortex (OFC) were used as predefined hypothesis-driven regions of interest.

Neural responses following stress differed between controls and siblings during reward feedback (group x stress interaction OFC $p=0.003$, ventral striatum $p = 0.031$), showing increased ventral striatum and OFC responses following stress in healthy controls only. Exploratory analyses revealed that this effects was most pronounced during *hit* trials (compared to when a reward was omitted), and independent of monetary value. Stress did not affect subsequent reward processing in siblings of schizophrenia patients. We found no significant differences between controls and siblings in ventral striatum and OFC responses during reward anticipation following stress.

This study shows that ventral striatum and OFC responses to positive task feedback are increased in the aftermath of stress in healthy male controls, regardless of monetary value. This indicates a dynamic shift from previously reported reduced responses in the striatum and OFC to reward feedback directly after stress to increased responses to both reward and non-reward feedback during the recovery phase of stress. These increased neural responses following stress were absent in siblings of schizophrenia patients. Together, these findings indicate that stress recovery is affected in this at-risk group, particularly in responses to positive feedback following stress.

Introduction

The acute stress response facilitates a shift in (neural) resource allocation, increasing vigilant responding to environmental stimuli at the cost of higher-order cognitive functions (Hermans *et al.*, 2014). Likewise, dealing with acute stress comes at the cost of the processing of rewards. Behaviorally, acute stress was found to increase the preference for immediate rewards (Maier, Makwana and Hare, 2015) but to decrease reward responsiveness (i.e. the ability to learn from positive feedback) (Bogdan and Pizzagalli, 2006; Berghorst *et al.*, 2013), and to induce anhedonia-like behavior in rodents (Anisman and Matheson, 2005). In addition, functional activity within key brain areas of the reward circuitry is affected during or directly after stress. Specifically, increases in the striatum were found during reward anticipation (Kumar *et al.*, 2014; Lewis, Porcelli and Delgado, 2014) (but see Ossewaarde *et al.*, 2011), and decreases in the orbitofrontal cortex (OFC) and striatum when the reward is received (Porcelli, Lewis and Delgado, 2012; Kumar *et al.*, 2014). In other words, acute stress is generally considered to increase stimulus-response behavior but reduce reward learning and the hedonic value of the consumed reward.

The effects of stress on neural activity and accompanying behavior follow a distinct temporal pattern. In contrast to the effects of stress hormones and neuromodulators such as cortisol during or shortly after stress that drive emotional vigilance, the aftermath of stress –starting approximately 45-60 min after exposure to the stressor– is characterized by a normalization of cognitive abilities and emotional reactivity (Henckens *et al.*, 2010; Hermans *et al.*, 2014). This may also hold true for reward processing, however, evidence on the delayed effects of stress on reward processing is limited. A recent study found reduced differential neural activation during the anticipation of rewarding cues compared to non-rewarding cues 40 minutes after psychosocial stress (Kruse *et al.*, 2018). Other studies have administered hydrocortisone to measure the delayed effects of stress on reward processing. Fifty to 60 minutes after hydrocortisone administration, pallidum responses during reward anticipation were decreased (Kinner, Wolf and Merz, 2016), as well as ventral striatum responses during both reward and non-reward anticipation (Montoya *et al.*, 2014). These results indicate that time-dependent opposing effects of stress on reward processing exist. However, although hydrocortisone administration increases salivary cortisol in a similar timeline as psychosocial stress, concentrations are much higher (Kinner, Wolf and Merz, 2016). Moreover, brain responses during reward feedback during this time window have not been reported, and therefore the neural correlates of reward consumption during the recovery of stress remains unknown.

The dopamine (DA) system plays a crucial role in reward processing (Schultz, 2016), and alterations in the DA system are a well-established and profound feature of schizophrenia (Grace and Gomes, 2018). Moreover, altered mesolimbic responses to stress are hypothesized to play an important role in the onset, exacerbation and relapse of psychosis (Howes *et al.*, 2016). However, the effects of stress on reward processing during the recovery phase of stress in schizophrenia patients are unexplored to date. The use of antipsychotics in a prominent portion of schizophrenia

patients would complicate the interpretation of data from such investigations. Therefore, in this study we investigated the effects of stress on reward processing in unaffected siblings of schizophrenia patients who do not take any antipsychotics but who are at risk for multiple psychiatric disorders including schizophrenia, bipolar disorder and major depressive disorder (Cheng *et al.*, 2017). Siblings and offspring of schizophrenia patients share on average 50% of the genetic material with the affected patient and exhibit increased baseline dopamine synthesis capacity and transmission (Huttunen *et al.*, 2008; Brunelin *et al.*, 2010) and altered ventral striatum and OFC responses during reward processing in the absence of stress (de Leeuw, Kahn and Vink, 2014; Vink *et al.*, 2015). These findings suggest that the recovery of stress-induced changes in reward processing could be dysfunctional in this at-risk group.

We here report on reward processing in the ventral striatum and the OFC during the recovery of stress (50 min after stress) in two groups: healthy controls and unaffected siblings of schizophrenia patients. We hypothesize that 1) in healthy controls, a shift towards reduced ventral striatum and OFC responses will be observed in the aftermath of stress during reward anticipation, and increased ventral striatum and OFC responses during reward feedback and 2) that unaffected siblings of schizophrenia patients show a reduction in this shift.

Methods and Materials

Participants

A total of 40 healthy controls and 40 healthy siblings of schizophrenia patients were recruited from the GROUP (Genetic Risk & Outcome of Psychosis) study (Korver *et al.*, 2012) and via advertisements. Because of the influence of gender and the menstrual cycle on stress-induced cortisol levels (Kirschbaum *et al.*, 1999) we only included male participants. Participants were randomly assigned to the validated stress or no-stress condition of the Trier Social Stress Test (see below for detailed description). Three subjects were excluded due to technical problems with the MRI-scanner (control-no-stress = 1, sibling-stress = 2). Moreover, three subjects were excluded because of poor task performance (never responding during non-rewarding trials) (control-no-stress = 1, sibling-no-stress = 2). This resulted in four experimental groups: control-no-stress (n = 18), control-stress (n = 20), sibling-no-stress (n = 18), sibling-stress (n = 18). None of the participants were suffering from a psychiatric disorder. Furthermore, controls did not have first-degree relatives with a psychiatric disorder. None of the participants were using any synthetic corticosteroids. Current use of psychoactive substances (amphetamines, cocaine, opiates, methadone, benzodiazepines and cannabinoids) was determined with a urine multi-drug screening device (Multi-line) and self-report questionnaire. Two subjects (1 control and 1 sibling) tested positive for cannabis. Exclusion of these participants did not influence any of the results.

Prior to the experiment, all participants gave written informed consent. All procedures were checked and approved by the University Medical Center Utrecht ethical review board and performed according to the guidelines for Good Clinical Practice and the declaration of Helsinki.

Questionnaires

Current psychiatric disorders were excluded in all individuals using a semi-structured interview by a trained researcher (the Mini-International Neuropsychiatric Interview (MINI (Sheehan *et al.*, 1998)). Because trauma is known to influence reward processing (Novick *et al.*, 2018), participants completed two validated questionnaires on life events: the childhood trauma questionnaire (CTQ), Dutch version (Bernstein and Fink, 1998; Vinkers *et al.*, 2014) and the Life Stressor Checklist – Revised (LSC-R) (Wolfe *et al.*, 1996). Moreover, we assessed punishment and reward sensitivity using the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS) (Hermans *et al.*, 2010) because of its known association with ventral striatum activity during reward anticipation (Simon *et al.*, 2010). During the experiment, subjective stress levels were assessed using a 100 mm visual analogue scale (VAS) which was completed before, during and after the stress or control test (-10, +5 and +20 min after onset).

General procedures and stress induction

The present study is part of a larger project investigating the temporal dynamics of stress on neural responses in siblings of schizophrenia patients. The experimental scan session started with a resting state scan, followed by an emotion processing task (viewing and rating pictures from the international affective picture system (IAPS) van Leeuwen *et al.*, 2018) which are or will be reported elsewhere. The reward task was carried out directly after the emotion task.

All experiments were carried out between 4:30-8:30 PM to minimize variation in diurnal cortisol secretion. The TSST was carried out as previously published (van Leeuwen *et al.*, 2018). In short, participants received instructions five minutes prior to the stress or control condition, which was carried out outside the scanner in a separate room. The stress condition consisted of a 5 min job interview, followed by a 5 min mental arithmetic task in front of a committee (one woman and one man). The control condition consisted of a free speech (5 min) followed by a simple arithmetic task (3 min) (Het *et al.*, 2009). The experimenter was in the same room but did not evaluate the participant, nor was there a committee present. The monetary incentive delay (reward processing) task started approximately 50 minutes after onset of the stress or no-stress condition. Participants were instructed to refrain from heavy exercise (2 hours prior to participation) and caffeine intake (4 hours prior to participation).

Monetary incentive delay task

The reward task was carried out as described previously (de Leeuw, Kahn and Vink, 2014). At the start of each trial a cue (smiling or neutral face) was presented for 750 ms, indicating a potential rewarding or non-rewarding outcome, respectively. The cue was followed by a fixation point (779 – 6729 ms), the target (exclamation point), and the feedback screen (target presentation + feedback screen was 2000 ms). The duration of target presentation varied, and participants were instructed to press a button as fast as possible when the target was on the screen, irrespective of cue type. Trials were categorized as either *rewarding*, in which money could be earned, or *non-rewarding*, in which no money could be earned or lost. Furthermore, responses were categorized as *hits*, in which the button was pressed within the time limit (duration of the target presentation), or *misses*, in which the button was pressed after target presentation which resulted in no financial change. For each reward hit, participants gained €1.00. The button press was immediately followed by a feedback screen, indicating whether the response was in time or not (*hit* or *miss*), whether any money was earned, and the cumulative earned money at that time. The task was preceded by a practice run of the same task consisting of 20 trials. Directly after the practice run, the actual task started. The duration of target presentation during the actual task was adjusted based on the reaction time during these practice trials, aiming at a success rate of 50% (Figure 1). Target duration during the actual task was calculated as follows: slowest response to target during practice + 200 ms for aimed hits, slowest response to target during practice – 150 ms for aimed misses. The time between cue and target onset, and between target onset and the next trial, was jittered. The time from target presentation to the end of the feedback screen was 2000 ms. The inter-trial-interval range was 1029–6979 ms. Participants that never pressed the button during non-rewarding trials were excluded.

Figure 1 | Reward task. The task consisted of two phases: reward anticipation and reward feedback.

Participants were instructed to press a button as fast as possible during target presentation. There were two types of anticipation: reward anticipation and neutral (non-rewarding) anticipation. Depending on whether the button was pressed within time limit, there were four possible types of feedback: reward hit, reward miss, non-reward hit and non-reward miss.

Salivary cortisol and alpha-amylase

In total, seven saliva samples were obtained throughout the experiment using salivettes (Sarstedt, Nümbrecht, Germany) for the quantification of cortisol and alpha-amylase (−10, +5, +20, +30, +65, +90, and +120 min relative to TSST onset). Samples were temporarily stored at 4 °C and subsequently stored at −20 °C. Cortisol and alpha-amylase levels were analyzed as described previously (Vinkers *et al.*, 2013). Three out of 497 cortisol samples were missing (all non-peak values) and were calculated based on the mean group decline. Exclusion of participants with missing data did not affect any of the results. The alpha-amylase percentage increase was based on the change from the first (before TSST) to the second (during TSST) sample as previously published (van Leeuwen *et al.*, 2018).

Functional MRI

All imaging was performed on a Philips 3.0-T whole-body MRI scanner (Philips Medical Systems). First, a whole-brain 3-dimensional T1 weighted structural image was acquired with the following scan parameters: voxel size 1 mm isotropic; repetition time (TR) = 10 ms; echo time (TE) = 4.6 ms; 200 slices; flip angle = 8°. Functional images were obtained using a 2-dimensional echo planar imaging-sensitivity encoding (EPI-SENSE) sequence with the following parameters: voxel size 3 mm isotropic; TR = 2000 ms; TE = 35 ms; 30 slices; gap = 0.43 mm; flip angle = 70°. Two hundred ninety-two functional scans were acquired during the task (acquisition time: 9 min 42 s).

Data were realigned, corrected for differences in acquisition time between slices, co-registered, spatially normalized into standard stereotactic space (Montreal Neurological Institute, MNI, 152 space), and spatially smoothed using a 6-mm FWHM Gaussian kernel to increase spatial smoothness of whole brain results.

Statistical analyses

fMRI

Imaging data were analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). The effects of reward (reward/non-reward) on brain activity during the anticipation and feedback phases were estimated during individual first-level analyses. The design matrix consisted of six regressors modelling the onsets and duration of the anticipation (time between cue presentation and target presentation) and feedback phases (time from target presentation to end feedback) of each trial. The regressors were as follows: *reward anticipation*, *non-reward anticipation*, *reward hit*, *reward miss*, *non-reward hit*, *non-reward miss*. These regressors were convolved with a canonical hemodynamic response function. The realignment parameters (three translations and three rotations) obtained from realignment were added as factors to correct for head movement. A high-pass filter with a cut-off period of 128 s was applied to correct for signal drift.

To confirm task-specific effects, we examined whole-brain activation patterns to (potential) rewards during the anticipation and feedback phases across all participants using the contrasts *reward anticipation > non-reward anticipation* and *reward hit > non-reward hit*. We used a threshold of $p < 0.05$, whole-brain family-wise error (FWE) corrected using Gaussian Random Field Theory-based methods.

The ventral striatum and orbitofrontal cortex (OFC) ROIs were created using the automatic anatomical labeling atlas (Tzourio-Mazoyer *et al.*, 2002) and the WFU PickAtlas Toolbox implemented in SPM. The ventral striatum consisted of the part of the caudate nucleus below the z-coordinate of 0 mm (Hoogendam *et al.*, 2013; de Leeuw, Kahn and Vink, 2014; Vink *et al.*, 2015). This ROI overlapped with a map generated by Neurosynth (Yarkoni *et al.*, 2011) which was based on a meta-analysis from 310 studies containing the search term 'ventral striatum' (Figure S1). The OFC was defined as the medial part of the orbitofrontal cortex, entailing the bilateral gyrus rectus and medial orbital gyrus (Vink *et al.*, 2015). The mean regression coefficient over all voxels within each ROI (combining left and right hemispheres) was extracted for each subject and for each of the six regressors. During anticipation, we compared BOLD responses of each ROI using a mixed model ANOVA with group (control/sibling) and stress (stress/no-stress) as between-subject factors and reward (reward/non-reward) as within-subject factor. During feedback, we compared BOLD responses of each ROI using a mixed model ANOVA with group (control/sibling) and stress (stress/no-stress) as between-subject factors and reward (reward/non-reward) and response (hit/miss) as within-subject factors.

Participants were removed from the analysis if their parameter estimates exceeded ± 2 SD from the group mean on more than one ROI and more than one regressor. Based on this criterion, we found four outliers (control-no-stress = 2, control-stress = 1, sibling-stress = 1). This resulted in the following groups sizes: control-no-stress ($n = 16$), control-stress ($n = 19$), sibling-no-stress ($n = 18$), sibling-stress ($n = 17$).

Cortisol and alpha-amylase

For changes in cortisol levels over time, the effects of stress (stress/no-stress) and group (control/sibling) and their interaction with time were analyzed using a repeated measures analysis of variance (ANOVA). Alpha-amylase percentage change between samples was calculated using SPSS 23.0 (Statistical Package for the Social Sciences, Chicago, Illinois) and analyzed using two (control/sibling) by two (stress/no-stress) ANOVAs.

Behavior

We performed a two-way ANOVA to test for the effects of stress and group and their interaction on mean reaction times and percentage hits during rewarding and non-rewarding trials using SPSS 23.0.

Correlations between alpha-amylase, cortisol, life stress, and ROI activity

We investigated the association between alpha-amylase, cortisol, life stress, and BOLD responses in the ventral striatum and OFC during reward and non-reward anticipation and feedback following stress in healthy controls and siblings using Pearson's correlation. Results were defined significant if they survived multiple comparison correction of $p < 0.0083$ ($p < 0.05/6$ comparisons: LSC-R, alpha-amylase and cortisol during anticipation and feedback).

Results

Group characteristics

Data from the life stress (CTQ and LSC-R) questionnaires was missing for one subject (sib-stress). There were no significant differences between the four groups on age, life stress, BIS/BAS score, ethnicity, handedness, BMI or smoking (Table 1).

	Con-no-stress (n=18)	Con-stress (n=20)	Sib-no-stress (n=18)	Sib-stress (n=17)	Statistics
Age (years)	33.1 $\pm$ 2.0	35.4 ($\pm$ 2.0)	33.4 ($\pm$ 2.6)	32.6 ($\pm$ 1.7)	F = 0.363, p = 0.780
Childhood	33.2 $\pm$ 1.9	35.7 $\pm$ 3.0	35.9 $\pm$ 2.4	34.2 $\pm$ 1.5	F = 0.300, p =

maltreatment (CTQ total score)					0.825
Major life events (LSC-R total score)	3.3 ±0.5	3.0 ±0.4	3.6 ±0.8	3.9 ±0.7	F = 0.453, p = 0.716
BIS	17.7 ±0.6	18.0 ±0.7	18.5 ±0.5	18.1 ±0.8	F = 0.253, p = 0.859
BAS - drive	12.0 ±0.4	11.7 ±0.6	11.0 ± 0.6	10.6 ±0.7	F = 1.213, p = 0.312
BAS – fun seeking	11.5 ±0.5	11.8 ±0.5	10.9 ±0.4	11.2 ±0.3	F = 0.723, p = 0.542
BAS – reward responsiveness	17.1 ±0.6	17.3 ±0.5	17.2 ±0.3	16.9 ±0.4	F = 0.073, p = 0.974
Handedness (right/left)	16/2	19/1	12/4	16/2	χ^2 (3) = 9.6, p = 0.142
Education Level	7.5 ±0.4	7.1 ±0.4	6.9 ±0.4	7.6 ±0.3	F = 0.485, p = 0.694
Body Mass Index	24.1 ±0.7	24.2 ±0.5	23.8 ±0.7	24.3 ±0.7	F = 0.132, p = 0.941
Ethnicity (Caucasian/other)	15/3	18/2	17/1	15/3	χ^2 (3) = 1.5, p = 0.681
Smoker (yes/no)	1/17	7/13	6/12	6/12	χ^2 (3) = 5.6, p = 0.134
Smokers: daily cigarettes	2.0	6.1 ±2.5	7.3 ±2.9	5.3 ±1.4	F = 0.279, p = 0.840

Table 1 | Group characteristics. Con: control; Sib: sibling of schizophrenia patient; BIS/BAS: behavioral inhibition/avoidance system. Mean values ± standard error of the mean are denoted for age, education and body mass index. All other values are reported in frequency. Group statistics represent comparisons between the four groups.

Stress comparably increases cortisol, alpha-amylase and subjective stress levels

Stress increased salivary cortisol over time (time x stress interaction $F = 10.185$, $p = 8.073 \times 10^{-8}$) (Figure 2). There were no significant differences between controls and siblings on cortisol levels (no main effect of group or group x stress interaction on all measures, all p-values > 0.05). Cortisol reached its peak 30 min after TSST onset and remained elevated until the final sample (main effect of stress on cortisol levels on all time points between +20 and

+120 min $p < 0.005$). Stress increased salivary alpha-amylase (main effect of stress on percentage increase from -10 min to +5 min; $F = 4.907$, $p = 0.030$) and subjective stress (time x stress interaction $F = 6.025$, $p = 0.004$), which did not differ between healthy controls and siblings (for both measures main effect of group and time x group interaction $p > 0.05$, see van Leeuwen et al., 2018 for alpha-amylase and subjective stress figures). Salivary alpha-amylase returned to baseline 30 min after TSST onset (main effect of stress on percentage change from -10 min to +30 min; $F = 3.924$, $p = 0.052$, main effect of stress on percentage change from -10 min to +60 min; $F = 1.522$, $p = 0.221$). The reward task started 50 min after onset of the TSST.

Figure 2 | Salivary cortisol response to trier social stress test (TSST). Stress increased salivary cortisol significantly, which did not differ between groups. The reward task was carried out between 50 and 60 min after TSST onset. Con: control; Sib: sibling of schizophrenia patient. Error bars represent standard error of the mean (SEM).

Behavior

Participants responded faster and more accurate during rewarding trials compared to non-rewarding trials (main effect of reward on reaction time $F = 46.6$, $p < 0.001$, main effect of reward on percentage hits $F = 34.1$, $p < 0.001$). Mean reaction times did not differ between the groups (main effect of group $F = 2.4$, $p = 0.126$), between stress conditions (main effect of stress $F = 0.935$, $p = 0.337$) and did not differentiate the two groups in the different stress conditions (group x stress interaction $F = 0.331$, $p = 0.567$) (Table 2). Similarly, percentage hits did not differ between groups (main effect of group $F = 0.740$, $p = 0.393$), between stress conditions (main effect of stress $F = 0.322$, $p = 0.572$) and did not differentiate the two groups in the different stress conditions (group x stress interaction $F = 3.982$,

$p = 0.050$) (Table 2). Maximum scan-to-scan head movement was not different between siblings and controls ($F = 0.390$, $p = 0.534$).

		Con-no-stress	Con-stress	Sib-no-stress	Sib-stress
Mean reaction time (ms) $\pm$ SEM	<i>Reward</i>	269.4 $\pm$ 6.4	274.0 $\pm$ 6.0	276.2 $\pm$ 6.4	286.9 $\pm$ 7.8
	<i>Non-reward</i>	288.0 $\pm$ 7.4	288.5 $\pm$ 4.9	293.9 $\pm$ 6.5	303.4 $\pm$ 10.0
Percentage hits (%) $\pm$ SEM	<i>Reward</i>	46.7 $\pm$ 1.1	47.8 $\pm$ 0.8	48.3 $\pm$ 0.7	47.6 $\pm$ 1.5
	<i>Non-reward</i>	38.5 $\pm$ 2.4	44.0 $\pm$ 1.5	44.3 $\pm$ 2.1	41.3 $\pm$ 2.0

Table 2 | Performance during reward task. Con: control; Sib: sibling of schizophrenia patient; SEM: Standard error of the mean.

Effects of stress on brain responses during reward anticipation and feedback

Whole-brain analyses

To confirm that the task activated the reward circuitry, we performed whole-brain analyses across all participants. We found significant clusters within the caudate, ventral striatum, supplementary motor cortex, anterior cingulate gyrus, cerebellum, precentral gyrus, anterior insula, supramarginal gyrus, middle frontal gyrus, middle occipital gyrus and the postcentral gyrus in the contrast *reward anticipation > non-reward anticipation*. Furthermore, the contrast *reward hit > non-reward hit* revealed significant clusters in the orbitofrontal cortex, precuneus, and angular gyrus (all significant at $p < 0.05$, whole-brain FWE corrected; Figure S2, Table S1).

ROI analyses: anticipation

The anticipation of potential rewards elicited stronger activity compared to the anticipation of non-reward trials within the ventral striatum (main effect of reward $F = 33.063$, $p = 2.493 \times 10^{-7}$) across all individuals. No effects of stress or interactions between stress, group, and reward were found in any of the ROIs (group $\times$ reward, stress $\times$ reward and group $\times$ stress $\times$ reward interaction $p > 0.05$ in both ROIs; Figure S3).

ROI analyses: feedback

A mixed-model ANOVA on ventral striatum BOLD responses during feedback was performed to test for a differential effect of stress between siblings and controls. This analysis revealed a group by stress interaction ($F = 4.858$, $p = 0.031$), with higher responses in healthy controls in the stress condition compared to the no-stress condition and no effect of stress in siblings of schizophrenia patients (Figure 3). This did not differ between reward and non-rewarding conditions or hits and misses (group $\times$ stress $\times$ reward, group $\times$ stress $\times$ response, and group $\times$ stress $\times$ reward $\times$ response interaction all p -values > 0.05).

OFC BOLD responses following stress differed between healthy controls and siblings (group x stress interaction $F = 9.268$, $p = 0.003$), showing higher responses in the OFC in healthy controls in the stress condition compared to healthy controls in the no-stress condition and no difference between siblings in the stress and no-stress condition (Figure 3). This did not differ between reward and non-rewarding conditions, or hits and misses (group x stress x reward, group x stress x response, and group x stress x reward x response interaction all p -values > 0.05 , for results without exclusion of participants see Table S2). We take these results to indicate a clear increase in brain responses after stress in healthy controls only.

Figure 3 | BOLD responses to feedback in the aftermath of acute stress or a control condition, in healthy controls and siblings of schizophrenia patients. Fifty min following stress, responses within the ventral striatum and OFC during feedback were increased in healthy controls only. In siblings of schizophrenia patients there was no difference between the no-stress and stress condition. There was no interaction with reward (reward/non-reward) or response (hit/miss), therefore BOLD responses were averaged across all types of feedback. Con: control; Sib: sibling of schizophrenia patient; OFC: orbitofrontal cortex; a.u.: arbitrary units. * group x stress interaction $p < 0.05$. Error bars represent SEM (standard error of the mean).

	Ventral striatum		OFC	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Reward	10.193	0.002	13.755	4.290 x 10⁻⁴
Response	48.726	1.755 x 10⁻⁹	27.724	1.640 x 10⁻⁶
Reward x response	1.973	0.165	9.157	0.004
Group x stress	4.858	0.031	9.268	0.003
Group x stress x reward	0.109	0.742	0.000	0.999
Group x stress x response	1.054	0.308	1.403	0.240

Group x stress x reward x response	0.018	0.893	0.020	0.888
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Table 3 | Statistics from the group (control/sibling) x stress (stress/no-stress) x reward (reward/non-reward) x response (hit/miss) ANOVA on BOLD responses during the feedback phase. OFC: Orbitofrontal cortex. Significant comparisons are presented in bold.

To investigate whether the observed increase in healthy controls following stress was mainly driven by rewarding compared to non-rewarding trials, or hits compared to misses, we performed an explorative mixed model ANOVA in healthy controls only. We found that this effects was mainly observed in hits (stress x response interaction $F = 5.329$, $p = 0.027$), irrespective of reward (stress x reward interaction $F = 0.496$, $p = 0.486$). We observed a trend towards a similar effect in the OFC (stress x response interaction $F = 3.916$, $p = 0.056$, stress x reward interaction $F = 0.023$, $p = 0.881$). These results show that stress increases responses of the reward circuitry in healthy controls particularly to positive task feedback (Figure S4).

Due to the non-normal distribution of smokers among the four groups, we performed the four-way mixed ANOVA with all participants again with the number of cigarettes a day as a covariate. This did not change the group x stress interaction for both the ventral striatum ($F = 4.273$, $p = 0.043$) and OFC ($F = 8.210$, $p = 0.006$).

To inspect laterality effects, we investigated the group by stress interaction in left and right OFC and ventral striatum separately, which yielded similar results (ventral striatum left $F = 4.912$, $p = 0.030$, right $F = 4.307$, $p = 0.042$; OFC left $F = 10.141$, $p = 0.002$, right $F = 7.620$, $p = 0.007$).

Association between alpha-amylase, cortisol, life stress, and BOLD responses

We investigated the association between BOLD responses during reward anticipation and feedback following stress and life stress, alpha-amylase during the TSST, and peak cortisol in healthy controls and siblings using Pearson's correlation. Ventral striatum BOLD responses were negatively correlated with life stress in siblings, and OFC BOLD responses were negatively correlated with alpha-amylase in healthy controls. However, these results did not survive multiple comparison correction (p -values $\Rightarrow 0.028$). See table S3 for all comparisons.

Discussion

We investigated reward processing in the aftermath of acute stress in healthy controls and unaffected siblings of schizophrenia patients. In healthy controls, we found increased ventral striatum and OFC responses to positive task feedback following stress which was absent in siblings of schizophrenia patients. This is the first study to show that in the aftermath of stress, i.e. 50-60 min after stress onset, responses of the reward circuitry are *increased* in healthy controls. By contrast, previous studies reported *diminished* striatal and OFC responses to reward feedback immediately after stress (Porcelli, Lewis and Delgado, 2012; Kumar *et al.*, 2014). Together, these findings support a

dynamic and time-dependent neural response of the reward system in association with stress in healthy controls but not in siblings of schizophrenia patients.

Effects of stress on reward response in healthy controls

Previous studies in healthy controls found increased anticipatory processes (wanting a reward) during acute stress, while consummatory responses (the hedonic value of a reward) are diminished, leading to habitual, impulsive and anhedonia-like behavior shortly after stress (Bogdan and Pizzagalli, 2006; Porcelli, Lewis and Delgado, 2012; Berghorst *et al.*, 2013; Kumar *et al.*, 2014).

We hypothesized that responses to reward anticipation would be decreased in the aftermath of stress in healthy controls, similar to a previous study that employed exogenous hydrocortisone administration (Montoya *et al.*, 2014). However, we found no differences among the four groups in OFC and ventral striatum responses during the anticipation of reward. This may be explained by the 9-fold higher peak in cortisol levels achieved in previous studies using the same dosage hydrocortisone as presented by Montoya *et al.*, 2014 (Putman, Hermans and van Honk, 2010) as compared to our results. Moreover, it should be appreciated that exogenous hydrocortisone administration may result in different neural responses than those induced by psychosocial stress, which causes the release of many stress-related hormones and neurotransmitters in addition to cortisol.

In the aftermath of stress (i.e. at least 45-60 min after onset of the stressful event), delayed effects of cortisol are considered to be important for stress recovery and the cognitive reappraisal of the situation, including reward-related events. Based on this, we hypothesized to find increased responses to reward feedback in the aftermath of stress in healthy controls. Indeed, this group showed an up-regulation of the OFC and ventral striatum to task feedback 50 min after stress, particularly to hits. This effect was independent of monetary value, indicating that there was no additional effect of monetary reward on the effects of stress. A possible explanation for this finding is that positive feedback is rewarding in itself (Kinner, Wolf and Merz, 2016) and that our design does not actually include a non-rewarding condition. Unfortunately, our results are restricted to the neurobiological level as our task does not feature a sensitive behavioral measure to detect effects of stress on reward responsiveness ('liking' of the rewards/reward learning), but previous work suggests that there is an increase in the likeability of stimuli in the same time-domain (Ehlers and Todd, 2017). Our data shows that the previously reported reduction in neural responses of the reward circuitry during stress are reversed in the aftermath of stress, along with increased responses to general positive feedback, suggesting a dynamic and time-dependent opposing effect of stress the reward system in healthy controls.

Reward feedback response in siblings of schizophrenia patients

We found robust differences in responses to reward in the aftermath of stress between siblings of schizophrenia patients and healthy controls. Given the well-established role of dopamine (DA) in schizophrenia and reward processing, it could be argued that our results are partly mediated by alterations in the DA system of siblings.

The activation of the hypothalamic–pituitary–adrenal (HPA) axis quickly stimulates the release of DA in the striatum and OFC (Abercrombie *et al.*, 1989; Piazza *et al.*, 1996; Payer *et al.*, 2017), driving stimulus-response behavior (Belujon and Grace, 2015). However, there is evidence from animal research for a second peak in DA release after stress termination, that remains high until 80 minutes after stress (Holly and Miczek, 2015). This secondary peak is hypothesized to be the effect of negative reinforcement (the removal of a stressor) (Holly and Miczek, 2015), and may support the ability to modulate behavioral strategies aimed to avoid future similar aversive events (Mayer *et al.*, 2018). The latter may involve interactions with corticosteroids which exert delayed effects in a similar time-domain, aimed to better prepare individuals for the future (de Kloet *et al.*, 2018). Interestingly, siblings of schizophrenia patients fail to increase DA release in response to stress (Brunelin *et al.*, 2010), and a similar failure to increase DA in the aftermath of stress was observed in a mouse model of schizophrenia (Lillrank *et al.*, 1999). Accordingly the lack of DA up-regulation in the aftermath of stress may be related to the here reported attenuated ventral striatum and OFC response in this at-risk group and reflect impaired neural flexibility following stress. Of note, the direct link between DA release and neurovascular responses has not been well-established. More specifically, studies in rodents that used optogenetic stimulation of dopaminergic VTA neurons have shown both increased striatal activity (Ferenczi *et al.*, 2015; Lohani *et al.*, 2017) and no effect on striatal activity (Brocka *et al.*, 2018) and therefore it remains unknown whether dopaminergic activity plays a causal role in striatal activity. In support of a link between DA functioning and striatal neurovascular response, human studies found a correlation between reward-induced striatal activity as measured with fMRI and reward-induced DA release (Schott *et al.*, 2008) or dopamine transporter availability (Dubol *et al.*, 2018) as measured with PET. In conclusion, these results suggest that DA functioning plays a role in striatal responses to rewards and that alterations in the DA system in siblings may underlie altered reward responses following stress. However, no conclusive statements can be done regarding this relation.

Strengths and limitations

Our study has several important strengths. We carefully selected a group of unaffected siblings and matched healthy controls with comparable trauma scores. We excluded any current psychiatric disorders as well as medication that could have influenced the cortisol response. However, there are some limitations. First, we only included male participants. Acute stress-induced effects on reward processing differ between females and males (Lighthall *et al.*, 2012) and therefore the effects during the aftermath of stress may differ as well. Additionally, income was previously shown to be associated with striatal responses to reward (Tobler *et al.*, 2007). Unfortunately, we have no information on the socioeconomic status of the participants which is a limitation of the study. Another limitation is the fact that we

did not assess subclinical symptoms in the participants. Subclinical symptoms such as depression may differ between the groups and account for potential differences in striatal responses to reward. We previously assessed subclinical symptoms in siblings of schizophrenia patients and found no deviations from healthy controls. (de Leeuw, Kahn and Vink, 2014). However, we cannot exclude that subclinical symptoms may have been present in our sibling group. Finally, with regard to stress-induced cortisol levels, our sample size may have been too small to detect smaller group differences.

Given the strong connection between stress, reward processing and psychiatric disorders, there has been a vast number of studies investigating the link between stress and reward processing in healthy individuals. Even though studies in healthy controls are an essential part of understanding basic neuroscience, our study shows that there is a large difference in the neural stress response between symptom-free individuals at risk for psychopathology and healthy controls. These results underscore the importance of studying a group of at-risk individuals.

Conclusion

In conclusion, our results demonstrate increased ventral striatum and OFC responses of the reward circuitry to positive task feedback in the aftermath of stress in healthy controls, but not in siblings of schizophrenia patients. Combined with previous findings of a decrease in these areas to rewards during acute stress, we take our results to indicate that there are dynamic and time-dependent opposing effects of stress on reward processing in healthy controls. This interpretation is consistent with the well-documented neural temporal dynamics of psychosocial stress. Although we provide no direct evidence for an impaired response to stress in at-risk individuals, these results provide novel insights into how siblings of schizophrenia patients recover from stressful events. As this group is at increased risk for many psychiatric disorders, understanding their neural responses to such an important risk factor is of crucial importance. These data may therefore provide a stepping stone for further research of stress-related psychopathology.

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