Reward anticipation in individuals with subclinical psychotic experiences: A functional MRI approach

Stijn Michielse[a],[*], Iris Lange[a], Jindra Bakker[a],[b],
Liesbet Goossens[a], Simone Verhagen[a], Silvia Papalini[c],
Marieke Wichers[d], Ritsaert Lieverse[a], Koen Schruers[a],[e],
Therese van Amelsvoort[a], Jim van Os[a],[f],[g],
Graham K Murray[h],[i],[1], Machteld Marcelis[a],[j],[1]

[a] Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, EURON, Maastricht University Medical Centre, PO Box 616, 6200 MD, Maastricht, the Netherlands
[b] Department of Neuroscience, Center for Contextual Psychiatry, KU Leuven, Leuven, Belgium
[c] Laboratory of Biological Psychology, Faculty of Psychology and Educational Sciences, Leuven Brain Institute, KU Leuven, Belgium
[d] Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[e] Faculty of Psychology, Center for Experimental and Learning Psychology, University of Leuven, Leuven, Belgium
[f] King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, England
[g] Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands
[h] Department of Psychiatry, University of Cambridge, Cambridge Biomedical Campus, Cambridge, United Kingdom
[i] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, United Kingdom
[j] Institute for Mental Health Care Eindhoven (GGzE), Eindhoven, the Netherlands

* Corresponding author.
    E-mail address: stijn.michielse@maastrichtuniversity.nl (S. Michielse).
[1] Dr Graham K Murray and Dr Machteld Marcelis have contributed equally to this work.

Abstract

Previous research in patients with psychotic disorder has shown widespread abnormalities in brain activation during reward anticipation. Research at the level of subclinical psychotic experiences in individuals unexposed to antipsychotic medication is limited with inconclusive results. Therefore, brain activation during reward anticipation was examined in a larger sample of individuals with subclinical psychotic experiences (PE). Participants in the PE-group were included based on CAPE scores. A sample of emerging adults aged 16-26 years ($n = 47$) with PE and healthy controls (HC) ($n = 40$) underwent fMRI scanning. The Monetary Incentive Delay task was conducted with cues related to win, loss or neutral conditions. fMRI nonparametric tests were used to examine the reward versus neutral cue contrast. A significant main effect of the large win (€3.00) > neutral contrast was found in both groups showing activation in many brain areas, including classic reward regions. Whole brain analysis on the group comparison regarding the large win > neutral contrast showed significantly decreased activation in the right insula, putamen and supramarginal gyrus in the PE-group compared to controls. There was no group difference in the hypothesized reward-related region. Decreased activation in the right insula, putamen and supramarginal gyrus during reward anticipation in individuals with PE may be consistent with altered processing of sensory information, related to decreased emotional valuing and motivational tendencies and/or altered motor-cognitive processes. The absence of group differences in striatal activation suggests that activation here is intact in the earliest stages of psychosis and may exhibit progressive deterioration in as the disease develops.

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1. Introduction

Development of the adolescent brain towards adulthood continues until the age of 25 years and a broad range of developmental and environmental factors impact during this time frame. The same developmental phase is also associated with a high risk of developing a mental disorder, 75% of psychiatric morbidity presenting with an onset before the age of 24 years (Kessler et al., 2005). The emergence of a first psychotic episode is often preceded by a phase of subclinical psychotic experiences comprising mild positive (e.g., hallucinations and delusions) or negative symptoms (e.g., affective flattening, anhedonia and motivational impairment) with accompanying distress. The prevalence of these broadly defined subclinical psychotic experiences is estimated at 7% in the general population (Linscott and van Os, 2013), and they have been found to predict persistence and severity of later psychopathology including psychotic disorder (Chan, 2017; Kline et al., 2014; Yung et al., 2003; McGorry, 1998). Motivation for or engagement in activities that involve getting rewards and gaining pleasure is generally lower in patients with psychotic disorder (Strauss et al., 2014). The processing of reward can be parsed into (at least) two stages; the anticipation and the consumption of reward, and these are thought to have dissociable neural substrates (Berridge and Kringelbach, 2015). Reward anticipation is the expectation of reward, often associated with a learned, therefore expected, positive reinforcement of an action, which often stimulates behavior by engaging motivation. In order to investigate the brain circuitry underlying reward anticipation, functional MRI (fMRI) can be used for in vivo functional assessment of this psychological function. The neural correlates of reward anticipation can be assessed in vivo in an fMRI scanner using the Monetary Incentive Delay task (MIDt); in this task the participant can win money according to performance, which consists of a rapid button press in response cues signaling the magnitude of rewarding feedback available (Knutson et al., 2001, 2000). The most widely reported measure in this task is brain activation at the time of the cue signaling the potential for a large reward versus activation at the time of a cue associated with a neutral outcome; this contrast evokes robust activation in the ventral striatum (VST) and widespread cortical regions (Jia et al., 2016). Reward anticipation is important to investigate in psychosis research, given the large preclinical literature implicating dopamine in reward anticipation and prediction error signaling, and prior well-established findings of dopamine abnormalities in schizophrenia (Ziauddeen and Murray, 2010). It has been proposed that patients with psychosis have formed altered associations induced by dopamine dysregulation in the striatum; this concept is known as "aberrant salience", which proposes that psychotic symptoms may arise from inappropriately attributing salience to irrelevant stimuli (Heinz, 2002; Kapur, 2003).

A substantial body of fMRI literature has confirmed striatal involvement in reward anticipation (Wang et al., 2016). In a large-scale synthesis of fMRI studies of healthy participants, the VST was presented as a key region in reward anticipation (Yarkoni et al., 2011). To date, studies show some difference in fMRI activation during reward consumption between patients with psychotic disorder and controls (Simon et al., 2010; Nielsen et al., 2012). Furthermore, several studies have reported alterations in reward anticipation in patients with psychotic disorder in comparison with healthy controls using the MIDt (Howes and Kapur, 2009;

Maia and Frank, 2017). In drug-naïve first episode patients with schizophrenia, decreased activation was observed in the VST during reward anticipation, compared to controls (Esslinger et al., 2012; Horga et al., 2016). Another study in unmedicated patients with schizophrenia showed reduced VST activation during reward anticipation compared to healthy controls, with decreased activation in the left VST being inversely correlated with severity of negative symptoms (Juckel et al., 2006; Wotruba et al., 2014). Furthermore, a neuro-functional meta-analysis examining specifically the VST, combined 23 studies in patients with schizophrenia spectrum disorders compared to controls concluded that VST was hypoactive during reward anticipation (Radua et al., 2015).

There is less literature on individuals with subclinical psychotic experiences and available studies generally have modest samples sizes, with about 20-30 participants per group. Alterations in VST activation have been described during reward anticipation in some studies (Juckel et al., 2012; Wotruba et al., 2014), but another found no differences in VST activation in people with schizotypal personality trait symptoms ($n = 26$) compared to controls (Kirschner et al., 2016). In contrast, decreased VST activation with increasing levels of psychotic experiences based on the Community Assessment of Psychic Experiences (CAPE) in a fairly limited healthy sample ($n = 11$) has been reported (Simon et al., 2015). A study of siblings of psychotic patients, investigating higher than average risk for psychotic disorder, in a comparison with controls, also showed reduced activation in the VST, insula, and supplementary motor area during reward anticipation (de Leeuw et al., 2015). Another study in first-degree relatives found no differences in striatal areas related to reward processing, but did find deactivation in the insula, posterior cingulate cortex and medial frontal gyrus (Hanssen et al., 2015). The findings in relatives suggested that part of the genetic susceptibility to psychosis may be expressed as altered reward anticipation. This is in agreement with a study on 22q11.2 deletion syndrome (a genetic model to study elevated risk for psychotic disorder in people who have a microdeletion on the long arm of chromosome 22), which reported reduced activation in the medial frontal regions during reward anticipation compared to controls (van Duin et al., 2016). Furthermore, one study with a larger sample of participants from the general population using polygenetic risk profile scores (PRS), found a positive association between psychosis PRS and VST activation during reward anticipation (Lancaster et al., 2016). This may indicate hyperactivation in the VST related to PRS and seems to oppose other smaller studies on genetic susceptibility to psychosis (although note that study used a slightly unusual contrast, thus differs in methodology from most other studies on the MID) (Bossong and Kahn, 2016). Overall, these studies provide some suggestion that elevated genetic risk for psychotic disorder may be associated with alterations in reward anticipation; it remains unknown whether individuals at clinical risk of psychosis have reward anticipation deficits.

As the literature on reward anticipation in individuals with subclinical expression of psychosis is sparse and inconsistent, the current study investigated reward anticipation in emerging adults (aged 16 to 25 years) at psychometric risk

for psychotic disorder, compared to healthy controls, analyzing a larger sample size than previous studies. Based on what has been described in the literature, it was hypothesized that in a group of emerging adults with subclinical psychotic experiences (PE), reward anticipation related brain activation would be changed with respect to healthy controls. This was examined, first, at the whole brain level and, second, more specifically, focussing on the VST as *an priori* defined region of interest to investigate in the context of reward anticipation. Explorative analyses were conducted to investigate the relationship between fMRI reward anticipation and mild psychopathology (CAPE positive and MADRS).

2. Experimental procedures

2.1. Participants

This cross-sectional study took place within the Smartscan project (Dutch Trial Register Number: NTR3808), comprising a sample of emerging adults aged 16-25 years with subclinical psychotic experiences (PE-group) as well as a comparison group without psychopathology, in the region of Southern Limburg in the Netherlands. Participants were recruited via advertisements, posters, or via referral by primary health care professionals. The inclusion criteria for the PE-group were based on a Community Assessment of Psychic Experiences (CAPE (Stefanis et al., 2002)) positive subscale frequency score of ≥ 10 and/or a CAPE distress score on the positive subscale of ≥ 2, in combination with a Global Assessment of Functioning (GAF (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 2000)) of <70. The sample also included participants with a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score ≥ 10 who met the subclinical PE inclusion criteria. The Mini International Neuropsychiatric Interview (MINI) was used to identify addictive substance abuse and additional axis I diagnoses. A short summary of current medication use was provided by participants.

Inclusion for the control group was based on a depression score derived from the Montgomery-Åsberg Depression Rating Scale (MADRS (Montgomery and Asberg, 1979)) of <10, a CAPE positive subscale frequency score of <10 in combination with a distress score of <2. Level of education was indexed by the completed level of education ranging from 0 (no education completed) to 7 (completed master degree). Individuals with a history of psychiatric diagnosis or treatment were excluded from the control group.

Exclusion criteria were current psychological or psychiatric treatment, significant need for care, left-handedness, a history of neurological disorder (e.g. severe brain injury with unconsciousness, meningitis, migraine or epilepsy) or MRI contraindications (e.g. cardiac arrhythmia, diabetes, and claustrophobia). In addition, participants with implanted ferromagnetic materials were excluded from the study, as were women with (suspected) pregnancy.

The medical ethics committee of Maastricht University Medical Center approved this study according to the declaration of Helsinki. All participants gave written informed consent in person and additionally via a proxy (a parent) when younger than 18 years of age ($n = 4$).

2.2. Monetary incentive delay task

An adapted version of the Monetary Incentive Delay task (MIDt) by Knutson et al. (2001) was used to investigate brain activity during reward anticipation. In the MIDt, participants start with €5 and can win or avoid losing money, depending on their response to the target (Fig. 1). To minimize learning effects during the scan,
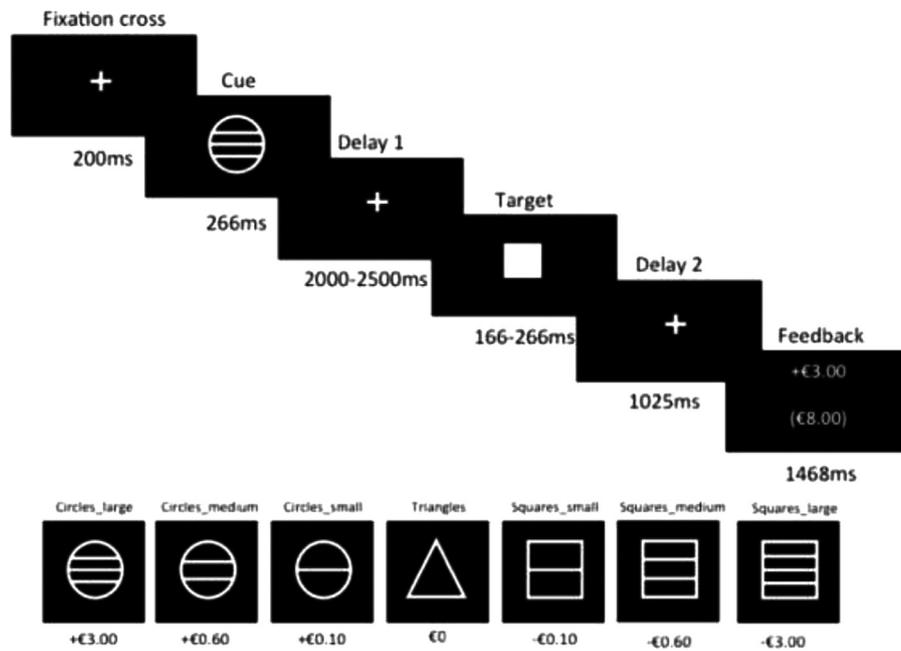
Fig. 1 MID task (Knutson et al., 2001) with different cues. Timings are provided in milliseconds (ms).

the task was explained and practiced twice before the start: once outside the MRI scanner and once inside, just before the start of scanning. The task included two runs (each 6 min, 12 s) of 72 randomly ordered trials. Each trial started with a fixation cross (duration 200 ms), followed by a cue (266 ms) and a variable delay of 2000–2500 ms (Fig. 1). Visual cues were presented indicating reward (circle), loss (square) or neutral (triangle) conditions. In each run, each reward/loss cue was shown nine times, while the neutral cue was shown 18 times. The reward and loss amount increased with the number of lines from €0.10 to €0.60 and €3.00, and the money gain was paid as an incentive after completion. After the cue and first delay phase, the participants had to respond to the target via a button press with the right index finger in order to get the reward or avoid losing (e.g. at level 5, target durations were 266 ms, 216 ms and 166 ms; slow, medium and fast), followed by the second delay phase (1025 ms) and a feedback phase (1468 ms). The feedback phase showed win or loss and the current amount of money.

Task difficulty was set by the researcher after the practice trial and adjusted after the first run (if the success rate was >66%). Difficulty settings were based on RTs and varied between slow, medium and fast target duration. The task was shown on a screen (resolution 1920 × 1200 pixels) via E-prime v2.0.10.242 software (Psychology Software Tools, Inc. Pittsburgh, PA) (Schneider et al., 2002) in the fMRI scanner using a Windows computer. Responses were recorded via a fiber optic button box (Current Designs, Inc., Philadelphia, PA). Event onsets were recorded and synchronized with the fMRI start. At the first delay start (delay 1 in Fig. 1), the reward anticipation was determined and related to specific cue shapes.

2.3. Acquisition

MRI scans were acquired at Scannexus, Maastricht, The Netherlands, on a 3T Siemens Magnetom Prisma system (Siemens, Erlangen, Germany) equipped with a 64-channel head/neck coil. Whole brain T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) images with a voxel size of 1.0 × 1.0 × 1.0 mm were acquired (repetition time (TR) = 2250 msec, echo time (TE) = 2.21 msec, flip angle = 9°, field of view (FOV) = 256 × 256,

192 sagittal orientated slices, GRAPPA = 2, no fat suppression, acquisition time (TA) = 5.05 min). Whole brain functional scans were acquired using a T2*-weighted echo-planar imaging (EPI) sequence (TR = 2450 msec, TE = 28 msec, flip angle = 75°, interleaved ascending order, FOV = 72 × 72, 47 slices in axial orientation, A > P phase encoding, GRAPPA = 3, TA = 6.33 min) with a voxel size of 3 × 3 × 3 mm. For each run 155 volumes were acquired.

2.4. fMRI processing

After conversion of raw DICOM images to NIfTI format (Rorden and Brett, 2000), first level analysis of the FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to standard space images was carried out using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson et al., 2002; Jenkinson and Smith, 2001) and registration to high resolution anatomical data was done using BBR (Boundary-Based Registration) (Greve and Fischl, 2009).

The following pre-processing steps were applied: motion correction with the middle volume as the reference using MCFLIRT (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; fMRI non-brain removal using BET (Smith, 2002); on the anatomical scans, after removing 50 axial slices of the neck and five sagittal slices on each side of the head, skull stripping was done using a hybrid watershed/surface deformation procedure incorporated in FreeSurfer v5.3 recon-all (www.freesurfer.net) (Segonne et al., 2004); spatial smoothing using a Gaussian kernel of FWHM 6.0 mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with cutoff = 100 s). Normalization using FNIRT was done into the Montreal Neurological Institute 152 stereotaxic 2 mm^3 space (Andersson et al., 2007). The general linear model (GLM) was created with 16 regressors for the first level: circles_small_hit, circles_small_miss, circles_medium_hit, circles_medium_miss, circles_large_hit, circles_large_miss, triangles_hit, triangles_miss, squares_small_hit, squares_small_miss,

squares_medium_hit, squares_medium_miss, squares_large_hit, squares_large_miss, button_press and non_response. Note: hit and miss conditions were split up in the model and hit conditions were added to the model to link a positive outcome to the anticipation of the reward. The model incorporated only the early delay phase; the anticipation just after cue representation until target onset.

Time-series statistical analysis was carried out using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich et al., 2001). A total of four Contrasts Of Parameter Estimates (COPEs) were created for the hit conditions: small reward (circles_small>triangles), medium reward (circles_medium>triangles), high reward (circles_large>triangles) and total reward (circles>triangles). The standard (three rotations and three translations) and extended (the derivative of the motion parameters and the squares of the parameters and derivatives) motion parameters and button press were added as confounders. Motion above the threshold of 3 mm in any of the directions lead to exclusion of the dataset. A manual data quality check was conducted for each dataset to check for any errors in the registration. Next, for each individual, the two runs were averaged to obtain one COPE by using fixed effects GLM in FSL FEAT.

2.5. Whole brain fMRI analysis

Whole brain group analysis was conducted using the mixed effects model FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 + +2 in FSL with two contrasts for hypothesis testing: PE>HC, and HC>PE. Also, the main effects per group were checked to illustrate that the task robustly elicited brain activation in relevant regions in both groups (Beckmann et al., 2003, Woolrich, 2008, 2004). Z-statistic images were cluster thresholded at $Z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001). Non-parametric permutation for inference testing was implemented using FSL's randomise tool using family-wise error correction at $p = 0.05$ (Winkler et al., 2014). A total of 5000 permutations were done for the same four contrasts to compare results. Statistical analyses were done for the high reward anticipation condition, i.e., comparing the COPE for circles_large > triangles cue shapes, providing parameter estimates as a proxy for task related brain activation. In line with previous studies this COPE has been selected and the non-response is expected to be lowest for the high reward.

In two separate models, a voxelwise regression against CAPE positive symptom frequency and MADRS total score was conducted. The models included age, sex and educational level as the a priori hypothesized confounding factors.

2.6. Region of interest (ROI) analysis

In addition to the whole brain analysis, a specific ROI analysis was conducted in the ventral striatum (STR), based on the ROI defined by Mawlawi, Martinez and colleagues (Mawlawi et al., 2001;Martinez et al., 2003) (see Fig. 1 in the supplementary materials). With the application of FSL's featquery the mean parameter estimate per participant was extracted and exported for use in statistical analysis in STATA (release 13) (StataCorp, 2009). In STATA, linear regression models were applied to examine group differences with age, sex and educational level as the a priori hypothesized confounding factors. Groups were coded '0' for HC-group and '1' for PE-group.

Furthermore, to investigate the association between mild psychopathology and reward anticipation, analyses on symptom scales has been performed. The associations between CAPE positive frequency, distress and MADRS total score were examined with mean

Table 1 Demographic information per group.

	PE-group (n = 47)	HC-group (n = 40)
Age (mean (SD))	21.5 (2.50)	21.9 (1.73)
Sex (%female)	40 (85%)	33 (82%)
Education level (mean (SD))	5.85 (0.62)	6.17 (0.64)
CAPE positive score (mean (SD))	4.45 (3.07)	0.90 (1.41)
CAPE positive distress score (mean (SD))	4.47 (3.14)	0.17 (0.38)
MADRS total score (mean (SD))	13.53 (7.18)	1.42 (1.85)
GAF global functioning (mean (SD))	63.74 (10.90)	86.65 (6.50)

PE; subclinical psychotic experiences and HC; healthy controls. Means and standard deviations are provided, sex is in% female. CAPE; Community Assessment of Psychic Experiences, MADRS; Montgomery-Åsberg Depression Rating Scale, GAF; Global Assessment of Functioning.

parameter estimates for the VST in separate regression models including the a priori hypothesized confounders.

2.7. Behavioral analyses

The task was split usp in two runs. Both runs were analyzed separately and combined. In order to study the validity of the reward-anticipation test, learning effects and group effects in the behavioral data were examined (Knutson et al., 2000). Mean reaction time (in milliseconds) and number of non-responses, indicating task compliance and engagement, were recorded per cue shape and differences between groups were examined. Comparability between groups with regard to the difficulty level per individual and incentive outcome (gain in euros) was also examined. For these purposes, t-tests and χ^2-tests were done in STATA release 13 (StataCorp, 2009).

3. Results

Eighty-seven participants completed the entire interview assessment, had quality approved fMRI scans and were assigned to the PE ($n = 47$) or HC ($n = 40$) group. Mean age and sex did not differ between groups (see Table 1). On average, participants were 22 years old, with slightly more females in the PE-group ($n = 40$) compared to the HC-group ($n = 33$). Educational level was lower in the PE-group compared to the HC-group ($\chi^2 = 8.006$, $p = 0.046$). CAPE and MADRS scores were significantly higher in the PE-group while GAF scores were significantly lower. In the HC-group no addiction or substance abuse was reported, while in the PE-group one participant had marihuana dependence, three alcohol dependence and two alcohol abuse. One participant in the PE-group used quetiapine medication (25 mg per day).

3.1. MIDt behavioral analysis

Table 2 shows the descriptive results of the MIDt; the mean RT with standard deviation per cue and the total money gain, per run and per group. For the RT towards the circle

Table 2 Overview of MIDt reaction times overall, per run and per cue shape and total money gain.

	HC-group ($n = 40$)	PE-group ($n = 47$)	Difference	P-value
Overall				
RT Reward (circles) (ms)	208 (24)	205 (22)	−3.18	$p = 0.52$
RT Loss (squares) (ms)	209 (25)	207 (19)*	−1.83	$p = 0.70$
RT Neutral (triangles) (ms)	221 (25)	214 (25)	−7.07	$p = 0.18$
Non-response Reward	20 (4.2)	21 (5.1)	1.01	$p = 0.32$
Non-response Loss	20 (4.3)	22 (4.7)	1.87	$p = 0.06$
Non-response Neutral	17 (4.0)	17 (4.0)	0.13	$p = 0.88$
Money gain (euro)	15.17 (4.89)	13.17 (5.66)	−2.00	$p = 0.08$
Run 1				
RT Reward (circles) (ms)	210 (26)	207 (22)	−2.79	$p = 0.59$
RT Loss (squares) (ms)	211 (25)	212 (19)*	1.54	$p = 0.75$
RT Neutral (triangles) (ms)	223 (27)	214 (24)	−9.21	$p = 0.10$
Run 2				
RT Reward (circles) (ms)	207 (26)	203 (28)	−3.56	$p = 0.54$
RT Loss (squares) (ms)	208 (28)	204 (25)	−4.32	$p = 0.45$
RT Neutral (triangles) (ms)	219 (27)	214 (30)	−4.92	$p = 0.43$

Means and standard deviations (between brackets) are provided (PE; subclinical psychotic experiences and HC; healthy controls, * = one missing value due to nonresponse by one participant on the square_small cue). Reported values are based on t-tests. The difference is reported as HC-group minus PE-group. Note: Too early or too late responses are counted as non-responses here.

(win), square (loss) and triangle (neutral) cue, no differences were found between the PE-group and HC-group (RT reward $p = 0.52$, loss $p = 0.70$ and neutral $p = 0.18$).

RTs for neutral cues were longer in both groups compared to the reward and loss cues. The difference on the money gain between the HC (15.17±4.89 euro) and PE-group (13.17±5.66 euro) did not reach significance ($p = 0.08$). The mean difficulty level (ranging from 1 to 5) was 4.19 in the PE-group and 4.05 in the HC-group in the first run. For the second run, the mean was 3.74 in the PE-group and 3.92 in the HC-group. Difficulty levels were not significantly different between groups (run 1 $p = 0.4614$; run 2 $p = 0.45$). The RTs to the cue shapes were equal for both groups (Table 2). Non-responses were equal in both groups for the reward ($p = 0.59$), loss ($p = 0.06$) and neutral ($p = 0.88$) shapes.

3.2. Whole brain fMRI findings

3.2.1. Main effects

The whole brain analysis, family-wise error corrected for multiple comparisons, showed increased (high reward contrast; circles_large > triangles) activation in widespread regions the ventral striatum, frontal cortex (including VMPFC and OFC), VTA, insular cortex and occipital lobe in the PE and control group (a similar pattern to that observed by Jia et al. 2016). This analysis yielded a significant cluster for the high reward contrast in both groups. In the HC-group, the cluster included a large part of the brain, with $Z = 12.4$ as the peak voxel in the occipital lobe at Montreal Neurological Institute (MNI) coordinate 12, −86, −6 (x,y,z) (Fig. 2). In the PE-group the cluster included a large part of the brain, with $Z = 11.4$ as its peak located in the insular cortex at MNI
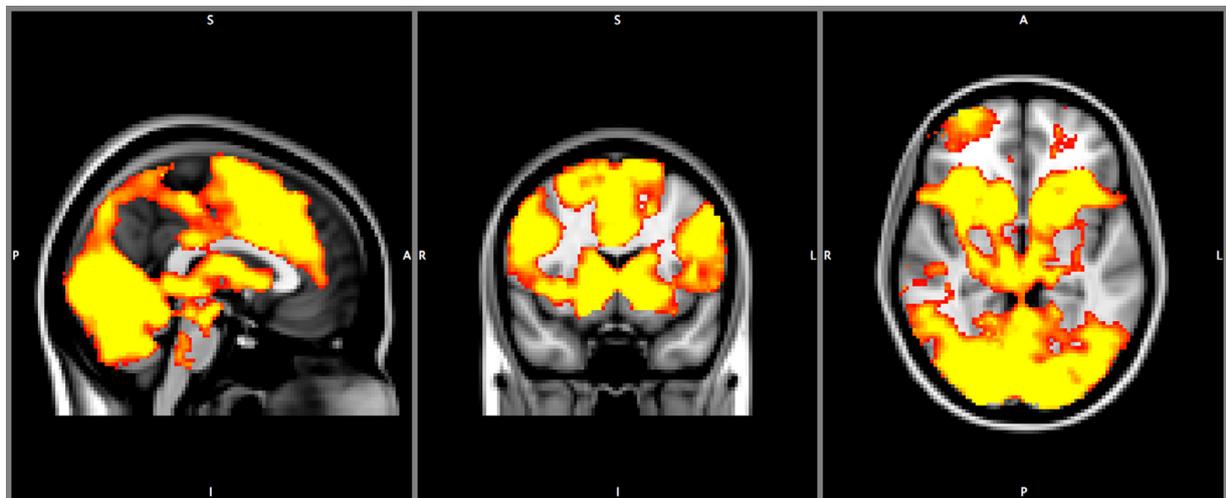

Fig. 2 Main effects in healthy controls (HC) group on the circles_large > triangles contrast at MNI coordinate 0, 8, −4 (x, y, z).
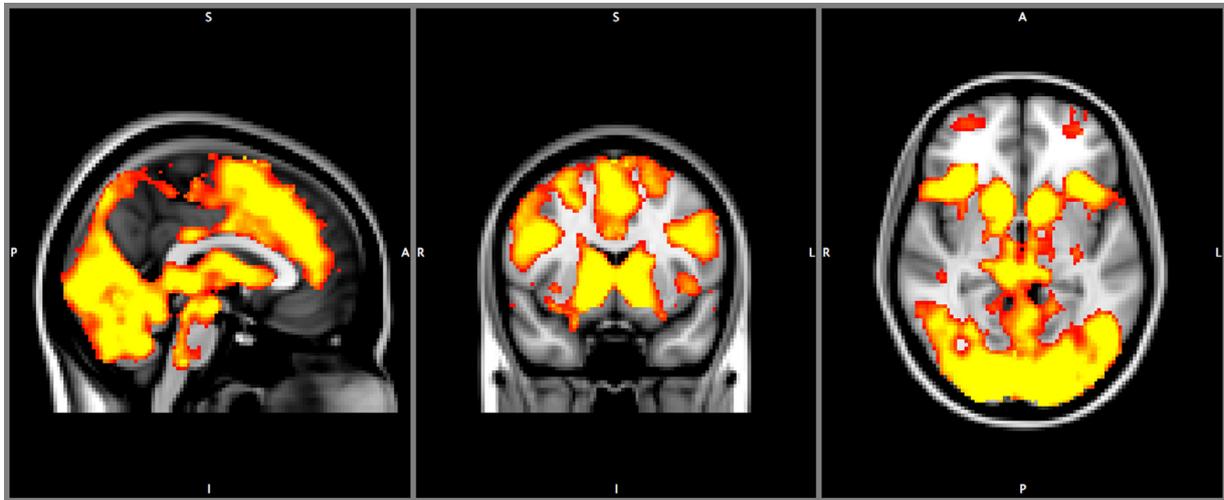
Fig. 3 Main effects in psychotic experiences (PE) group on the circles_large > triangles contrast at MNI coordinate 0, 8, −4 (x, y, z).
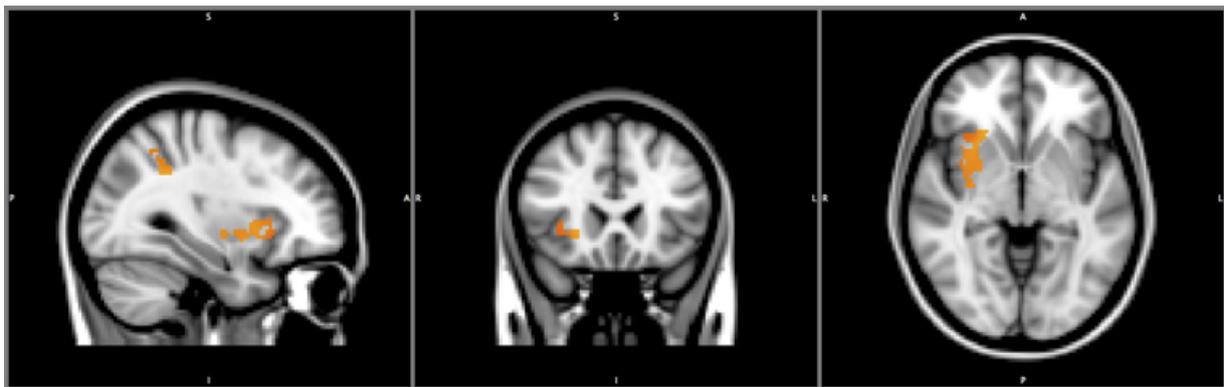

Fig. 4 Significant group difference comparing the psychotic experiences group (PE) < healthy control (HC) group on the big reward contrast. The peak cluster is located in the right insula (Z = 4.02, MNI 32, 22, −4). This figure is also available as download on FigShare; https://figshare.com/s/df50952043f1ecf8ad0e.

32, 22, −4 (Fig. 3). A table with local maxima per group is provided in the supplementary material (Table 1 in the Supplementary material).

3.2.2. Group differences

Two significant clusters were found when examining the PE-group < HC-group on the high reward contrast (Fig. 4). These clusters were located in the right supramarginal gyrus (551 voxels at 2 mm^3 voxel size = 4.41 mL; Z = 3.87; MNI 42, −42, 38; BA40, Fig. 5) and the right insula and putamen (487 voxels at 2 mm^3 voxel size = 3.90 mL; Z = 4.02; MNI 32, 22, −4; BA13, Fig. 6). The other contrast (PE-group > HC-group) did not show significant effects above the threshold.

The findings were confirmed by non-parametric testing showing overlap in the group main effect for the high reward and the two largest clusters in the right supramarginal gyrus (382 voxels; Z = 3.35 MNI 38, −44, 38) and the right insula (273 voxels; Z = 3.09, MNI 22, 36, −12).

3.2.3. Symptom regression

Whole brain voxelwise regression analyses showed no significant voxels below the p < 0.05 threshold in the CAPE
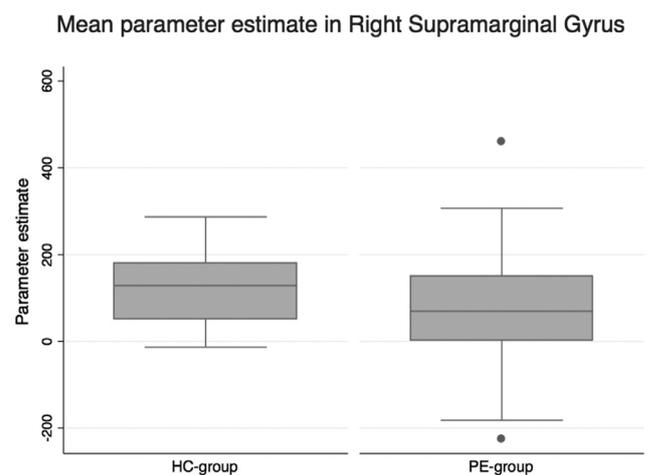

Fig. 5 Boxplot of the mean parameter estimate per group in the right supramarginal gyrus (whole brain analyses). HC-group; Healthy Control group and PE-group; Subclinical Psychotic Experiences group.
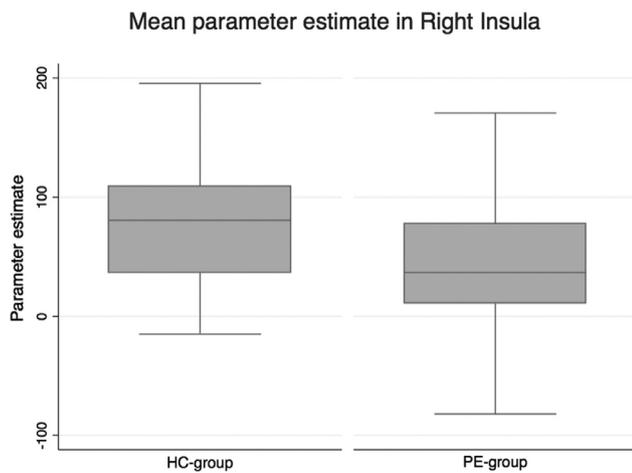
Mean parameter estimate in Right Insula

Fig. 6 Boxplot of the mean parameter estimate per group in the right insula (whole brain analyses). HC-group; Healthy Control group and PE-group; Subclinical Psychotic Experiences group.

Table 3 Region of interest (ROI) differences for the big reward (circles_large > triangles) contrast.

ROI	PE-group	HC-group	B	P
Striatal cortex	55.37 (±46.27)	64.80 (±44.23)	−7.77	0.45

PE: subclinical psychotic experiences, HC: healthy control. Mean and standard deviation for parameter estimate in STR is provided. The linear regression model included age, sex and educational level as confounding factors.

positive frequency symptom score and MADRS total score models.

3.3. ROI analyses

The linear regression analysis on the STR did not indicate any significant difference between the PE-group and the HC-group on the big reward contrast (see Table 3).

3.4. ROI and symptom analysis

Based on the regression analysis there was no significant association between the parameter estimate in the STR ROI and CAPE positive frequency score ($B = 1.99$, $p = 0.23$), CAPE positive distress score ($B = 1.36$, $p = 0.39$) and MADRS total score ($B = -0.16$; $p = 0.80$).

4. Discussion

The current study presents findings in fMRI alterations during reward anticipation in a sample of individuals with subclinical psychotic experiences (PE) compared to healthy controls during reward anticipation. The behavioral task outcomes (money gain, reaction times and non-responses) were similar in both groups while some differences related to reward anticipation were found at the brain level.

The right supramarginal gyrus and right insula/putamen showed decreased activation during reward anticipation in the PE-group compared to the controls. No group differences were found in the *a priori* hypothesized specified region of interest of ventral striatum. There were no significant associations between the region and mild symptoms of psychopathology.

4.1. Whole brain reward anticipation

Both the PE-group and healthy controls showed increased (high reward contrast; circles_large > triangles) activation during reward anticipation in regions including the occipital lobe, insular cortex, ventral striatum, frontal cortex (including VMPFC and OFC) and VTA, consistent with previous studies (Jia et al., 2016). This finding confirms brain reward-related activation during reward anticipation while performing the MID task. In the group comparison on reward anticipation, two significant clusters were found. Particularly, the PE-group showed decreased activation in the right supramarginal gyrus and the right anterior insula and putamen during reward anticipation. The anterior insula has been associated with salience processing over a specific functional network (Seeley et al., 2007), and prior studies using the MID and other reward tasks have indicated its involvement in reward processing (Wang et al., 2015). Interestingly, previous work using the MIDt in healthy controls showed increased activation in the right anterior insula when rewarding stimuli were presented (Knutson et al., 2000; Rademacher et al., 2010; Juckel et al., 2006). The current study in individuals with PE showed decreased activation in this area, in line with a MIDt study in patients with schizophrenia with about the same sample size, but somewhat older in age (Koch et al., 2015; Esslinger et al., 2012). In research focusing on reward prediction in patients with psychosis, abnormal responses in the insula have been reported (Murray et al., 2008). Decreased activation in the insula has also been found in siblings of patients with schizophrenia (de Leeuw et al., 2015; Hanssen et al., 2015) while MIDt research in so-called 'ultra high-risk' (for psychosis) groups of the same age did not find alterations in this region (Schmidt et al., 2017). However, this study was conducted in a sample of 27 participants meeting ultra-high risk criteria and may have been underpowered. The insula is a key cortical region receiving sensory information from all modalities, and in turn it projects heavily to the ventral striatum (Haber, 2011). Furthermore, decreased activation in the right anterior insula in the PE-group may be related to potential motivational deficits in this group. The insula is linked to stimulus evaluation and for allocating the appropriate arousal for task performance and motor preparation, as highlighted in a sample of 11 participants (Eckert et al., 2009). Motor preparation and selective attention features play a role in the MIDt, since participants prepare to engage a button press and have to pay attention to the task. Furthermore, the insula is involved in emotional arousal, neural mapping of body states and subjective feeling states (Namkung et al., 2017). This interoceptive process may be dampened in individuals with mild psychotic experiences and therefore lead to decreased activation during the anticipation of reward. Valueing emotions in the anticipation of

reward may be related to the anterior insula (Craig, 2009). Another explanation for the decreased insular activation that was present in the current study may be a developmental shortfall in individuals with psychotic experiences, given that during adolescence, brain activation in the insula related to reward anticipation tends to increase with age (Hoogendam et al., 2013). Decrease in activation during reward anticipation in the PE-group was also partly located in the right putamen (dorsal striatum). Decreased reward-related activation has been found in the right putamen in patients with major depressive disorder (Zhang et al., 2013) and psychotic disorder (Waltz et al., 2010). It has been suggested that a reduced putamen response is associated with lowered motivational tendencies in young adolescents (Joseph et al., 2016), but its precise role requires further research.

The finding of decreased activation in the right supramarginal gyrus (inferior parietal lobe) in the PE-group with respect to the healthy controls, has previously been reported in unmedicated first episode patients with schizophrenia (Esslinger et al., 2012). In ultra high-risk groups this finding has not been described (Schmidt et al., 2017). Furthermore, this region seems to be engaged in a functional network related to reward anticipation in youngsters at 14 years of age (Jia et al., 2016). The right supramarginal gyrus (inferior parietal lobe) is involved in sensory processing, but also supports mathematical operations as it plays an important role in number comparisons (Chochon et al., 1999). During the MIDt, individuals may process numerical information (i.e., calculate how much they won). The supramarginal gyrus may thus be involved in (but not directly related to VST) reward processing by means of numerical processing. Reward deficits in the parietal lobe may be specific for psychotic disorder, as a prior study showed reward processing deficits in this area in schizophrenia but intact activation in depression (Segarra et al., 2016). An abnormal activation in the parietal region has previously been associated with reward-related activation during highly uncertain outcomes (Paulus et al., 2003). This finding of reduced activation during reward anticipation in the PE-group requires further research and replication.

4.2.   Region of interest analysis

In line with the whole-brain group analyses, no group difference was found in the VST region of interest. One explanation is that the region remain contained, while at the whole brain level alterations in other regions (right insula and supramarginal gyrus) are apparent. In turn, a ROI approach is focused on *a priori* selected region and thus less sensitive compared to whole brain analysis, since the method captures mean activation per region instead of a voxel-based approach (Poldrack, 2007). The right insula and supramarginal gyrus were not *a priori* hypothesized areas for the ROI analysis. Previous literature showed an absence of group differences between individuals with subclinical psychotic experiences and healthy controls in VST (and other areas outside the VST) activation during reward anticipation (Juckel et al., 2012). Based on the results of the current study, it seems that VST is unaffected in emerging adults with PE and remains functionally engaged

during reward anticipation. This is in contrast to findings of decreased activation in the VST in patients (Simon et al., 2015) and siblings of patients (Grimm et al., 2014), but is in line with one study in people with schizotypical personality traits (Kirschner et al., 2016). One difference between our study and those in many (though not all) previous patient studies is that our participants are unmedicated (except for one) non-help seeking individuals at the mildest end of the psychosis spectrum. This may raise medication as a possible explanation for previous patient versus control differences; though this would not explain the previous abnormal striatal activation in relatives. The previous findings thus indicate that ventral striatal dysfunction is associated with schizophrenia and genetic risk for schizophrenia but is not associated with subclinical psychotic symptom spectrum in the population. Furthermore, there were no significant associations between regions and CAPE positive (frequency and distress) symptom and MADRS scores. This may indicate that both subclinical psychotic experiences and depressive symptoms are unrelated to reward anticipation in the VST.

4.3.   MIDt behavioral reward anticipation

The reaction times on the different reward shapes and performance outcome (money gain and non-response) on the MIDt were similar across both groups. The absence in behavioral differences between groups agrees with previous research in subclinical samples (Kirschner et al., 2016; Simon et al., 2015) as well as findings in siblings of patients with psychotic disorder (de Leeuw et al., 2015; Grimm et al., 2014; Hanssen et al., 2015). These behavioral results validate the fMRI application of the MIDt in this sample.

4.4.   Methodological considerations

Although a careful design, setup and methodological approach were applied, some limitations should be taken into consideration. First, as the sample had mixed mild psychotic and depressive symptoms, effects on activation during reward anticipation may be confounded. Of the participants in the PE-group, 79% also had depressive symptoms (based on a MADRS score ≥ 10). Findings on reward processing in depression has indeed some similarity (such as decreased VST activation) with reward processing in psychotic disorder (Luking et al., 2016), but it has not been investigated in a mixed mild symptomatology sample like the current. Previous research has focused on isolated groups of people with either psychotic or depressive symptomatology, but these samples may be less representative than the current as PE are strongly associated with affective psychopathology (van Rossum et al., 2011) and genetic risk for psychosis is expressed in both the psychotic and affective domains (van Os et al., 2017). Second, the spatial resolution is limited to 3 mm voxel size capturing many neurobiological processes in one voxel. The currently used fMRI scan technique operating at 3T only provides an estimate of the average activation (as measured via the parameter estimate) in the VST. Furthermore, fMRI acquisitions are influenced by noise factors such

as system-related instabilities and physiological fluctuations unrelated to the task. These can have an effect on the fairly low task-related signal measured via fMRI in general (Liu, 2016). With more advanced fMRI techniques at higher field strength, increased spatial resolution can provide a more fine-grained examination of the reward system.

Additionally, it needs to be noted that the sample mainly consisted of females, which may be explained by the recruitment strategy, since many students were included from a university that has a focus on health sciences. This may also explain the considerable overlap between PE and affective dysregulation, the latter which might be a driving force in the development of (subclinical) psychosis, especially in females (Myin-Germeys et al., 2004).

5. Conclusion

The current study showed that emerging adults with subclinical psychotic experiences have decreased activation in the right supramarginal gyrus, right insula and putamen during reward anticipation with respect to healthy controls. The decrease in activation may be explained as a deficit in motor preparation and selective attention and/or altered motivational and emotional processing (insula), altered motivational tendencies (putamen) or altered numerical processing (in the supramaginal gyrus). At the behavioral level (reaction times, non-response and monetary gain) the groups displayed similar results. No group differences were found in a reward anticipation-related area such as VST, which was confirmed by ROI-based analysis. This may be related to the relatively low psychometric risk levels and, as yet, non-detectable reward-system alterations. It is speculated that more regions besides the reward system are engaged during reward anticipation.

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Contributors

Authors MW, JvO, KS, RL and TvA designed the study. Authors SM, IL, JB, SV, SP and LG did the experimental setup and data collection. Authors SM, GM and MM performed the methods and analyses. Authors SM, JvO and MM wrote the manuscript.

Conflict of interest

Jim van Os is or has been, in the last 3 years, an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from: Lundbeck and Janssen. Machteld Marcelis has received, in the last 3 years, financial compensation as an independent symposium speaker from Janssen. All other authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.002.

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