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The role of cognitive control in the positive symptoms of psychosis

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ABSTRACT

Background: Positive symptoms of psychosis (e.g., hallucinations) often limit everyday functioning and can persist despite adequate antipsychotic treatment. We investigated whether poor cognitive control is a mechanism underlying these symptoms.

Methods: 97 patients with early psychosis (30 with high positive symptoms (HS) and 67 with low positive symptoms (LS)) and 40 healthy controls (HC) underwent fMRI whilst performing a reward learning task with two conditions; low cognitive demand (choosing between neutral faces) and high cognitive demand (choosing between angry and happy faces – shown to induce an emotional bias). Decision and feedback phases were examined.

Results: Both patient groups showed suboptimal learning behaviour compared to HC and altered activity within a core reward network including occipital/lingual gyrus (decision), rostral Anterior Cingulate Cortex, left precentral gyrus and Supplementary Motor Cortex (feedback). In the low cognitive demand condition, HS group showed significantly reduced activity in Supplementary Motor Area (SMA)/pre-SMA during the decision phase whilst activity was increased in LS group compared to HC. Recruitment of this region suggests a top-down compensatory mechanism important for control of positive symptoms. With additional cognitive demand (emotional vs. neutral contrast), HS patients showed further alterations within a subcortical network (increased left amygdala activity during decisions and reduced left pallidum and thalamus activity during feedback) compared to LS patients.

Conclusions: The findings suggest a core reward system deficit may be present in both patient groups, but persistent positive symptoms are associated with a specific dysfunction within a network needed to integrate social-emotional information with reward feedback.

1. Introduction

Cognitive impairments are a core characteristic of psychotic disorders, including deficits in attention, working memory, emotion regulation and flexible learning. These impairments are often conceptualised as the result of a core deficit in cognitive control - the ability to integrate, contextualise and maintain information in order to direct goal-oriented behaviour (Kouneiher, Charron, & Koechlin, 2009). Deficits in cognitive control have been consistently described in schizophrenia (Fett et al., 2019). Cognitive impairments have traditionally been related to negative symptoms, disorganisation and poor functional outcomes (Lesh, Niendam, Minzenberg, & Carter, 2011), but also to positive symptoms such as hallucinations and delusions because of the role of cognitive control in distinguishing relevant from irrelevant stimuli (Kapur, 2003), flexibly updating beliefs and adapting behaviour in changing environments (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). Positive symptoms are often disturbing to patients and limit everyday functioning and delaying treatment of these symptoms has been shown to predict poorer long-term outcomes (Marshall et al., 2005; Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014). Understanding the pathophysiology of dysfunctional cognitive control may be critical to developing novel interventions to treat these symptoms.

Cognitive control is understood as a 'top-down' process in the brain. Broadly, this means that higher levels of the cortical hierarchy (e.g. in prefrontal cortex) are responsible for monitoring and controlling lower-order processes such as sensory, motor, emotion and reward processing

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(Kveraga, Ghuman, & Bar, 2007). A classic example of exerting top-down control is captured in the Stroop task; individuals are slower, and less accurate, at naming the font colour of a word when the semantic meaning of the word is incongruent rather than congruent with the colour (Barch, Carter, Hachten, Usher, & Cohen, 1999). In the incongruent condition, the colour and meaning of the word are thought to compete for attentional demand so increased cognitive control is needed to monitor and filter out conflicting distractors (semantic meaning of word), bias attention towards task-relevant stimuli (font colour) and inhibit the prepotent responses. In schizophrenia, patients have been shown to have increased Stroop interference compared to healthy controls indicating a reduction in cognitive control (Westerhausen, Kompus, & Hugdahl, 2011). Moreover, Thomas et al (2021) reported that cognitive control was significantly more impaired (increased Stroop reaction time) in treatment-resistant patients (with persistent positive symptoms) than treatment-responsive patients and overall impaired cognitive control was related to increased positive symptoms (Thomas et al., 2021). Cognitive control deficits are often underpinned by reduced (or altered) activity in regions of the cognitive control network including the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), thalamus, parietal regions and supplementary motor areas (SMA/pre-SMA) (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Impairments in more dynamic aspects of cognitive control in schizophrenia have also been studied using variants of reward learning tasks. Within the predictive coding and Bayesian brain framework, top-down predictions about incoming sensory information (generated using prior beliefs) are compared against the lower-level sensory evidence to form prediction errors (bottom-up signals) that are transferred back up the cortical hierarchy and act to update the higher-level representations (Rao & Ballard, 1999; Sterzer et al., 2018). Reward learning tasks require top-down predictions about stimulus-reward associations that are required to be iteratively updated on each trial (using a reward prediction error) in order to optimise learning. Our earlier work has demonstrated that when individuals were tasked with learning to associate specific facial stimuli (happy or angry expressions) with rewards, the participants demonstrated an emotional bias towards choosing happy over angry faces such that they overweighted positive outcomes associated with happy faces (Averbeck and Duchaine, 2009). These data suggested that social-emotional cues influence cognitive control and are readily integrated into decision-making. This task was demonstrated to engage partially separable networks where reward feedback was related to activity in classical reward circuitry such as ventral striatum and sub-callosal ACC, while the social-emotional value of the face was associated with activity in dorsal ACC and right temporo-parietal junction (TPJ) (Evans et al., 2011a; Evans et al., 2011b). Patients with schizophrenia showed a similar emotional bias favouring happy faces but were significantly more averse to the angry faces compared to healthy controls; with patients selecting the angry face less often even when the reward feedback supported it as the optimal choice (Evans et al., 2011a; Evans et al., 2011b). This supported a putative cognitive control deficit in people with schizophrenia making it more difficult to integrate social-emotional information with reward feedback to support effective decision making.

Building on this body of work, we have shown that cognitive control is impaired in treatment-resistant patients (i.e., with persistent positive symptoms) with chronic schizophrenia. Using the same reward learning task, treatment-resistant patients had intact striatal reward prediction error (RPE)-related activity, but a differential (positive) relationship between the RPE signal and the degree of emotional bias expressed during the task compared to both treatment-responsive patients and healthy controls (Vanes, Mouchlianitis, Collier, Averbeck, & Shergill, 2018). This suggested that while the RPE signal generation was intact in treatment-resistant patients, the cognitive control needed to overcome the emotional bias to make optimal predictions was impaired. We were then able to use dynamic causal modelling to demonstrate that while the treatment-responsive patients had increased top-down connectivity from ACC to sensory regions (fusiform gyrus and amygdala) and reduced connectivity from all regions into the striatum during this task, the treatment-resistant group did not show any enhanced top-down connectivity from the ACC (Horne et al., 2021). This supported the proposition that increased cognitive control - indexed by enhanced top-down connectivity over incoming sensory information - may provide the striatum with contextual information to appropriately integrate with incoming sensory information in treatment responsive patients. In contrast, the absence of this top-down cognitive control may contribute to persistence of psychotic symptoms in the treatment-resistant patients. Moreover, top-down connectivity from ACC to sensory regions was inversely related to positive symptoms in the treatment-responsive group further suggesting that effective cognitive control may be important in controlling positive symptoms (Horne et al., 2021).

However, the classification of patients into treatment resistant and responsive groupings is not without issues. We studied patients with an established diagnosis of schizophrenia with a long duration of illness and significant exposure to antipsychotic medication, which can both impact brain structure and function (Abbott, Jaramillo, Wilcox, & Hamilton, 2013; Smieskova et al., 2009). The aim of the current study was therefore to understand whether poor top-down cognitive control functioning is a neural mechanism underlying high levels of positive symptoms in a larger sample of patients with early psychosis (<5 years duration) and healthy controls. We did this by splitting patients into high symptom (HS) and low symptom (LS) groups based on the positive symptom threshold for determining treatment resistance (Conley & Kelly, 2001), comparable to our previous study (Horne et al., 2021). We investigated fMRI activation during the same reward learning task used in our earlier paper (Horne et al., 2021) but focused on two conditions with varied levels of cognitive demand: a 'neutral' condition (low demand) and an 'emotional' condition (high demand). By contrasting emotional vs. neutral condition activity, we proposed a more powerful design that could specifically probe cognitive control function i.e., controlling the inherent emotional bias to make informed decisions based on reward feedback. We hypothesized that 1) all participants would show an emotional bias towards choosing happy over angry faces (Evans et al., 2011a; Evans et al., 2011b), 2) both patient groups with psychosis would show impaired behavioural performance and dysfunction within an extended reward network (including striatum) in the neutral condition compared to healthy controls (Evans et al., 2011a; Evans et al., 2011b; Strauss, Waltz, & Gold, 2014) and 3) patients with high positive symptoms (HS) would show impaired integration of social-emotional information compared to patients with low positive symptoms (LS) as indexed by reduced top-down cognitive control in ACC during the high cognitive demand (emotional vs. neutral) condition. We also hypothesized that HS patients may have increased amygdala activity during this emotional vs. neutral condition due to extra processing of emotional faces and reduce top-down control.

2. Methods and materials

2.1. Participants

The study recruited 97 patients with early psychosis from the South London and Maudsley (SLaM) NHS foundation trust, and from the Oxleas NHS Foundation Trust and North East London NHS Foundation Trust (NELFT) and 40 healthy controls (HC). Inclusion criteria for patients included a first episode of psychosis within the last 5 years (mean illness duration = 1.6 years); 30 were categorised as 'high symptom' (HS) based on having at least 1 positive symptom item of 5 (moderate severe) or higher, or at least 2 positive symptom items of 4 (moderate) or higher measured using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The other 67 patients were categorised as 'low symptom' (LS) as they did not meet the positive symptom threshold. Categorisation of patients was determined using the

same symptom threshold that is part of the widely-accepted criteria for defining treatment-resistant schizophrenia (Conley & Kelly, 2001) without including the medication requirements, although all patients were medicated.

The patient exclusion criteria included a history of neurological illness, current major physical illness, diagnosed drug dependency over the past six months or a contraindication for MRI. The HC exclusion criteria included a history of psychiatric illness or a first-degree relative currently or previously suffering from a psychotic illness. Functional MRI data from a subset of the HC group have been previously reported elsewhere (Vanes et al., 2018). Ethical approval was obtained by the Camberwell and St. Giles NHS National Research Ethics Committee and the study was compliant with the Declaration of Helsinki. All participants provided written informed consent prior to taking part in the study and were compensated for their time and travel.

2.2. Reward learning task

A schematic of an example trial sequence is presented in Fig. 1A and has been reported previously in (Horne et al., 2021; Vanes et al., 2018). In brief, all participants completed a reward learning task whilst undergoing fMRI scanning. Participants were presented with a fixation cross (1000 ms) followed by two faces (side-by-side) and selected one of the faces using a button box and right index finger. Participants then received feedback (either 'You win 10p!' or 'You lose') on the screen for 1500 ms. Over a series of iterative trials (30 trials per block), participants were required to learn which of the two faces was associated with a higher probability of reward (reward contingencies were 60%/40%). Participants received additional payment based on their performance in this task. There were 4 blocks in total: 2 'emotional' blocks, where participants chose between happy and angry facial expressions (with the same identity), and 2 'neutral' blocks where participants chose between two neutral faces of different identities. Combinations of identities and reward contingencies were counterbalanced across blocks and participants (Evans et al., 2011a; Evans et al., 2011b). The task lasted approximately 15 min.

2.3. Scanning parameters

T_1-weighted images (structural images) were acquired using a rapid acquisition gradient echo sequence ($T_R = 7321$ ms, $T_E = 3$ ms, $T_I = 400$ ms, field of view $= 240 \times 240$ mm^2, slice thickness $= 1.2$ mm, 196 slices). A T_2* echo planar sequence sensitive to BOLD contrast was used to acquire functional MRI scans ($T_R = 2$ s, $T_E = 35$ ms, field of view $= 24$ cm, slice thickness $= 3$ mm, matrix $= 64 \times 64$, flip angle $= 75°$, 430 volumes) on a 3 T GE Excite 11 MR scanner (GE Healthcare, Chicago, IL).

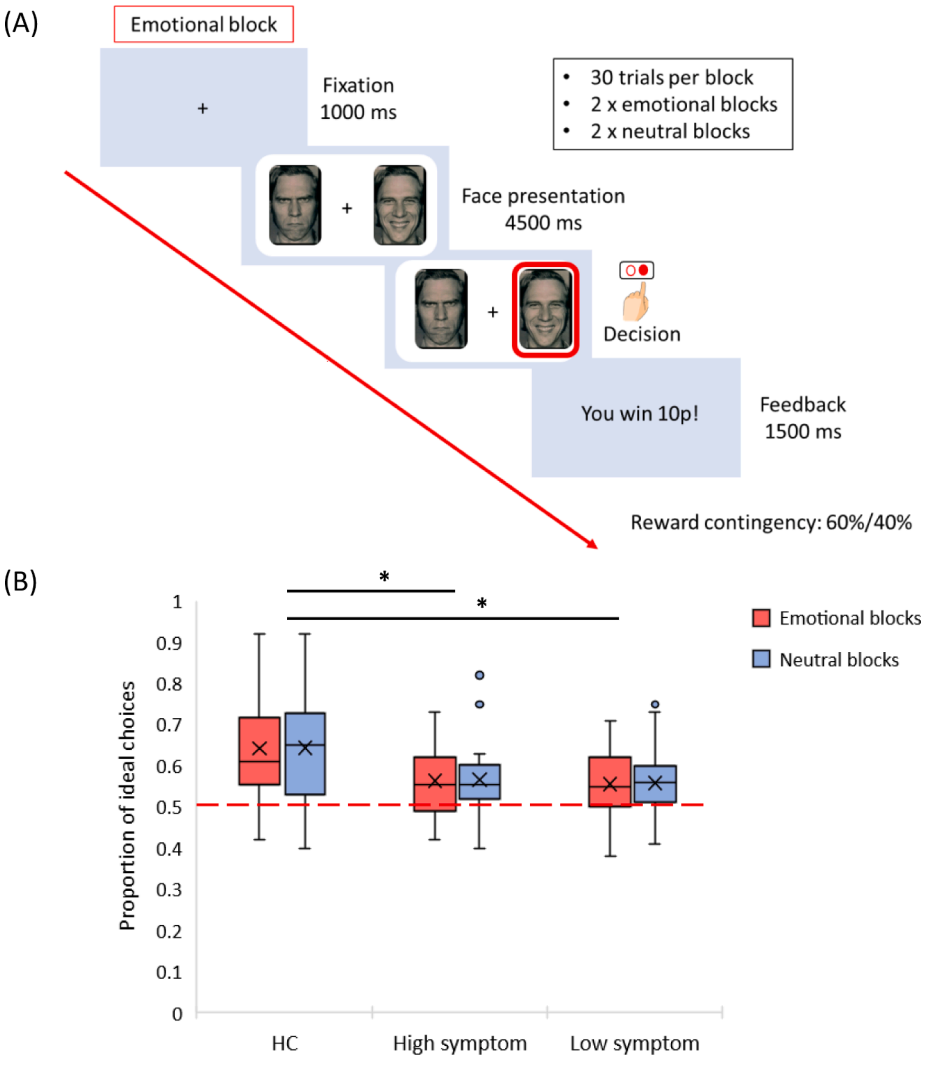

Fig. 1. Overview of reward learning task and behaviour. A) shows schematic of the fMRI task where participants learnt to associate one of two facial expressions with a 60% chance of being rewarded. There were two conditions; emotional (choice between happy and angry faces) and neutral (choice between neutral faces of different identities). B) shows a box plot of the mean proportion of ideal choices made in each condition by healthy controls (HC), high symptom (HS) and low symptom (LS) groups. There is a main effect of group where HC make more ideal choices than both patient groups (* = $p < 0.05$). All groups perform significantly above chance level (shown by red dashed line at 0.5) with a one-sample *t*-test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Behavioural analysis

2.4.1. Ideal choices

A 'double update' reinforcement learning model was used to assess learning performance in this task. The model, which is the same used in (Schlagenhauf et al., 2014; Vanes et al., 2018), uses the same Q-learning algorithm as the standard Rescorla-Wagner model but with the addition that the Q values (or expected outcomes) for both the chosen and unchosen face are updated on every trial. The two free parameters (β – inverse temperature, α – learning rate) were estimated for each group (healthy controls, patients) by minimising the negative log likelihood of the observed data, pooled across each group. To assess learning performance, the participant's choice on each trial was classified as 'ideal' when their expected reward for the chosen face (Q1(t), estimated using the model) was greater than their expected reward for the unchosen face (Q2(t)). The first trial was always considered ideal. Therefore, an ideal choice can be interpreted as how well the participant estimates the value representation of each face and translates that into their choice action. Since reward contingencies were not extremely different (60%/40%), the task is difficult and so we expected the number of ideal choices to increase gradually over successive trials, and for participants to perform above chance level (0.5) as an index of learning.

The proportion of ideal choices made in each condition (emotional, neutral) was computed (excluding missing trials). First, one-sample t-tests were used to test whether each group was making significantly more ideal choices than chance (0.5). Then, a repeated-measures ANOVA was used to test for a main effect of group (HC, high symptom, low symptom), a main effect of condition (emotional, neutral) and a group × condition interaction on ideal choices. Post-hoc tests (corrected for multiple comparisons using Tukey HSD) were used to examine significant effects.

2.4.2. Initial bias

The proportion of participants choosing the happy face on trial 1 of the first emotional condition was calculated. This gives an indication of initial bias (or 'prior') towards favouring happy over angry faces. A chi-squared test was used to compare groups.

2.4.3. Emotional bias

Using the ideal choices calculated above, an overall emotional bias was calculated to give an indication of bias towards choosing happy over angry faces during the two emotional blocks. As in Vanes et al (2018), emotional bias was defined as the difference between the proportion of happy faces chosen given the angry face would have been ideal, and the proportion of angry faces chosen given the happy face would have been ideal. A one-way ANOVA was used to compare emotional bias scores between groups.

2.5. Imaging data analysis

The fMRI data were pre-processed and analysed in Statistical Parametric Mapping, version 12 (SPM12, available at https://www.fil.ion.ucl.ac.uk/spm/software/spm12, Wellcome Department of Cognitive Neurology, London, England). The structural and functional images were first skull-stripped and manually reoriented so that the origin was reset over the anterior commissure. Then, the functional images were realigned to correct for the effects of head motion, co-registered to the structural images and normalised to Montreal Neurological Institute (MNI) space. Finally, the data was filtered using a temporal high pass filter of 100 s and spatially smoothed using a 6 mm FWHM Gaussian kernel.

The fMRI data were analysed using the general linear model in SPM. For the first-level analysis, there were 6 regressors that modelled the three phases of the task (face presentation, decision (button press) and feedback) separately for the two conditions; emotional and neutral. Each regressor was modelled with a delta function (duration = 0) and was convolved with a canonical haemodynamic response function (hrf) and its temporal derivative. Six standard subject-specific motion parameters were added as regressors of no interest to the model. Decision and feedback phases were examined as these were identified as two key points of interest in the task: making reward predictions and a button response (decision phase), responding to feedback and updating reward predictions accordingly (feedback phase). First, these two phases were examined in the neutral condition (low cognitive demand condition) to understand social reward learning function in early psychosis without the influence of emotional bias. In particular, social and reward-related activity (e.g., in temporal lobes, striatum and PFC/ACC) was of interest. Next, the primary contrast of interest was constructed; emotional vs. neutral condition, to examine the effect of cognitive bias on reward functioning during this task. In particular, top-down cognitive control-related activity (e.g., in PFC/ACC) was of interest.

At the group-level, contrasts of interest were submitted to separate mixed-effects analyses. First, to assess differences between HC and patients with psychosis (HS and LS combined), T-tests were constructed (e.g., 1–0.5–0.5) to compare groups. As the HC group was on average older than the patient groups, age was added as a covariate in this model. Then, brain function related to positive symptoms was assessed by modelling the effect of group (HC, HS, LS) on each contrast of interest using a one-way ANOVA (F test) and post-hoc independent sample t-tests were used to compare activity between HS and LS groups. For group comparisons performed on the emotional vs. neutral contrast of interest, this therefore tested for a group-by-condition interaction. As the HC group had significantly higher IQ than both patient groups, additional analyses were conducted to rule out a potential confounding effect of IQ on differences in cognitive control. Mean contrast estimates in key clusters of activation that differed significantly between HC and patients (occipital cortex, rACC and left precentral gyrus/superior front gyrus) were extracted for each subject using marsbar and compared between groups with age and IQ added as a covariate (using an ANCOVA). Post-hoc ANCOVAs were performed in this way in order to maximise power at the whole-brain level (as 12 participants had missing IQ data) and because IQ deficits are an inherent part of psychotic illnesses.

2.6. Region of interest analyses

To test for differences between groups, analyses were primarily conducted using 5 *a priori* regions of interest (ROIs); 1) bilateral amygdala, 2) anterior cingulate cortex (ACC), 3) right temporo-parietal junction (TPJ), 4) bilateral striatum (and subcortical structures including pallidum and thalamus) and 5) bilateral midbrain. The ROIs were selected based on independent data samples from our previous work using this task (Evans et al., 2011a; Evans et al., 2011b; Horne et al., 2021; Vanes et al., 2018) and the key literature emphasising the important role of cognitive control and dysfunction within limbic, cortical and striatal areas in psychosis (Brown & Braver, 2005; Kerns et al., 2004; Minzenberg et al., 2009). All ROIs were binary masks that were anatomically defined using the probabilistic Harvard Oxford Subcortical Structural atlas or cortical atlas (for ACC) thresholded at 30%, except for the right TPJ (defined below). For the decision phase, bilateral amygdala was chosen as a key emotional processing region along with the ACC and right TPJ. The ACC is involved in both reward prediction and cognitive control (Brown & Braver, 2005; Kerns et al., 2004) whereas the TPJ has been shown to be involved in both social evaluation and mentalizing (Van Overwalle, 2009). Specifically, the TPJ ROI was defined using three 10 mm spheres centered over three regions of the right TPJ that had activity previously shown to be correlated with reward prediction (MNI xyz = [51, −21, 6]), a prior preference for happy faces during feedback (MNI xyz = [45, −54, 36]) and an evidence bias based on emotional content during feedback (MNI xyz = [36, −51, 39]) during this task (Evans et al., 2011a; Evans et al., 2011b). The three spheres were then merged into a single ROI mask. The ACC and right TPJ

were also used as ROIs during the feedback phase along with key subcortical structures known to play a role in reward learning; bilateral striatum (caudate nucleus, putamen, nucleus accumbens) including pallidum and thalamus, and midbrain (Schultz, 2016). Separate ROI analyses were conducted using a cluster defining threshold of $p < 0.001$ uncorrected and significant effects are reported if they survive small volume correction (SVC) with a peak level threshold of $p < 0.05$ FWE-corrected. All significant activations are reported from the coordinates of the peak activation in MNI space (xyz).

Exploratory whole-brain analyses were also conducted to examine whether any group differences in activity existed outside of the pre-defined ROIs that were complementary to these effects. These whole-brain analyses were performed using a cluster-level FWE-corrected threshold of $p < 0.05$ (cluster defining threshold of $p < 0.001$).

2.7. Correlations

Post-hoc exploratory correlations were performed between key clusters of activation that were significantly different between HS and LS groups, and symptoms (total positive and total negative). This was achieved by extracting the parameter estimates for each participant from the peak voxel using the marsbar toolbox in SPM and conducting non-parametric Spearman's rank correlations with symptom scores. We investigated: 1) if differences in activity between HS and LS groups would also show a linear correlation between peak activity and positive symptoms across groups, and 2) whether these correlations were specific to positive symptoms, as hypothesized, or if activity related to negative symptoms as well. Since four key clusters of activation were identified as different between HS and LS groups (SMA/pre-SMA, left amygdala, left thalamus and left pallidum) and both positive and negative symptoms were of interest, an adjusted p-value of $0.05/8 = 0.006$ was used to correct for multiple comparisons.

3. Results

Demographic information for all three groups is reported in Table 1. The HC group showed significantly higher average IQ and age compared to the HS and LS groups, but no differences were observed in sex distribution between groups. The two patient groups did not differ significantly in IQ, illness duration, medication dose (chlorpromazine equivalent) or age of psychosis onset and HS had higher scores on all PANSS symptom dimensions (positive, negative, general) compared to LS.

4. Behavioural results

4.1. Ideal choices

All three groups made, on average, ideal choices that were significantly above chance level (0.5) (p's < 0.001) in both conditions (emotional, neutral) (Fig. 1B). As expected, all three groups showed a stable proportion of ideal choices and a gradual increase in correct responses made across trials for both conditions (Figures S1 and S2).

There was a significant main effect of group ($F(2,134) = 17.2$, $p < 0.001$, $\eta^2 = 0.20$) on the proportion of ideal choices (Fig. 1B). Post-hoc tests revealed that HC ($M = 0.64$, S.E. $= 0.012$) made significantly more ideal choices than both HS ($M = 0.56$, S.E. $= 0.014$, $p < 0.001$) and LS ($M = 0.56$, S.E. $= 0.009$, $p < 0.001$) groups. There was no significant main effect of condition ($F(1,134) = 8.15$, $p < 0.001$, $\eta^2 = 0.073$) or significant group × condition interaction on ideal choices. Adding age as a covariate to the model did not change these findings.

4.2. Initial bias

106/137 participants (77% of sample) chose the happy face on the first trial of the first emotional block indicating a prior emotional bias towards happy faces. The proportion of happy faces chosen did not differ between groups.

4.3. Emotional bias

All groups, on average, showed an emotional bias towards choosing happy over angry faces (HC: $M = 0.078$, S.E $= 0.023$, HS: $M = 0.066$, S.E. $= 0.019$, LS: $M = 0.053$, S.E. $= 0.017$) but this did not differ significantly between groups.

5. Neuroimaging results

5.1. Neutral condition

5.1.1. HC group

Task activation was examined in the HC group as an indication of normative functioning. In response to neutral decisions, ROI analyses showed activation in dorsal ACC, bilateral amygdala and right TPJ.

Table 1
Table of demographic and clinical variables.

Demographics	HC (n = 40)		HS (n = 30)		LS (n = 67)		Group statistics	
	M	**SD**	**M**	**SD**	**M**	**SD**	**Stat.**	**Sig.**
							F (df)	***p***
Age	33.9	9.7	26.8	5.4	26.4	6.1	14.58 (2, 132)	<0.001 *
							***X*2 (df)**	***p***
Sex (number of males)	26		21		48		1.96 (4)	0.743
							F (df)	***p***
IQ (WASI)	117.9	11.6	97.5	16.0	99.9	16.9	19.94 (2, 124)	<0.001 *
							t (df)	***p***
Age of onset (years)			25.1	5.5	25.2	6.5	−0.10 (65.89)	0.919
Illness duration (years)			1.8	1.1	1.6	1.3	0.92 (67.02)	0.36
Medication dose (CPZ equivalent)			242.2	139.5	240	142.1	0.07 (59.81)	0.942
PANSS Positive			18.7	5.1	10.4	2.9	8.24 (36.93)	<0.0001 *
PANSS Negative			16.1	5.7	11.2	4.2	4.11 (42.03)	<0.0001 *
PANSS General			35.7	7.8	26.6	6.2	5.55 (44.77)	<0.0001 *
PANSS Total			70.5	13.9	48.2	11.4	7.56 (45.73)	<0.0001 *

Means (M) and standard deviations (SD) are shown for each group. HC = healthy controls, HS = high symptom patients, LS = low symptom patients, CPZ = chlorpromazine, df = degrees of freedom, WASI = Wechsler Abbreviated Scale of Intelligence, * highlights significant differences between groups ($p < 0.05$) where HC were older and had higher IQ than both HS and LS groups. IQ data was missing for 12 participants (n = 37 HC, 26 HS, 62 LS). Variables compared using independent sample t-tests report statistics assuming variances are *not* equal (according to Levene's test for equality of variances).

There was also whole-brain activation in superior frontal gyrus, left postcentral gyrus, left supramarginal gyrus, bilateral thalamus, putamen, internal capsule, angular gyrus and anterior insula as well as in occipital lobe, calcarine cortex, lingual gyrus, superior occipital gyrus, and cerebellum (Fig. 2A, Table S1). Activation tables containing all fMRI results are available in Supplementary materials (Tables S1 – S8).

In response to reward feedback in the neutral condition, ROI analyses showed activation in left caudate. There was also whole-brain activity in a network that included enhanced activations in bilateral superior parietal lobe, bilateral precentral gyrus, occipital pole, lingual gyrus, calcarine cortex, cuneus and cerebellum, and enhanced deactivations in medial PFC, ACC, bilateral middle frontal gyri, supramarginal gyri, precentral gyri, superior temporal gyri, insula, posterior cingulate cortex and precuneus (Fig. 2A, Table S2). A similar pattern of activation was observed in both HS and LS groups (shown in Figure S3).

5.1.2. *Patients vs HC*

In response to neutral decisions, ROI analyses showed no significant differences between HCs and patients in amygdala, ACC or right TPJ. Exploratory whole-brain group comparisons showed HCs had significantly greater activation in the occipital pole extending into the right lingual gyrus (Fig. 3A, Table S5, peak at 14, −88, 0, T = 5.68, p = 0.001 cluster-level FWE-corrected) compared to patients. This group difference remained significant after controlling for age and IQ ($F(1,125) = 25.54$, $p < 0.001$).

In response to feedback in the neutral condition, ROI analyses showed patients had increased activity in left and right rostral ACC (Fig. 3B, Table S6, peaks at −6, 28, 18 and 8, 40, 20, T = 4.1, p < 0.05 ROI small volume corrected) compared to HCs. Exploratory whole-brain analysis also showed patients had significantly reduced activity in left precentral gyrus extending into left middle frontal gyrus, superior frontal gyrus and supplementary motor cortex compared to HCs (Fig. 3C, peak at −34, −14, 50, T = 4.13, p < 0.001 whole-brain cluster-level FWE-corrected). Group differences in rACC remained after age and IQ were controlled for $F(1,125) = 6.67$, $p < 0.05$). Group differences in left precentral gyrus remained after adjusting for age but not age and IQ: $F(1,125) = 2.68$, $p = 0.10$).

5.1.3. *High symptom vs low symptom vs HC*

In response to neutral decisions, the ROI analyses showed no significant between-group differences. However, exploratory whole-brain analyses showed a significant main effect of group in the supplementary motor area (SMA) extending to pre-SMA (Fig. 3D, Table S5, peak at 2, 12, 68, F = 13.5, p < 0.05 cluster-level FWE-corrected) where the HS group had significantly reduced activity (deactivation) compared to both HC and LS groups (p < 0.05 small volume corrected). Individual data points are presented in Figure S4. There were also two sub-peaks of the SMA/pre-SMA cluster where LS had significantly greater activity compared to HC (peaks at 2, −6, 68 and 0, 12, 56).

There were no differences between HS and LS groups in neutral feedback phase.

5.2. *Emotional vs. Neutral contrast*

5.2.1. *HC group*

Bilateral superior temporal gyri showed increased activation in

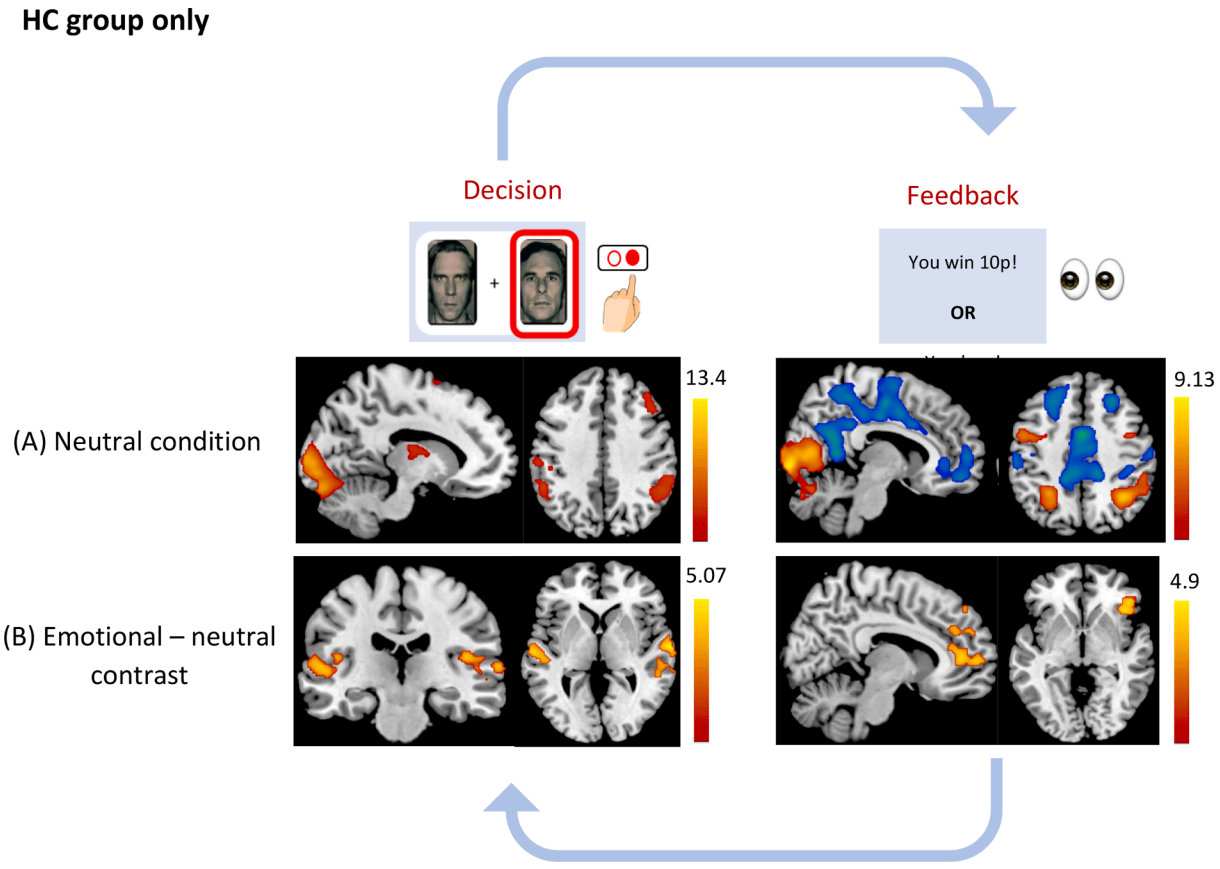

Fig. 2. Contrast-related activity in healthy control group. Whole-brain related activity (red/yellow = activation, blue/green = deactivation) associated with the decision and feedback phases of the task during (A) the neutral condition and (B) emotional-neutral contrast. Images presented using a cluster-level statistical threshold of p < 0.05 FWE-corrected and vertical colour bars represent associated T values. Light blue arrows represent the iterative nature of the task where decisions inform feedback responses and in turn the feedback updates decisions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

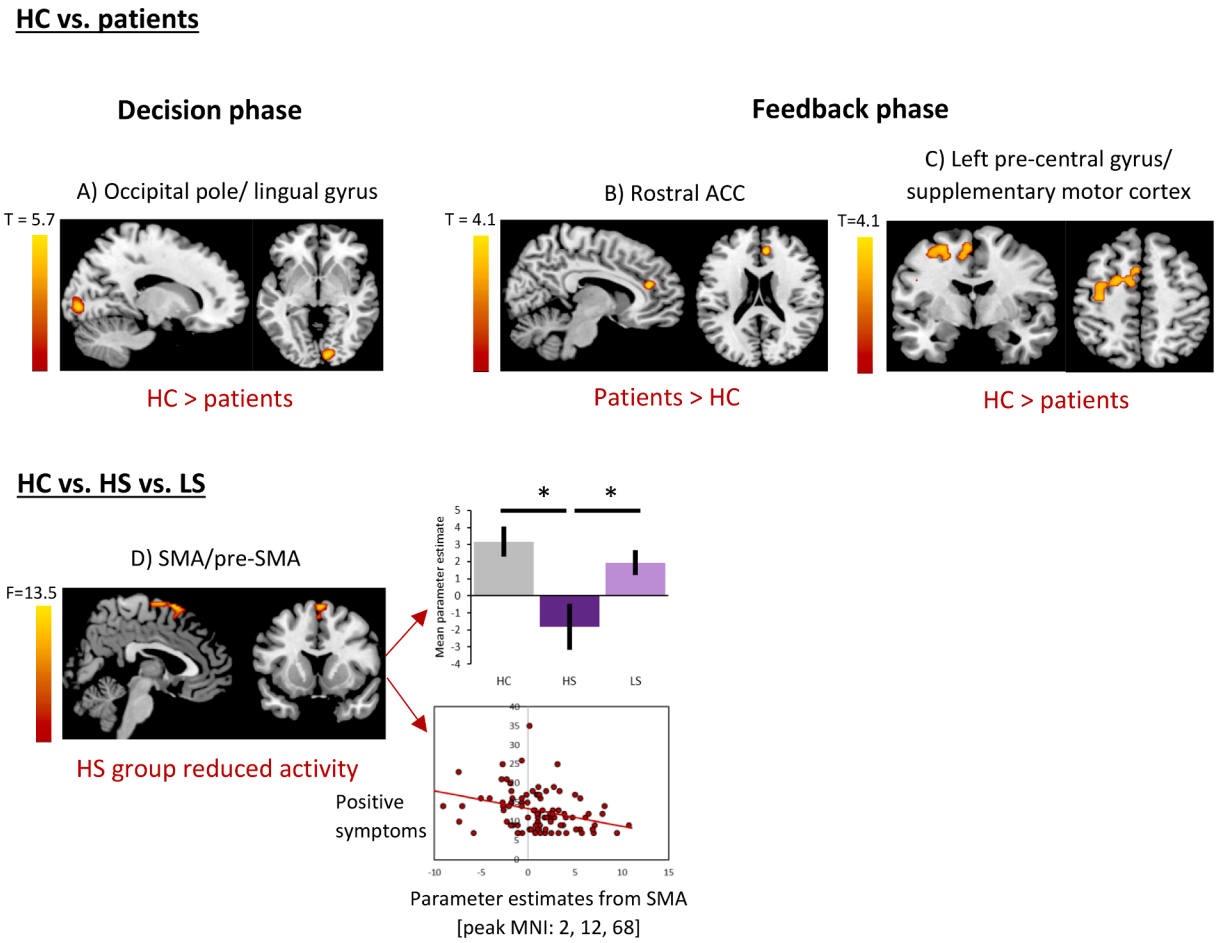

Fig. 3. Group differences in activity during neutral condition. The top row shows three clusters that are significantly different in patients compared to healthy controls: A) occipital pole/lingual gyrus (neutral decision), B) rostral ACC (neutral feedback), and C) left pre-central gyrus extending into left supplementary motor cortex (neutral feedback). Vertical colour bars indicate the associated T values. The bottom row shows one cluster that is significantly different between HS and LS patient groups: D) SMA/pre-SMA (neutral decision), and associated F value. A bar chart (right) shows the associated parameter estimates for each group (HC = healthy controls, HS = high symptom group, LS = low symptom group) where the horizontal lines indicate the post-hoc significant differences between groups (* = $p < 0.05$ FWE-corrected). A significant correlation between parameter estimates (from SMA/pre-SMA) and positive symptoms is also presented.

emotional relative to neutral blocks in the decision phase (Table S3). In the feedback phase, this contrast activated the medial PFC (mPFC), rostral ACC (rACC) and ventrolateral PFC (vlPFC) (Fig. 2B, Table S4).

5.2.2. *Patients vs HC (group × condition interaction)*

There were no significant differences between HC and patients for decision or feedback phases.

5.2.3. *High symptom vs low symptom vs HC (group × condition interaction)*

During the decision phase, ROI analyses showed a significant main effect of group in the left amygdala (Fig. 4A, Table S7, peak at −18, 0–16, F = 10.5, $p < 0.01$, ROI small volume corrected); where post-hoc tests showed the HS group had significantly greater activity than HC and LS groups. The were no significant effects between groups during exploratory whole-brain analyses.

During the feedback phase, there were two significant main effects of group; one in left thalamus (Fig. 4B, Table S8, peak at −10, −8, 0, F = 9.2, $p < 0.01$ ROI small volume corrected) where HS had reduced activity (deactivation) compared to HC and LS, and the other in left pallidum (Fig. 4C peak at −16, −4, −2, F = 14.2, $p < 0.01$ ROI small volume corrected) where LS had increased activity compared to HC and HS groups. Individual data points are presented in Figure S4. The were no significant effects between groups during exploratory whole-brain analyses.

5.3. *Correlations*

5.3.1. *Symptoms*

Post-hoc exploratory analyses showed that across patient groups, all clusters that showed significant differences between HS and LS groups (SMA/pre-SMA [MNI peak: 2, 12, 68] ($r_s(93) = -0.34$, $p = 0.001$), left amygdala [-18, 0–16] ($r_s(93) = 0.37$, $p < 0.001$), left thalamus [-10, −8, 0] ($r_s(93) = -0.32$, $p = 0.002$) and left pallidum [-16, −4, −2] ($r_s(93) = -0.23$, $p < 0.05$)) also showed linear correlations with total positive symptoms (Fig. 3D and Fig. 4A – 4C). However, the correlation between left pallidum and positive symptoms did not survive multiple correction. Negative symptoms were also weakly associated with activity in left amygdala ($r_s(93) = 0.28$, $p < 0.01$), left pallidum ($r_s(93) = -0.23$, $p < 0.05$) and left thalamus ($r_s(93) = -0.28$, $p < 0.01$) but not SMA/pre-SMA (Fig. 4A – 4C). Again, the correlation between left pallidum and positive symptoms did not survive multiple correction.

6. Discussion

The current findings suggest that impairments in cognitive control are present in the early stages of psychosis and may be important for symptomatic control. Similar to previous studies, this task engaged both reward and cognitive control networks and induced an emotional bias towards choosing happy faces in all participants that was evident from the first trial (Evans et al., 2011a; Evans et al., 2011b). Both patient

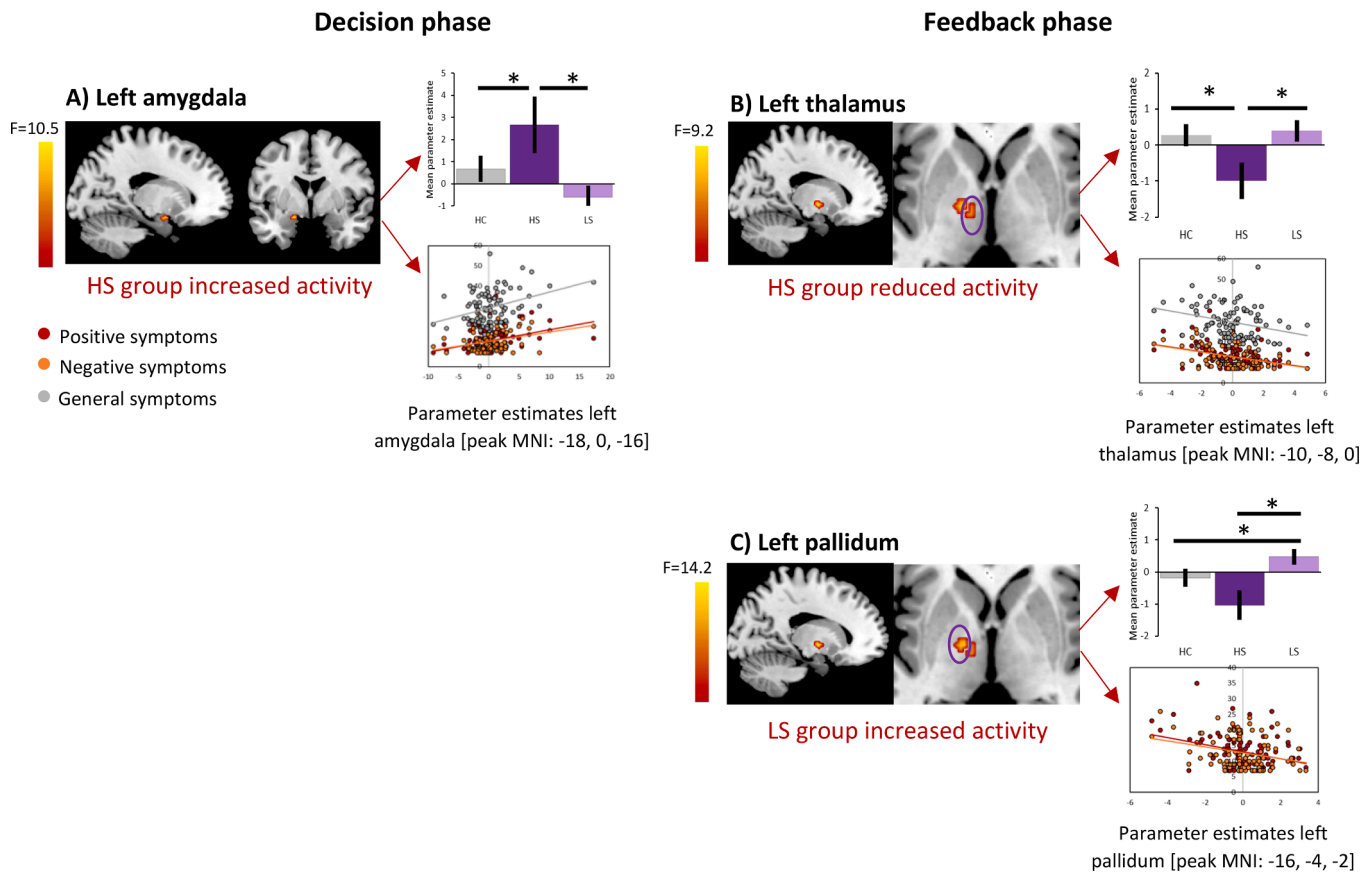

Fig. 4. Group differences in activity during emotional – neutral contrast. Displayed are three clusters showing significant differences between HS and LS groups: A) left amygdala (decision), B) left thalamus (feedback) and C) left pallidum (feedback). The vertical colour bars indicate associated F values. The bar charts to the right show the associated parameter estimates for each group (HC = healthy controls, HS = high symptom group, LS = low symptom group) and post-hoc differences between groups (* = $p < 0.05$ FWE-corrected). Also shown to the right are the significant correlations between the parameter estimates (for each region) and symptoms (red = positive, orange = negative symptoms). There were no significant differences between HC and patients (HS and LS groups combined). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

groups showed suboptimal reward learning and altered activity within the core reward network compared to HC as noted in earlier studies (Strauss et al., 2014). In the neutral (low cognitive demand) condition, this included reduced activity in occipital/lingual gyrus when making decisions, increased activity in rACC in response to feedback and reduced activity in left pre-central gyrus extending into supplementary motor cortex (SMC) and middle frontal gyrus during feedback. Whilst there were no group differences in our pre-defined ROIs, exploratory whole-brain analyses showed that the HS group had significantly reduced SMA/pre-SMA activity during neutral decisions whilst activity was increased in the LS group compared to HC. Recruitment of this region may therefore be a compensatory mechanism allowing effective top-down contextualisation of abnormal perceptual experiences and relating to effective control of positive symptoms. When additional cognitive load was added to the task (emotional vs. neutral contrast) the HS group also had increased amygdala activity during decisions and reduced thalamic activity during feedback compared to LS and HC groups, whereas LS had increased activity in left pallidum during feedback. This suggests a core reward system deficit may be present in both patient groups, but persistent positive symptoms may be associated with dysfunction within a, partially separable, social-emotional network.

Effective reward learning during this task requires cognitive control processes responsible for integrating sensory, emotional and reward feedback information, contextualising information in relation to prior preferences and adjusting behaviour accordingly (Newman, Creer, & McGaughy, 2015). The present findings suggest poor top-down processing in early psychosis patients with high positive symptoms during this task. In the neutral condition, this was evident in the SMA/pre-SMA during decision-making; a region often involved in cognitive control by translating reward predictions into motor actions (Nachev, Kennard, & Husain, 2008). Although this region was not one of our pre-defined ROIs based on previous studies in this task (Horne et al., 2021; Evans et al., 2011a; Evans et al., 2011b), previous findings from the same sample of early psychosis patients also showed a negative relationship between positive symptoms and SMA activity during a Stroop task (Vanes et al., 2019). A comprehensive *meta*-analysis of 41 fMRI studies of executive functioning in schizophrenia suggested that increased activity in SMA was a compensatory response to maintain task performance (Minzenberg et al., 2009). Since we observed altered activity in an extended reward network needed for visual perception, reward detection, performance monitoring and planning motor movements in both patient groups during this task, we also suggest that increased SMA/pre-SMA activity in the LS group could be a compensatory mechanism to support reward learning and maintain performance. SMA and pre-SMA dysfunction has also been associated with a reduced sense of agency (Nachev et al., 2008) and consequent alien limb syndrome – where affected individuals experience their own limb movements as being outside of their control (Farrer et al., 2003; Wolpe, Hezemans, & Rowe,

2020; Yomogida et al., 2010). Given that reward learning is based on the premise that one's action determines the reward, altered SMA/pre-SMA activity could translate to dysfunctional beliefs about the consequences of one's actions - and to inefficient learning. Moreover, an inability to distinguish between internally and externally generated actions has parallels with delusions of control; a common positive symptom of psychosis. Therefore, reduced/absent top-down functioning of this region may contribute to poor reward learning and could represent a mechanism underlying the maintenance of positive symptoms in early psychosis. However, future studies are needed to replicate this finding.

In the emotional vs. neutral condition, we only observed differences between HS and LS groups (as opposed to patients vs. controls). This suggests patients with persistent positive symptoms had a specific deficit in processing the additional cognitive demand associated with the emotional bias (including processing emotion). The HS group showed increased amygdala activity during decisions and reduced activity in left pallidum and thalamus during feedback compared to the LS group. Both disruptions in amygdala function and thalamo-cortical interactions have been reported in schizophrenia and related to symptoms (Andreasen et al., 1994; Giraldo-Chica & Woodward, 2017). Amygdala dysfunction is associated with impaired emotion perception/regulation (especially to negative emotions such as anger and fear) and social cognition, both of which are impaired in schizophrenia (Aleman & Kahn, 2005; Duggirala, Schwartze, Pinheiro, & Kotz, 2020; Green, Horan, & Lee, 2015; Gur et al., 2002; Hempel etal. 2003; Lemmers-Jansen, Fett, Hanssen, Veltman, & Krabbendam, 2019). However, a previous study showed that patients with schizophrenia were able to correctly identify happy and angry expressions during this task suggesting explicit emotion recognition was intact (Evans et al., 2011a; Evans et al., 2011b). Instead, Taylor and colleagues (2002) reported that positive symptoms were associated with increased amygdala activity to emotionally salient images (Taylor, Liberzon, Decker, & Koeppe, 2002) suggesting our HS patients may have assigned enhanced salience or attention to angry or happy faces (Evans et al., 2011a; Evans et al., 2011b)) when making decisions. This may also relate to decreased or inaccurate error signalling in thalamus during feedback in these HS patients since the thalamus is considered an integration 'hub' that has diffuse connections with limbic, striatal and cortical regions (including amygdala and ACC). The thalamus is important for sensory gating and sending error signals to the prefrontal cortex (including ACC) in order to adjust mental representations (Wolff & Vann, 2019). In HS patients, impaired error signalling by thalamus may therefore have led to a failure to update reward predictions. This, in turn, could lead to inappropriate assignment of salience to emotional cues and contribute to poor reward learning. In contrast, LS patients showed intact amygdala and thalamic activity but increased activity in left pallidum suggesting aberrant reward evaluation (Pujara & Koenigs, 2013) but intact cognitive control associated with low levels of psychotic symptoms. This suggests the HS group were less able to integrate social-emotional information with reward feedback and this contributed to impaired reward learning via a different mechanism to the LS group.

Interestingly, although both patient groups showed reduced top-down related activity in rACC in neutral condition compared to healthy controls, rACC activity was not significantly different between HS and LS groups, and not evident in the emotional vs. neutral condition. Previous studies have showed disrupted cognitive control -related ACC activity related to positive symptoms in early psychosis (Thomas et al., 2021; Vanes et al., 2019). Moreover, our earlier study that showed that treatment-resistant patients with chronic schizophrenia had a lack of top-down connectivity from ACC to amygdala and fusiform gyrus and enhanced ACC-striatal (including thalamus) connectivity compared to treatment-responsive patients (Horne et al., 2021). A lack of difference in ACC activity between HS and LS groups in the current sample may reflect their reduced chronicity or antipsychotic medication exposure - or a difference in clinical status between patients with high symptoms and treatment resistance. Alternatively, it may be that ACC connectivity with reward regions more specifically differentiates HS from LS patients. Differences in activity within this network (including amygdala, pallidum and thalamus) may therefore be a function of impaired top-down connectivity and this warrants further investigation.

The current findings evaluate cognitive control deficits that relate to the positive symptoms of psychosis. However, it is worth noting that the HS group also showed significantly higher negative and general symptoms compared to the LS group. In post-hoc, exploratory analyses, key clusters of activation were correlated against symptoms and a general pattern emerged where only positive symptoms were related to top-down cognitive control region activity (i.e., in SMA/pre-SMA) whereas the 'bottom-up' regions (left amygdala, left pallidum and left thalamus) were related to both positive and negative symptoms (although correlations between left pallidum and positive and negative symptoms did not survive corrections for multiple comparisons). Previous studies have shown that positive and negative symptoms can co-occur in schizophrenia but they are related to putatively different circuitry (Eaton et al., 1995). Indeed, blunted responses to emotion and reward have been associated with amotivation and anhedonia in schizophrenia (Rømer Thomsen, 2015). Our findings therefore suggest that impaired cognitive control is specifically important for positive symptoms but dysfunction within task-related subcortical structures (including amygdala, pallidum and thalamus) may represent a mechanism that overlaps with the maintenance of negative symptoms although further studies are needed to clarify this. It is also noted that almost all the current findings were constrained to the left hemisphere. This pattern is similar to other studies showing left hemisphere dominance for cognitive control functions including action planning and task-switching - regardless of handedness (Serrien & Sovijärvi-Spapé, 2013). Finally, HS and LS patients performed very similarly during this task. A lack of difference in behavioural performance may reflect the difficulty of the task (reward contingencies 60/40%) and therefore the fact that model parameters were not able to be computed at the single subject level (see limitations below). Additionally, this would have reduced the accuracy of creating single-subject Reward Prediction Errors (RPEs) as was done in our previous study of chronic schizophrenia (Vanes et al., 2018), especially due to the more variable nature of the illness in our sample of early psychosis patients, resulting in reduced power. Therefore, future studies that perform finer-grained analysis of reward learning behaviour between HS and LS groups would be useful to elucidate the neural differences observed.

6.1. Limitations

The study should be considered with respect to some limitations including that the study is cross-sectional. We recruited medicated patients with early psychosis (mean illness duration 1.7 years) and classified patients with high/low positive symptoms based on the symptom cut-off criteria for treatment response in schizophrenia (Conley & Kelly, 2001). However, medication was not controlled and a robust assessment of treatment (non) response could not be determined at this early, often variable, stage of the illness. Therefore, the sample represents a 'snapshot' of psychosis and future prospective studies are warranted. It would also be preferable to have non-medicated patients, but this is logistically complicated when subjects are experiencing active psychotic symptoms. Secondly, individual behaviour was broadly determined because the two free parameters (inverse temperature and learning rate) used to calculate 'ideal choices' could only be estimated at the group level (patients and HC groups separately) which assumes that all patients with psychosis perform similarly on these parameters. Future studies would benefit from an easier task (e.g., 70/30% reward contingency instead of 60/40%) or more trials so that single-subject parameters could converge, and more fine-grained analyses of behaviour could be conducted and related to brain activity. Finally, mean age and IQ were significantly higher in the HC group compared to both patient groups. While we controlled for these variables in our analyses and the observed group differences are therefore unlikely to reflect effects of age or IQ,

statistical covariation is an imperfect means of controlling for confounders and potential residual effects of age and IQ cannot be fully excluded. In particular, whilst IQ (and related working memory deficits) are often an inherent part of psychotic illness, it is related to cognitive control function and therefore differences in activation between HC and patients may reflect an alternative strategy used by the patients to complete the task. Indeed, higher activity in precentral gyrus in HC compared to patients (neutral feedback condition) was non-significant when IQ was adjusted for and so this finding should be treated with caution. Including IQ as a covariate is a controversial issue as it plausibly removes important variance of interest (Dennis et al., 2009), however further work to tease these effects apart are warranted.

7. Conclusion

Our findings suggest that poor top-down control over the reward network may be an important mechanism underlying persistent positive symptoms in a large sample of early psychosis patients. Patients with high positive symptoms displayed a pattern of reward learning that was interpreted as driven by overweighting the prior bias for happy faces (top-down prediction) and underweighting the trial-by-trial reward feedback (bottom-up sensory evidence). This pattern of reward learning may relate to common positive symptoms of psychosis that manifest as fixed false beliefs not amenable to change. Future studies investigating how poor cognitive control relates to finer-grained measures of reward-learning behaviour and the positive symptoms of psychosis are needed. However, our findings suggest that cognitive control could be an important avenue for novel interventional approaches to the treatment of persistent positive symptoms and prevention of chronic illness. Preliminary work using psychological approaches, neuromodulation and pro-cognitive psychopharmacology (Cella et al., 2020; Lowe et al., 2018; Orlov et al., 2017) demonstrate some promise.

8. Disclosures

The authors report no competing interests.

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CRediT authorship contribution statement

Charlotte M. Horne: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Angad Sahni:** Methodology, Formal analysis. **Sze W. Pang:** Methodology, Formal analysis. **Lucy D. Vanes:** Investigation, Project administration, Methodology. **Timea Szentgyorgyi:** Investigation, Project administration. **Bruno Averbeck:** Resources, Methodology. **Rosalyn J. Moran:** Conceptualization, Methodology, Software, Visualization, Supervision. **Sukhwinder S. Shergill:** Conceptualization, Resources, Supervision, Funding acquisition, Project administration.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103004.

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