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Striatal dysfunction in patients with schizophrenia and their unaffected first-degree relatives

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ABSTRACT

Despite empirical findings showing that patients with schizophrenia and their unaffected first-degree relatives have deficits in processing monetary incentives, it is unclear whether similar deficits could be demonstrated for affective incentives. Twenty-six patients with schizophrenia and 26 age and gender matched healthy controls; 23 unaffected first-degree relatives and 23 matched healthy controls were recruited to complete a Monetary Incentive Delay (MID) task and an Affective Incentive Delay (AID) task in a 3-Tesla MRI scanner. Hypoactivation in the dorsal striatum when anticipating monetary incentives were found in patients with schizophrenia and their unaffected first-degree relatives compared with healthy controls. Furthermore, patients with schizophrenia showed hyperactivation in the ventral striatum when receiving both monetary and affective incentives. These findings suggest that disorganized striatal function, regardless of incentive types, may be present in patients with schizophrenia and before the onset of illness in their first-degree unaffected relatives.

1. Introduction

The latest formulation of the dopamine hypothesis of schizophrenia suggests that disorganized mesolimbic and mesocortical dopaminergic activity underlies the pathophysiology of psychosis (Howes and Kapur, 2009). The striatal dopaminergic system, especially the ventral striatum, serves as the cornerstone of this hypothesis (Berridge and Robinson, 1998; Berridge et al., 2009; Schultz et al., 1997). Impaired dopaminergic activity in the striatum of patients with schizophrenia is associated with negative and positive symptoms (Heinz, 2002; Heinz and Schlagenhauf, 2010; Kapur, 2003; Kapur et al., 2005).

The Monetary Incentive Delay (MID) task (Knutson et al., 2001, 2000) is designed to capture the anticipation and consummation of delayed incentives and is particularly useful in exploring striatal activation. Earlier studies have found hypoactivation in the ventral striatum of patients with chronic (Juckel et al., 2006a, 2006b) and first-episode (Esslinger et al., 2012; Hanssen et al., 2015; Nielsen et al., 2012b; Schlagenhauf et al., 2009) schizophrenia, their unaffected first-degree relatives (de Leeuw et al., 2015; Grimm et al., 2014) and other high-risk groups for schizophrenia (Juckel et al., 2012) during the anticipation of monetary incentives. The reduced ventral striatal haemodynamic activity has been linked to temporal dopaminergic bursts which impede the retrieval of incentive-specific signals from contextual activities (Knutson and Gibbs, 2007). However, few studies have examined the neural mechanisms for the anticipation and consummation of affective incentives in patients with schizophrenia and their unaffected first-degree relatives. Heerey and Gold (2007) found that patients with schizophrenia showed impaired motivational behavioural performance during the anticipation of affective incentives, and these findings were corroborated by another study (Lui et al., 2016). These results suggest that patients with schizophrenia may have impaired processing for not only monetary incentives, but also affective incentives. Examining the mechanisms of various types of incentive processing could provide more comprehensive insights into the psychopathological mechanisms of amotivation and anhedonia, as well as negative symptoms of schizophrenia. Even though monetary incentives could, to some extent, be regarded as affective stimuli, affective incentives are more specific and are often presented using affective pictures with more social information than monetary incentives.

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To the best of our knowledge, no study has explored the neural mechanisms for both affective and monetary incentives in patients with schizophrenia and their unaffected first-degree relatives simultaneously. Our preliminary findings suggest a distinct neural mechanism for affective incentives which is different from monetary incentives in healthy people using the Affective Incentive Delay (AID) and Monetary Incentive Delay (MID) tasks (Chan et al., 2015). We found that healthy volunteers showed activation in the nucleus accumbens when anticipating monetary, rather than affective incentives. However, similar striatal activation patterns were found in response to both monetary and affective stimuli (Izuma et al., 2008). These results suggest that affective and monetary incentives engage different brain regions during the anticipatory phase, but both engaged the striatal system during the consummatory phase.

The investigation of unaffected first-degree relatives of patients with schizophrenia could help to shed light on the psychopathology of dysfunctional striatal activation in schizophrenia when processing incentives. While previous studies have demonstrated impaired striatal activation in first-degree relatives of schizophrenia patients during the anticipation of monetary incentives (de Leeuw et al., 2015; Grimm et al., 2014), no study has investigated striatal dysfunction in patients with schizophrenia and their first-degree relatives simultaneously in the different phases of incentive processing. The influence of antipsychotic medications on striatal activation when anticipating monetary incentives has been reported in previous studies (Nielsen et al., 2012a, 2012b). Studying striatal dysfunction in unaffected first-degree relatives of patients with schizophrenia could avoid the confounding effect of antipsychotic medications and ascertain if this dysfunction exists along the schizophrenia spectrum, thereby providing evidence that this trait may be an endophenotype of schizophrenia (Chan et al., 2011; Gottesman and Gould, 2003).

In this study, we sought to examine the brain activations at the striatum during monetary and affective incentive processing in patients with schizophrenia and their unaffected first-degree relatives. Furthermore, in addition to the ventral striatum, reduced dorsal striatal activation has also been reported in patients with schizophrenia when anticipating monetary incentives (Mucci et al., 2015). Hence, we examined both dorsal and ventral striatal activation in both groups during the various phases of incentive processing. We hypothesized that patients with schizophrenia and their unaffected first-degree relatives would demonstrate dysfunctional striatal activation in anticipating and receiving both monetary and affective incentives.

2. Method

2.1. Participants

Twenty-six patients with schizophrenia and 23 unaffected first-degree relatives were recruited from the Shanghai Mental Health Centre. The diagnosis for the patients was ascertained using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996) by an experienced psychiatrist (ZHY). Twenty-two patients with schizophrenia were treated with second generation antipsychotics (SGA): four received aripiprazole, one received clozapine, one received quetiapine, four received amisulpride, two received risperidone, two received paliperidone, and eight received olanzapine. Four of the patients with schizophrenia were un-medicated. Potential participants were excluded if they had a co-morbid DSM-IV Axis I disorder, a history of other neurological, mental or substance disorder, and a history of receiving electroconvulsive therapy in the past six months. All participants were right-handed. Due to the "One-child Policy" in China, more than half of the relatives recruited in the present study were one of the parents of patients with schizophrenia, with significantly different demographics. Hence, we recruited two separate groups of healthy controls for comparison with the two groups from the local communities through advertisements. In total, 26 age and gender matched healthy controls for the patients with schizophrenia and 23 matched healthy controls for the unaffected first-degree relatives of schizophrenia participated in this study. In addition to the same exclusion criteria for patients with schizophrenia, people with a personal and family history of any Axis I psychiatric disorder were also excluded from the healthy control groups. This study was approved by the Ethics Committees of the Shanghai Mental Health Centre and the Institute of Psychology, the Chinese Academy of Sciences. We obtained written informed consent from the participants before the commencement of the study.

2.2. Functional MRI tasks

The MID and the AID (Chan et al., 2015) tasks were administered to all participants. In the MID task, a 250-millisecond cue that indicated different conditions was first displayed, followed by a blue cross target, and then the feedback. Participants were asked to hit the blue target as quickly as they could regardless of the cue type. The cues contained a triangle for which participants would gain five monetary points if the target was hit, a square for which participants would lose five monetary points if the target was missed, and a circle for which participants would neither gain nor lose any points irrespective of whether the target was hit or missed in the feedback period. The AID task shared the same procedure as the MID task in each trial except for the feedback when a triangle indicated that participants would see a positive affective picture if the target was hit; a square indicated that participants would see a negative affective picture if the target was missed and a circle indicated that participants would see a neutral affective picture irrespective of whether or not the target was hit. The interval between cue and target jittered from 2000 to 2500 milliseconds, while the interval between target and feedback jittered from 300 to 3500 milliseconds. The inter-trial interval was changed to make sure each trial lasted for 12 s. The jittered interval strategy was adopted to avoid habituation to the appearance time of the target. Participants were required to complete two runs of the MID and the AID tasks respectively in the scanner. Each run consisted of 30 trials with 10 positive conditions, 10 negative conditions and 10 neutral conditions. The order of trials in each run was pseudo-randomized. The initial duration of the blue target was 300 milliseconds and jittered in the following trials in each run based on the performance of the last trial such that the hit rate of each participant remained at about 60%. Affective pictures adopted in the AID task were taken from the International Affective Picture System. The validity of the adopted affective pictures has been ascertained in our initial behavioural study (Xie et al., 2014). All participants practiced the MID and the AID tasks with 30 trials each before entering the scanner. Please refer to our previous studies (Chan et al., 2015; Xie et al., 2014) for detailed parameters of both tasks and the criteria of affective picture selection.

2.3. Image acquisition

A 3-Tesla Siemens scanner equipped with 32-channel head coil was applied to acquire brain imaging data. A T2-weighted FLAIRE sequence was assessed by experienced radiologists to ascertain that each participant had no organic brain disorders (TR = 4000 ms; TE = 90 ms; FOV = 200 mm; slices = 19; flip angle = 120°; image matrix = 256 × 512; voxel dimensions = 0.9 × 0.4 × 5 mm^3). Functional images during task performance were acquired with gradient-echo echo-planner sequence (TR = 2000 ms; TE = 30 ms; FOV = 210 mm; slices = 31; flip angle = 90°; image matrix = 64 × 64; voxel dimensions = 3.3 × 3.3 × 4 mm^3). A high resolution T1-weighted structural image with 176 slices was acquired for anatomical reference (TR = 2300 ms; TE = 3 ms; FOV = 256 mm; flip angle = 9°; image matrix = 256 × 256; voxel dimensions = 1 × 1 × 1 mm^3). The head of each participant was fixed with a foam pad. All the participants had a mean head movement <2.5 mm. To further examine the match of head motion between groups, we also performed group comparisons on the frame-wise displacement (FD), a comprehensive head motion

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index calculated based on the three transitional and three rotational parameters (Power et al., 2012).

2.4. Clinical symptoms and self-reported measures of anhedonia

Symptom severity for patients with schizophrenia was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Before brain scanning, all participants were asked to complete a set of questionnaires for self-reported measures of anhedonia, including the Chinese versions of the Temporal Experience of Pleasure Scale (TEPS) (Chan et al., 2012a; Gard et al., 2006), the Chapman Physical Anhedonia Scale (RCPAS) and the Chapman Social Anhedonia Scale (RCSAS) (Chan et al., 2012b; Chapman et al., 1976). Intellectual functioning was estimated using a pro-rating method based on the short form (containing four subtests of verbal IQ: Information, Similarities, Arithmetic and Digit Span) of the Chinese version of the Wechsler Adult Intelligence Test Scale-Revised (Gong, 1992).

2.5. Data analysis

Chi-square test was used to assess gender matching between groups. Independent *t*-test was used to evaluate the match of linear demographics and to examine group differences in questionnaire measures. Since patients with schizophrenia and their unaffected first-degree relatives were matched with different healthy controls, two 2 (group: patients with schizophrenia or unaffected first-degree relatives of patients vs. healthy control) × 2 (affective vs. monetary incentives) × 3 (neutral, positive and negative conditions) mixed effects ANOVA were applied to explore the variance of hit rate and reaction time to targets in the MID and AID tasks. Genders, age, years of education, and IQ were included as covariates.

Imaging data were processed with Statistical Parametric Mapping 8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk). Brain functional images from the scanner were re-aligned first to correct head motion, followed by slice timing correction and co-registration. Then the images were non-linearly normalized to the brain template of the Montreal Neurological Institute (MNI) through the deformation field matrix from the segmentation of brain structure image of each participant with new segmentation and DARTEL tool in SPM8. All the functional images were resampled into $3 \times 3 \times 3$ mm^3 and the brain tissue was extracted from the T1 structure image of each participant by the Bet tool in FSL before segmentation (Smith, 2002). The functional images were finally smoothed with a Gaussian kernel of 8 mm FWHM (full width at half maximal). Data preprocessing was carried out using the DPABI toolbox, which integrates functions from SPM, AFNI and FSL (http://rfmri.org/DPABI).

Three anticipatory cues which contained monetary gain, monetary loss and monetary neutral, and six consummatory outcomes which contained monetary gain hit, monetary gain miss, monetary loss hit, monetary loss miss, monetary neutral hit, and monetary neutral miss were modelled into a general linear model (GLM) for the MID task. To avoid the influence of button pressing, the target hit period was also modelled into the GLM. Similarly, three anticipatory cues which contained positive, negative and neutral pictures, six consummatory outcomes which contained positive picture hit, positive picture miss, negative picture hit, negative picture miss, neutral picture hit, and neutral picture miss, and the target hit period were modelled into a general linear model for the AID task. Six head movement parameters of each participant during the task performance were included into the individual GLM of MID and AID respectively as covariates. During the anticipatory phase, we defined two contrasts: [monetary gain > monetary neutral] and [monetary loss > monetary neutral] in the MID task, and two: [positive picture > neutral picture] and [negative picture > neutral picture] in the AID task. During the consummatory phase, we defined two contrasts: [monetary gain hit > monetary neutral hit] and [monetary loss miss > monetary neutral miss] in the MID task, and two: [positive picture hit > neutral picture hit] and [negative picture miss > neutral picture miss] in the AID task.

Given our a-priori hypothesis and the moderate sample size in the present study, we applied Region of Interest (ROI) analysis to investigate the striatal activation of patients with schizophrenia and their unaffected first-degree relatives during monetary and affective incentives processing. A mask of the ventral striatum (VS) was made by binarizing the template from a publication-based probabilistic MNI atlas at the threshold of 0.5 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date: February 2, 2016). A dorsal striatum (DS) mask was defined as the remainder of the putamen and the caudate nucleus subtracting the ventral striatum mask that was made based on the Automated Anatomical Labeling (AAL) atlas.

The signal change of the four contrasts in the MID task and the four contrasts in the AID task were extracted from the VS and DS of each participant using the Marsbar toolbox. Two 2 (group: patients with schizophrenia or unaffected first-degree relatives of patients vs. healthy control) × 2 (Incentive: affective vs. monetary) × 2 (valence of contrast: positive vs. neutral, and negative vs. neutral; e.g., [monetary gain > monetary neutral] and [monetary loss > monetary neutral]) mixed effects ANOVA were done for anticipatory and consummatory phase independently, with gender, age, education year and IQ as covariates, were applied to explore the variance of striatal activation in the ventral and dorsal striatum, followed by post-hoc analysis with Bonferroni correction. The signal change of each contrast was also correlated with symptom measures in patients with schizophrenia, and self-reported questionnaires on anhedonia and pleasure experience in each group.

Although the rationale to directly compare the patients with schizophrenia and their unaffected first-degree relatives was relatively weak in this study due to poor matching, we nevertheless carried out exploratory comparisons between the two groups. Furthermore, the two healthy control groups were also compared to ensure that the sampling of healthy participants was unbiased.

3. Results

3.1. Demographics and behavioural performances

Patients with schizophrenia and healthy controls were matched on gender proportion, age and head motion in the AID and MID tasks, but schizophrenia patients were significantly less well educated and had lower IQ than healthy controls. Patients with schizophrenia reported significantly higher levels of physical and social anhedonia, and lower consummatory pleasure (consummatory component of the TEPS) than healthy controls. Unaffected first-degree relatives of patients were matched with healthy controls on gender proportion, age, education, IQ and head motion in both tasks. The self-reported anhedonia and pleasure experience of the relative group were not significantly different from that of healthy controls (Table 1).

The hit rate and reaction time data are shown in Supplementary Table 1. There was a significant interaction between group and incentive type in reaction time of target hitting ($F(1,46) = 4.08$, $p = 0.049$, $\eta^2 = 0.081$). Patients with schizophrenia showed significantly slower reaction time than healthy controls (mean difference = 19.72, $p = 0.003$). Patients with schizophrenia reacted more slowly to monetary incentives than affective incentives (mean difference = 12.72, $p < 0.001$). No significant group effect or interaction effect was found in hit rate and in the comparisons between relatives of patients with their healthy controls for both hit rate and reaction time.

3.2. Dysfunctional striatal activation in patients with schizophrenia

Significant interactions between groups and incentive types were found in ventral striatal activation during the anticipatory phase ($F(1,46) = 5.50$, $p = 0.023$, $\eta^2 = 0.107$). Post-hoc analysis

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Table 1
Demographics and clinic information of participants.

	SCZ (N = 26)	HC (N = 26)	t (df = 50) / χ^2	p	REL (N = 23)	HC (N = 23)	t (df = 44) / χ^2	p
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Gender (male/female)	15/11	15/11	0	1	10/13	15/8	2.19	0.139
Age	22.77 (6.21)	24.58 (5.38)	−1.12	0.267	35.78 (9.02)	33.31 (6.22)	1.08	0.285
Education	12.54 (2.47)	13.88 (2.03)	−2.15	0.037*	14.65 (18.57)	12.8 (2.85)	0.47	0.638
IQ_Est	105.04 (15.06)	113.5 (13.83)	−2.11	0.04*	101.04 (16.66)	106.03 (14.86)	−1.07	0.29
RCSAS	13.5 (7.22)	9.58 (4.96)	2.28	0.027*	10.65 (6.04)	9.9 (4.91)	0.45	0.657
RCPAS	22.88 (11.09)	16.84 (7.84)	2.24	0.03*	19.13 (9.25)	18.15 (8.63)	0.36	0.722
TEPS_TOT	75.54 (13.71)	80.31 (8.49)	−1.51	0.138	80.39 (11.4)	79.71 (9.63)	0.21	0.833
ANT	33.92 (7.7)	34.62 (5.22)	−0.38	0.706	34.65 (5.38)	33.9 (5.22)	0.47	0.643
CON	38.62 (8.39)	42.54 (5.06)	−2.04	0.046*	42.3 (7.46)	42.76 (6.3)	−0.22	0.828
FD_MID	0.15 (0.06)	0.14 (0.04)	0.51	0.613	0.15 (0.07)	0.16 (0.05)	−0.27	0.789
FD_AID	0.15 (0.06)	0.16 (0.1)	−0.41	0.687	0.17 (0.09)	0.18 (0.11)	−0.43	0.667
Onset age	18.68 (5.51)							
DUI (month)	45.94 (34.36)							
DUT (month)	4.79 (8.45)							
PANSS_TOT	56.2 (20.25)							
PANSS_POS	12.8 (4.97)							
PANSS_NEG	16.12 (7.08)							
PANSS_GE	29.44 (8.14)							

Note: *, $p < 0.05$; SCZ = People with schizophrenia; REL = Unaffected first-degree relatives of people with schizophrenia; HC = Healthy control; SD = Standard deviation; IQ_Est = Estimated Intelligence Quotient; RSCAS = Revised Chapman Social Anhedonia Scale; RCPAS = Revised Chapman Physical Anhedonia Scale; TEPS = Temporal Experience Pleasure Scale; ANT = Anticipatory component of TEPS; CON = Consummatory component of TEPS; AID = Affective Incentive Delay task; MID = Monetary Incentive Delay task; FD = frame-wise displacement; DUI = Duration of Illness; DUT = Duration of Treatment; PANSS = Positive and Negative Syndrome Scale; TOT = Total score; POS = Positive Symptom; NEG = Negative Symptom; GE = General Symptom.

demonstrated that healthy controls showed greater ventral striatal activation compared with patients with schizophrenia when anticipating monetary incentives (mean difference = 0.23, $p = 0.016$). In addition, the healthy control group showed greater ventral striatal activation during the anticipation of monetary incentives than affective ones (mean difference = 0.31, $p = 0.001$) (Table 2).

Significant interactions between groups and incentive types were also found in dorsal striatal activation during the anticipatory phase ($F(1,46) = 10.48$, $p = 0.002$, $\eta^2 = 0.186$). Healthy controls showed significant greater dorsal striatal activation than patients with schizophrenia when anticipating monetary incentives (mean difference = 0.18, $p = 0.012$). They also showed significantly greater dorsal striatal activation for monetary than affective incentives during the anticipatory phase (mean difference = 0.18, $p = 0.007$) (Table 2).

During the consummatory phase, a trend interaction between groups and contrast types were found in ventral striatal activation ($F(1,46) = 3.22$, $p = 0.079$, $\eta^2 = 0.065$), while significant interaction between groups and contrast types was found in dorsal striatal activation ($F(1,46) = 5.30$, $p = 0.026$, $\eta^2 = 0.103$). Post-hoc comparisons indicated significantly greater ventral (mean difference = 0.13, $p = 0.008$) and dorsal (mean difference = 0.082, $p = 0.01$) striatal activation in patients with schizophrenia than their healthy controls when they received both positive monetary and affective incentives. Furthermore, patients with schizophrenia showed significantly greater ventral (mean difference = 0.159, $p < 0.001$) and dorsal (mean difference = 0.069, $p < 0.001$) striatal activation when receiving positive incentives than negative incentives. This pattern was not present in their healthy control groups (Table 2).

Table 2
Region of interest group-comparisons between people with schizophrenia and healthy controls, their unaffected first-degree relatives and healthy controls for affective and monetary incentives.

		SCZ (N = 26)	HC (N = 26)	F(p) (group)	F(p) (interaction)	REL (N = 23)	HC (N = 23)	F(p) (group)	F(p) (interaction)
		Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Anticipation									
VS	AID: Neg.pic. > Neu.pic.	0.22 (0.26)	0.16 (0.44)	0.74 (0.394)	5.50 (0.023)*	0.02 (0.69)	0.25 (0.52)	1.82 (0.185)	\
	AID: Pos.pic. > Neu.pic.	0.27 (0.29)	0.17 (0.43)		(Group × incentive)	0.01 (0.7)	0.25 (0.49)		
	MID: Loss > Neutral	0.19 (0.2)	0.49 (0.53)			0.13 (0.4)	0.41 (0.48)		
	MID: Gain > Neutral	0.26 (0.14)	0.49 (0.53)			0.19 (0.46)	0.49 (0.48)		
DS	AID: Neg.pic. > Neu.pic.	0.27 (0.21)	0.16 (0.32)	0.35 (0.557)	10.48 (0.002)**	0.11 (0.26)	0.3 (0.33)	5.39 (0.025)*	4.411(0.042)*
	AID: Pos.pic. > Neu.pic.	0.3 (0.18)	0.19 (0.29)		(Group × incentive)	0.12 (0.28)	0.3 (0.31)		(Group × incentive ×
	MID: Loss > Neutral	0.14 (0.16)	0.33 (0.31)			0.15 (0.19)	0.28 (0.3)		contrast)
	MID: Gain > Neutral	0.18 (0.13)	0.38 (0.29)			0.16 (0.2)	0.38 (0.31)		
Consummation									
VS	AID: Neg.pic. > Neu.pic.	−0.1 (0.15)	−0.13(0.25)	5.26 (0.026)*	3.221 (0.079)†	−0.25 (0.21)	−0.11 (0.19)	0.01 (0.943)	\
	AID: Pos.pic. > Neu.pic.	0.08 (0.13)	−0.07(0.22)		(Group × contrast)	−0.02 (0.17)	−0.06 (0.18)		
	MID: Loss > Neutral	−0.01 (0.2)	−0.08(0.24)			−0.06 (0.22)	−0.06 (0.22)		
	MID: Gain > Neutral	0.13 (0.17)	−0.02(0.2)			0.01 (0.13)	−0.03 (0.21)		
DS	AID: Neg.pic. > Neu.pic.	−0.05 (0.13)	−0.09(0.16)	4.27 (0.044)*	5.30 (0.026)*	−0.13 (0.19)	−0.08 (0.09)	0.201 (0.656)	\
	AID: Pos.pic. > Neu.pic.	0.03 (0.1)	−0.06(0.12)		(Group × contrast)	−0.02 (0.08)	−0.05 (0.11)		
	MID: Loss > Neutral	0.01 (0.12)	−0.01(0.15)			0.01 (0.16)	0 (0.15)		
	MID: Gain > Neutral	0.06 (0.1)	−0.01(0.15)			−0.01 (0.07)	−0.02 (0.16)		

Note: †, marginal significant, *, $p < 0.05$, **, $p < 0.001$; AID = Affective Incentive Delay task; MID = Monetary Incentive Delay task; VS = Ventral striatum; DS = Dorsal striatum; Neg.pic. = Negative picture; Pos.pic. = Positive pictures; Neu.pic. = Neutral pictures; SCZ = People with schizophrenia; REL = Unaffected first-degree relatives of people with schizophrenia; HC = Healthy control; SD = Standard deviation.

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3.3. Dysfunctional striatal activation in unaffected first-degree relatives of schizophrenia patients

For the comparisons between first-degree relatives of schizophrenia patients and their healthy controls, a significant interaction between groups, incentive types and contrasts was found in dorsal striatal activation during the anticipatory phase ($F(1,40) = 4.41$, $p = 0.042$, $\eta^2 = 0.099$). Post-hoc analysis demonstrated that first-degree relatives of schizophrenia patients showed significantly less dorsal striatal activation than the healthy control group when anticipating monetary gain (mean difference = 0.206, $p = 0.016$), whereas the healthy control group showed significantly greater dorsal striatal activation during the anticipatory phase for monetary gain than loss (mean difference = 0.096, $p = 0.003$) (Table 2).

In our exploratory comparisons between patients with schizophrenia and their unaffected first-degree relatives, although significant interaction were not found in both the anticipatory and the consummatory phase for the two ROIs, a significant group effect was found for ventral ($F(1,43) = 6.38$, $p = 0.015$, $\eta^2 = 0.129$) and dorsal ($F(1,43) = 5.53$, $p = 0.023$, $\eta^2 = 0.114$) striatal activation when receiving monetary and affective incentives. Patients with schizophrenia showed comparable striatal activation with their unaffected first-degree relatives in anticipating incentives, but they exhibited significantly greater striatal activation during the consummatory phase. No significant main effect or interaction was found in the comparisons between the two healthy control groups, indicating that the two groups were comparable.

To further examine whether patients with schizophrenia and their unaffected first-degree relatives exhibited impaired brain activation outside the striatum, we also performed group comparisons using whole brain analysis. Patients with schizophrenia exhibited hypoactivation in the bilateral dorsal striatum for both contrasts in the MID task [monetary loss > monetary neutral] and [monetary gain > monetary neutral]. However, patients with schizophrenia showed hyperactivation in the bilateral ventral striatum for the contrast [monetary gain hit > monetary neutral hit] in the MID task, and the contrast [positive picture hit > neutral picture hit] a in the AID task (Fig. 1). The findings of whole brain analysis were largely consistent with results from the ROI analysis (for details please refer to the Supplementary materials).

3.4. Correlations with clinical symptoms and pleasure experience

Symptom severity was not significantly correlated with either activation at the ventral striatum or the dorsal striatum in patients with schizophrenia (Supplementary Table 4). There was no significant association between striatal activation and self-reported anhedonia and pleasure experience in patients with schizophrenia, their unaffected first-degree relatives and healthy controls.

4. Discussion

This is the first study that examines dysfunctional striatal activations in patients with schizophrenia and their unaffected first-degree relatives in processing monetary and affective incentives. Consistent with our hypothesis, both the patient and relative groups demonstrated dysfunctional striatal activations compared with appropriately matched healthy controls. During the anticipatory phase, patients with schizophrenia showed hypoactivation in the bilateral dorsal and ventral striatum for monetary incentives. During the consummatory phase, however, patients with schizophrenia showed hyperactivation in the ventral striatum for both affective and monetary incentives. In addition, unaffected first-degree relatives of patients with schizophrenia also showed hypoactivation in the dorsal striatum when anticipating monetary incentives.

Attenuated activation in the ventral striatum, which was previously reported in patients with schizophrenia treated with first generation antipsychotics (FGA) (Juckel et al., 2006a, 2006b), was found in our regions of interest (ROI) analysis. However, in whole brain activation analysis, patients with schizophrenia only exhibited impaired dorsal striatal activation, but relatively preserved ventral striatal activation, when anticipating monetary incentives. This may be related to the fact that most of the patients with schizophrenia recruited in the present study were treated with second generation antipsychotics (SGA). There is evidence that patients with schizophrenia treated with FGAs exhibit ventral striatum hypoactivation, whereas those treated with SGAs have relatively minor ventral striatal dysfunction during the anticipatory phase for monetary incentives in whole brain analysis (Simon et al., 2010; Walter et al., 2009; Waltz et al., 2010). This may explain why the ventral striatal hypoactivation in patients with schizophrenia treated with SGAs only became apparent on ROI analysis rather than whole

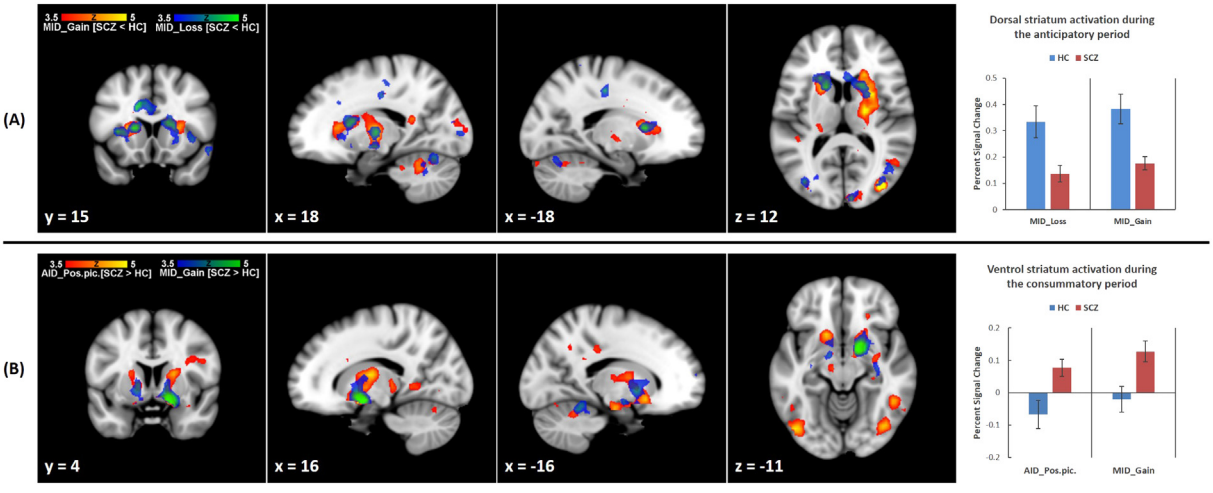

Fig. 1. Group comparison between patients with schizophrenia and healthy controls in whole brain activation of MID and AID tasks. Statistical threshold was set as $p < 0.0005$ without correction at the voxel level, cluster choice threshold was set at $p < 0.001$ with family-wise-error correction at the cluster level and at $p < 0.001$ without correction at the peak level, cluster size > 100 (Please refer to the Supplementary materials for details). (A) Patients with schizophrenia showed hypoactivation compared with healthy controls in the bilateral dorsal striatum for the contrasts [monetary loss > monetary neutral] (blue-green) and [monetary gain > monetary neutral] (red-yellow) during the anticipatory phase of the MID task. Signal change in response to each cue is shown at the top right. (B) Patients with schizophrenia showed hyperactivation compared with healthy controls in the bilateral ventral striatum for the contrast [monetary gain hit > monetary neutral hit] (blue-green) in the MID task and the contrast [positive picture hit > neutral picture hit] (red-yellow) in the AID task during the consummatory phase. Signal changes to each incentive are shown at the bottom right.

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brain analysis in the present study. Recent studies also suggest that FGAs and SGAs may have different effects on ventral and dorsal striatal activation patterns in patients with schizophrenia (Nielsen et al., 2012a; Schlagenhauf et al., 2008). In particular, Mucci et al. (2015) found attenuated activation in the dorsal striatum of patients with schizophrenia treated with SGAs during the anticipation of monetary incentives. The dorsal striatum is responsible for stimulus-response-reward association, action selection and initiation, and facilitates the implementation of goal-direct behaviour through efferent projections to the dorsal prefrontal cortex (Balleine et al., 2007; Grahn et al., 2008; Miller et al., 2014; O'Doherty et al., 2004; Volkow et al., 2002; Wang et al., 2013). Hypoactivation in the dorsal striatum in patients with schizophrenia during the anticipatory phase for monetary incentives may suggest that these patients are impaired in constructing associations between monetary rewards and cues that may further impede salience attribution, leading to amotivation.

Notably, we found hyperactivation in the ventral striatum in patients with schizophrenia during the consummatory phase for both monetary and affective incentives. This is consistent with results from a previous study by Walter et al. (2009). Lin et al. (2012) reported that activation in the ventral striatum for both social and monetary incentives were associated with prediction error during reward reception. Hyperactivation in the ventral striatum in patients with schizophrenia during the consummatory phase has been associated with impaired reward prediction (Walter et al., 2009). Another possible interpretation is impaired reward learning in patients with schizophrenia (Culbreth et al., 2016; Schultz, 2010). When the association between indicators of future reward is being constructed, ventral striatal dopaminergic firing would switch from the novel reward to its indicator or cue (Schultz et al., 1997). Hyperactivation in the ventral striatum during the consummatory phase may suggest dysfunctional reward learning for both monetary and affective incentives in patients with schizophrenia who have failed to build the anticipatory association between the cue and the reward that attenuates the response to the stimuli in healthy participants. However, this speculation needs to be clarified by future studies. Insufficient practice of task may also explain the previous inconclusive results during the consummatory phase (Heinz and Schlagenhauf, 2010; Radua et al., 2015). Lastly, hypoactivation in the medial prefrontal cortex and its reduced inhibitory connectivity to the ventral striatum in patients with schizophrenia may also contribute to hyperactivation in the ventral striatum (Schlagenhauf et al., 2009; Waltz et al., 2010). The absence of dysfunction during the consummatory phase for monetary incentives in previous studies may also be attributed to different experimental designs (Radua et al., 2015). Some designs used 66% positive feedback, which might reduce statistical power to detect separate anticipatory and outcome coupled responses given the sluggish Haemodynamic Response Function.

Hypoactivation in the dorsal and ventral striatum during the anticipation of monetary incentives was also observed in unaffected first-degree relatives of patients with schizophrenia in the ROI analysis. These data are consistent with previous studies which detected ventral striatal impairments in anticipating monetary incentives in ROI analysis rather than whole brain analysis (de Leeuw et al., 2015; Grimm et al., 2014). These minor impairments in individuals at risk of developing schizophrenia may not be detectable in whole brain analysis with limited sample size. These results suggest that disorganized striatal activation may already be present before the onset of schizophrenia. In addition, the group of unaffected relatives also showed hypoactivation in the bilateral dorsal striatum for affective incentives compared with healthy controls. This suggests that impaired striatal activation may be present regardless of the type of incentive. This possibility needs further corroboration in sufficiently powered future studies.

5. Limitations

This study had several limitations. The demographics of patients with schizophrenia and their unaffected first-degree relatives were not matched with each other. Hence different healthy controls were recruited to match both groups respectively. Due to the "One-child Policy" in China in the past 30 years, it was difficult to recruit siblings into the unaffected relative group. The second limitation was the lack of significant correlation between symptom severity and striatal dysfunction in patients with schizophrenia, which may be related to limited statistical power and our conservative correction for multiple comparisons. As the patients with schizophrenia recruited in the present study were treated with SGAs, it is possible that their treatment might have alleviated partly their negative symptoms, thus restricting the range of symptoms. However, our small sample size precluded any further exploration of the effect of SGAs on striatal activation. This issue deserves further investigation in future studies. Furthermore, the relatively young age of the patients and the use of the PANSS to assess symptoms, rather than a dedicated negative symptom assessment instrument may have also contributed to the lack of an association between symptoms and striatal dysfunction. Another limitation of this study is that the IQ and education of the patients with schizophrenia were significantly lower than that of healthy controls. However, attempts to match the education of people with schizophrenia and healthy volunteers may result in "matching fallacy" in which atypically highly educated schizophrenia patients would be matched with equally atypically poorly educated controls (Resnick, 1992).

6. Conclusions

In conclusion, patients with schizophrenia showed distinct striatal activation patterns consisting of hypoactivation during the anticipation of monetary incentives and hyperactivation during the consummation of both affective and monetary incentives. Hyperactivation in the ventral striatum during the consummation of both monetary and affective incentives suggest the presence of disorganized striatal mesolimbic function and impaired common reward circuits in patients with schizophrenia. Furthermore, hypoactivation in the striatum during the anticipation of monetary incentives in unaffected first-degree relatives of schizophrenia patients suggest that impaired striatal activation may be present before the onset of illness and may be a candidate endophenotype of schizophrenia.

Role of funding source

The funding agents had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the manuscript; and in the decision to submit the paper for publication.

Contributors

Zhi Li designed the study, analyzed the data, and wrote up the first draft of the study. Chao Yan collected and interpreted the data, and wrote up the first draft of the study. Qinyu Lv, Zheng-hui Yi, Simon S. Y. Lui and Yi-feng Xu performed clinical interview and administered clinical ratings to the participants. Jian-ye Zhang and Jin-hong Wang performed brain scans and related assessments. Eric F. C. Cheung, Raquel E. Gur and Ruben C. Gur made significant comments to the all drafts of the paper. Raymond Chan generated the idea, designed the study, interpreted the findings and wrote up the first draft. All authors contributed to and have approved the final text.

Conflict of interest

The authors declared no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.08.043.

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