Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

Zhi Li [a,b,1], Chao Yan [c,1], Qin-yu Lv [d], Zheng-hui Yi [d], Jian-ye Zhang [e], Jin-hong Wang [e], Simon S.Y. Lui [f], Yi-feng Xu [d], Eric F.C. Cheung [f], Raquel E. Gur [g], Ruben C. Gur [g], Raymond C.K. Chan [a,b,*]

[a] Neuropsychology and Applied Cognitive Neuroscience Laboratory, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[b] Department of Psychology, The University of Chinese Academy of Sciences, Beijing, China
[c] Key Laboratory of Brain Functional Genomics (MOE & STCSM), School of Psychology and Cognitive Science, East China Normal University, Shanghai, China
[d] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[e] MRI Center, Shanghai Mental Health Centre, Shanghai, China
[f] Castle Peak Hospital, Hong Kong Special Administrative Region
[g] Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 14 June 2017
Received in revised form 20 August 2017
Accepted 21 August 2017
Available online xxxx

Keywords:
Schizophrenia
First-degree relative
Dopamine
Neural circuits

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.

* Corresponding author at: R. Chan, Institute of Psychology, Chinese Academy of Sciences, Room 526, South Block, 16 Lincui Road, Beijing 100101, China.
E-mail address: rckchan@psych.ac.cn (R.C.K. Chan).
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.schres.2017.08.043
0920-9964/

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

Please cite this article as: Li, Z., et al., Striatal dysfunction in patients with schizophrenia and their unaffected first-degree relatives, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.08.043