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Altered cingulo-striatal function underlies reward drive deficits in schizophrenia

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ABSTRACT

Amotivation in schizophrenia is assumed to involve dysfunctional dopaminergic signaling of reward prediction or anticipation. It is unclear, however, whether the translation of neural representation of reward value to behavioral drive is affected in schizophrenia. In order to examine how abnormal neural processing of response valuation and initiation affects incentive motivation in schizophrenia, we conducted functional MRI using a deterministic reinforcement learning task with variable intervals of contingency reversals in 20 clinically stable patients with schizophrenia and 20 healthy controls. Behaviorally, the advantage of positive over negative reinforcer in reinforcement-related responsiveness was not observed in patients. Patients showed altered response valuation and initiation-related striatal activity and deficient rostro-ventral anterior cingulate cortex activation during reward approach initiation. Among these neural abnormalities, rostro-ventral anterior cingulate cortex activation was correlated with positive reinforcement-related responsiveness in controls and social anhedonia and social amotivation subdomain scores in patients. Our findings indicate that the central role of the anterior cingulate cortex is in translating action value into driving force of action, and underscore the role of the cingulo-striatal network in amotivation in schizophrenia.

1. Introduction

Amotivation represents problems in the subjective and behavioral aspects of goal-directed activities in schizophrenia (Foussias and Remington, 2010). In real life situations, goal-directed activities are pursued by sustaining anticipation of the rewarding value of an action towards the uncertain future. However, patients with schizophrenia are often amotivational due to a deficit in sustaining a representation of the reward value (Gold et al., 2008). Amotivation involves a deficit in the interrelated neurobehavioral components of the dopaminergic reward system such as reinforcement learning and incentive motivation (Wise, 2004).

Reinforcement learning occurs as the midbrain dopaminergic neurons, responding to unexpected and repeated rewards, begin to respond to the preceding stimuli that predict these rewards (Berridge and Robinson, 2003). Likewise, risk prediction is also incorporated in the reinforcement learning process in which the trade-off between expected reward and risk determines behavior (Preuschoff and Bossaerts, 2007). Behaviorally, the drive-like effect of motivation, called "incentive motivation", strengthens goal-directed behavior. It involves the stamping-in of motivational importance to neutral stimuli through prior association with a primary reward, via the dopamine system, which results in acceleration of the operant response (Wise, 2004).

The mesolimbic and nigrostriatal dopaminergic systems have been consistently implicated in various aspects of reward and motivation (Koob, 1992; Robbins and Everitt, 1996; Wise, 2009). Phasic dopaminergic activity projects to the ventral striatum and dorsal striatum that are involved in reward prediction and in modulation of stimulus–response association, respectively (Pagnoni et al., 2002; O'Doherty et al., 2004; Tricomi et al., 2004). Midbrain dopaminergic firing occurs when risky decisions are made with highly anticipated reward (Fiorillo et al., 2005). The anterior insula and ventral striatum also play an important role in risk avoidance and prediction (Kuhnen and Knutson, 2005; Preuschoff et al., 2008). Reinforcement learning is controlled by the anterior cingulate cortex (ACC), which decides voluntary behavior by integrating prediction error as well as risk and reward signals (Kennerley et al., 2006; Holroyd and Coles, 2008). In addition, the cingulo-striatal pathway is involved in self-conscious motivational behaviors (Takahashi et al., 2009).

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In a series of behavioral studies, Gold et al. (2008) suggest that early learning may be particularly affected by poor representation of value in schizophrenia. Previous functional imaging studies which examined the feedback-related processing using the probabilistic learning and classical conditioning paradigms have shown that putamen activity is attenuated in response to both expected and unexpected reward and that the striatum and cingulate cortex are hypoactive or hypo-responsive to the reward prediction error signals in patients with schizophrenia (Murray et al., 2008b; Waltz et al., 2009; Koch et al., 2010), suggesting that the dysfunctional error signals between expectancy and feedback may account for diminished reward anticipation in schizophrenia. It is unclear, however, whether the translation of neural representation of reward value to behavioral drive is affected in schizophrenia.

Therefore, we developed a deterministic reinforcement learning task with variable intervals of contingency reversals for a new fMRI study examining the neural processing of response valuation and initiation during incentive motivation. In the present study, we examined the neural basis of reward drive in relation to response value representation and response engagement using this task in patients with schizophrenia and healthy controls. We hypothesized that abnormal neural processing of response valuation and engagement would contribute to deficient incentive motivation in patients with schizophrenia.

2. Methods

2.1. Participants

Participants were 20 medicated outpatients with schizophrenia from university-affiliated hospitals and 20 age-matched healthy controls (Table 1), who provided written informed consent to the protocols approved by the local institutional review board. All patients met the DSM-IV-TR criteria (American Psychiatric Association, 2000) for schizophrenia without other comorbid psychiatric disorders. Healthy controls with past or present psychiatric illness and psychotropic medication use and any participants with past or present medical or neurological illness and substance use disorders were excluded. Trait anhedonia and symptom severity were measured using the Physical and Social Anhedonia Scale (Chapman et al., 1976) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), respectively. The expressive deficits and social amotivation subdomains of the PANSS were also assessed (Liemburg et al., 2013).

Table 1
Demographic and clinical characteristics.

	Control (n = 20)	Schizophrenia (n = 20)	χ^2/t	*P*
Gender				
Female/male	12/8	10/10	0.53	0.75
Age	26.1 ± 5.1	28.6 ± 8.4	1.16	0.25
Years of education	14.5 ± 1.7	13.8 ± 1.8	1.37	0.18
Anhedonia				
Physical[a]	8.8 ± 4.4	22.5 ± 10.7	5.31	<0.001
Social[a]	8.5 ± 4.3	13.0 ± 5.6	2.82	0.008
Years of illness		6.8 ± 6.5		
Years of antipsychotic medication		5.5 ± 6.4		
Dosage of antipsychotic[b]		436.5 ± 327.1		
PANSS				
Positive		13.5 ± 4.2		
Negative		17.2 ± 4.4		
General		30.1 ± 6.6		
N1. Expressive deficit		11.5 ± 3.4		
N2. Social amotivation		8.7 ± 2.3		

PANSS, Positive and Negative Syndrome Scale.
[a] Significant group difference at $P < 0.05$.
[b] In mg of chlorpromazine dose equivalent; clozapine (1), quetiapine (1), paliperidone (3), risperidone (1), aripiprazole (7), olanzapine (1), haloperidol + quetiapine (1), amisulpride + ziprasidone (1), blonanserin + amisulpride (1), quetiapine + aripiprazole (1), quetiapine + paliperidone + ziprasidone (1), and aripiprazole + haloperidol + paliperidone (1).

2.2. fMRI task and procedure

During fMRI scanning, participants performed the gambling task with contingency reversals at variable ratio. Participants chose "bet" or "pass" by pressing a left or right button when presented with a cue for 1000 ms, and received feedback for subsequent 1000 ms, which informed the result of the choice (Fig. 1A). The task included two kinds of blocks; the reward block consisted of trials with the potential to win (a monetary gain by betting or no gain by passing), whereas the punishment block consisted of trials with the potential to lose (a monetary loss by betting or no loss by passing). In both blocks, feedback on a monetary loss was shown whenever participants did not respond, and the sum of the money they earned was included in feedback information. During the neutral trials, participants pressed a button according to the direction of the cue triangle and received feedback on correctness without a monetary gain or loss.

The blocks were comprised of 6–10 reinforcement trials which were counter-balanced across the blocks (Fig. 1B). Three runs were performed; each run, lasting 5 min 20 s, contained 13 alternating reward or punishment blocks with a total of 315 trials. For an optimal stochastic rapid presentation design, inter-trial intervals were jittered between 500 and 3000 ms (mean 963 ms). In order to maintain participants' attention, 10 neutral oddball trials were pseudo-randomly included in each run. The button position was counterbalanced across participants.

In order to match learning performance between the groups, all participants were told that a condition of the trials was maintained and reversed at variable points. Before scanning, participants were also told that they would be rewarded with the amount they won, but were actually given a predetermined amount of money for participation.

2.3. Imaging data acquisition

Functional and structural MRIs were performed using a 3T Philips Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands). Blood oxygen level-dependent (BOLD) images were acquired using a T2*-weighted gradient echo echo-planar imaging sequence (39 slices of 3 mm thickness and no gaps, repetition time [TR] = 2500 ms, echo time [TE] = 30 ms, flip angle = 90°, image matrix = 128 × 128, and field of view = 220 mm) with the in-plane resolution of 1.719 mm × 1.719 mm. Structural images with a resolution of 0.859 mm × 0.859 mm × 1.2 mm were acquired using a 3D T1-weighted gradient echo sequence (170 slices, TR = 9.692 ms, TE = 4.59 ms, image matrix = 256 × 256).

2.4. Behavioral data analysis

Trials were classified into two response categories — "Reward Approach" and "Loss Avoidance" — according to the expected feedback, and then each category was divided into three phases — "Initiation", "Maintenance" and "Pre-reversal" (Fig. 1C). Because most participants could easily make correct responses (betting in the reward block and passing in the punishment block) after an expected failure to win or avoid loss due to the condition reversal in the first trial of each block, the 2nd and 3rd trials were defined as "Initiation." "Maintenance" referred to the 4th to 6th trials of continuously maintained responses without the risk of the condition reversal. "Pre-reversal" referred to the following variable 7–10th trials (i.e. 40 trials in each condition) of sustained responses at the risk of possible loss or missing reward. Reinforcement-related responsiveness was calculated by subtracting the mean reaction time of the correct responses in the "Initiation" phase from the mean reaction time in the two trials just prior to the "Initiation" phase.

The percent accuracy and reaction time were analyzed using 2 (groups) × 2 (response categories) × 3 (phases) mixed model ANOVAs. Reinforcement-related responsiveness was analyzed using a 2 (groups) × 2 (response categories) mixed model ANOVA.