Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Disrupted salience processing involved in motivational deficits for real-life activities in patients with schizophrenia

Byung-Hoon Kim [a,b], Yu-Bin Shin [b], Sunghyon Kyeong [b], Seon-Koo Lee [b,c], Jae-Jin Kim [a,b,*]

[a] Department of Psychiatry, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Department of Psychiatry, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea

ARTICLE INFO

Article history:
Received 7 June 2017
Received in revised form 29 November 2017
Accepted 18 January 2018
Available online xxxx

Keywords:
Schizophrenia
Negative symptom
Motivational deficit
Salience network
Functional magnetic resonance imaging

ABSTRACT

Motivational deficits in patients with schizophrenia adversely affect various domains of daily living. This symptom in everyday life situations manifests in a complex behavioral pattern whose root cannot be simplified to an impaired reward-motivation scheme. This study aimed to identify impairment of the salience network that underlies motivational deficits seen in patients with schizophrenia in real-life situations. During the functional magnetic resonance imaging scan, 20 patients with schizophrenia and 20 normal controls performed a task mimicking real-life situations, in which an avatar proposed participation in a daily activity with either an intrinsic or extrinsic reward. Group and type-of-reward effects were evaluated with respect to brain activity. Further, psychophysiological interactions were analyzed for the dorsal anterior cingulate cortex (dACC) and insula, which are the key nodes of the salience network. The acceptance of the proposal was significantly higher for intrinsic than for extrinsic rewards in controls, whereas patients showed no difference. The imaging results showed a group effect in the dACC, right insula, thalamus, and lingual gyrus. The dACC showed negative contrast interaction with regions of the left dorsolateral prefrontal cortex, and the right insula showed positive contrast interaction with the occipital gyrus and precentral gyrus. These results suggest that patients exhibit no different participation behavior between activities with intrinsic and extrinsic rewards, which can be explained by the floor effect. Disrupted salience processing in schizophrenia including aberrant salience network and a disconnection of the salience and reward networks may account for the lack of motivation for daily activities.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder with various positive and negative symptoms. In particular, negative symptoms, including affective flattening, alogia, apathy, anhedonia, and amotivation, account for much of the chronic psychosocial disabilities accompanying the illness, but treatment of these symptoms is challenging with few available options for effective biological pharmacotherapy (Arango et al., 2013; Campellone et al., 2016).

Motivational deficit is a major category of negative symptoms (Blanchard and Cohen, 2006), and arises from a lack of capability, expectation, or motivation itself (Ryan and Deci, 2000). This symptom complex is receiving increasing clinical attention as it causes other negative symptoms and deficits (Barch and Dowd, 2010; Foussias and Remington, 2010; Gard et al., 2009; Wolf, 2006), and affects various domains of daily life (Barch et al., 2008). Data-driven iterative approach of a large clinical data has revealed that motivational deficit in social, occupational, and recreational activities is one of the two core factors of negative symptoms (Carpenter et al., 2016; Kring et al., 2013).

Motivation can be distinguished as either intrinsic or extrinsic, depending on the reason or goal causing a motivated behavior (Ryan and Deci, 2000). Intrinsic motivation is driven by enjoyment or interest in the task itself, whereas extrinsic motivation is driven by the expectation of external reward or punishment following the task. Capacity to perform a task can differ based on whether the motivation driving the behavior is intrinsic or extrinsic (Deci et al., 1999). In what is known as the 'undermining effect', healthy individuals tend to participate more actively in a task when its reward appeals to intrinsic motivation, rather than extrinsic motivation (Murayama et al., 2010). However, patients with schizophrenia exhibit a different pattern from healthy individuals in terms of these two types of motivation. For example, a previous study using ecological momentary assessment demonstrated that patients with schizophrenia showed decrements in intrinsic motivation driven by autonomy and competency, but not in intrinsic motivation driven by relatedness and extrinsic motivation driven by a goal to evade a negative reward (Gard et al., 2014).

The biological substrate for motivated behavior has long been considered to be within the reward system, which includes the basal

* Corresponding author at: Department of Psychiatry, Yonsei University Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Republic of Korea.
E-mail address: jaejkim@yonsei.ac.kr (J.-J. Kim).

https://doi.org/10.1016/j.schres.2018.01.019
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ganglia, thalamus, dorsal anterior cingulate cortex (dACC), and prefrontal cortex (Haber and Knutson, 2010; Sesack and Grace, 2010). Motivational deficits in schizophrenia have been found to be related to an impairment of this reward system (Strauss et al., 2014). Aberrant activity in the basal ganglia, dACC, and orbitofrontal cortex has been associated with impairment of reinforcement learning, effort-value computations, and value representations in schizophrenia (Gold et al., 2012; Strauss et al., 2014; Waltz et al., 2011; Waltz et al., 2013). Although abnormal functioning of the cortico-basal ganglia-thalamo-cortical (CBGTC) circuits seems to be responsible for the debilitating negative symptom, it is uncertain whether these abnormalities also underlie motivational deficits in real-life situations because studies to date have used simplified behavioral tasks to measure motivation (Maia and Frank, 2011). This question is important since there are contradicting results that impairment of the reward system itself is not solely responsible for motivational deficits in real-life situations (Strauss et al., 2014). Therefore, the neural underpinning of motivational deficits in this real-life aspect is worth intensive study. This may be meaningful to patients with schizophrenia as increasing motivation for daily activities is a major path for improving their social functioning (Robertson et al., 2014).

When engaging in activities of daily living, patients with schizophrenia show preserved capacity to feel and experience subjective pleasure, but they still exhibit low motivation to start those activities (Oorschot et al., 2013; Ward et al., 2012). The dissociation of reward from motivation for behaviors may arise from impaired bottom-level processing of sensory inputs from the real-world into a meaningful pleasurable stimulus. This impairment is called as "*abnormal salience processing*", which is a well-known functional neural pathology of schizophrenia (Palaniyappan and Liddle, 2012). The salience network comprises key nodes in the anterior insula and dACC (Seeley et al., 2007). Given that abnormal interaction between the salience network and reward regions in patients with schizophrenia has been reported (Gradin et al., 2013; Manoliu et al., 2013), it can be hypothesized that the aberrant salience network may also play a major role in their impaired motivation in real-life situations.

Previous neuroimaging studies of motivational deficits in schizophrenia have focused on a bottom-up approach rather than addressing the symptom in real-life situations. A new approach that focuses on motivation in real-life is required to deepen our understanding on a novel treatment approach for the debilitating symptom. This study was designed to identify the brain regions with functional abnormality related to real-life motivational deficits observed in patients with schizophrenia. We hypothesized that the abnormal salience network function in patients with schizophrenia underlies their motivational deficits in real-life situations with respect to the engagement in daily activities.

2. Methods

2.1. Participants and clinical measurements

Participants were 20 patients with schizophrenia and 20 age- and sex-matched healthy controls. The inclusive diagnosis of schizophrenia in the patient group and the exclusion of psychiatric disorders in the control group were made using the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Spitzer et al., 1994). All patients were recruited at psychiatric outpatient clinics, and were not hospitalized or had no increment of anti-psychotic medication dosage for symptom control within 3 months from the recruitment. Exclusion criteria were the presence of neurological or significant medical illness, current or past substance abuse or dependence, and any contraindication for magnetic resonance image scanning. This study was approved by the Institutional Review Board of Yonsei University Severance Hospital. Informed consent was obtained from all participants.

Participants in both groups reported the three needs of autonomy, relatedness, and competence based on the 21-item Basic Psychological Needs Scale (BPNS) (Johnston and Finney, 2010). Additionally, immediately before the functional magnetic resonance imaging (fMRI) scanning, a trained psychiatrist employed the following clinician-rated scales: the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and three items (purpose, motivation, and curiosity) from the Quality of Life Scale (QLS) (Heinrichs et al., 1984) for all participants and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for the patients.

2.2. Task design

The fMRI event-related task was a 6 s trial in a virtual room consisting of a listening phase for 4 s and a response phase for 2 s. During the listening phase, a virtual gender-matched friendly avatar proposed that the participant could join a daily life activity and described a reward for the activity. The activity was either social (e.g., "Can you come to my birthday party?") or recreational (e.g., "Are you going to watch the new movie?"). There were 18 social and 18 recreational activities, which were derived from the examples presented in the CAINS (Kring et al., 2013). Each activity proposal was followed by a suggestion with an intrinsic or extrinsic reward. For instance, the reward suggestions for the above example activity proposals were "I'd be happy if you came (intrinsic)" or "It's thrown at a very luxurious restaurant (extrinsic)" and "I heard that it's really funny (intrinsic)," or "They're giving out extra free tickets if you go watch it (extrinsic)", respectively. Therefore, the vignettes consisting of the proposal and reward suggestion included four domains (social-intrinsic, social-extrinsic, recreational-intrinsic, and recreational-extrinsic), and each domain was comprised of 18 vignettes. In order to provide a control condition, 18 additional vignettes consisting of a question for true or false judgment about a fact-based thesis (e.g., "Do dogs live longer?") and a following comment (e.g., "I mean, than cats") were presented as a neutral domain. During the response phase, participants were instructed to click the left or right mouse button as a response of "yes" or "no." A black crosshair in a grey background was presented between the trials, jittered from 0.5 s to 9.5 s, to obtain the optimal hemodynamic response curve of the functional image. The total number of trials were 90 for 5 domains and 18 vignettes for each domain. The task was evenly divided into two sessions, and participants were given a short break between the sessions.

2.3. Behavioral data analysis

The behavioral responses were used to represent the '*acceptance rate*' as follows: we assigned 1 for *yes* responses (the participant is willing to participate) and 0 for *no* responses (the participant is not willing to participate) and averaged the scores over all of the proposals. We calculated the rates separately for proposals with intrinsic and extrinsic rewards. After the completion of the fMRI scan, participants reported their subjective feelings for every activity on a 10-point Likert scale. Post-scan ratings for extrinsic rewards offered during the task were obtained as well. These were measured to quantify motivational biases stemming from individual differences in experiences, personality, and preferences for the presented activities and extrinsic rewards in the task. The average value of the subjective feeling of burden for daily life activities was referred to as '*burden intensity*', and that of the offered extrinsic rewards as '*reward intensity*'.

We performed repeated-measures analysis of variance (ANOVA) for the acceptance rate to reveal the main and interaction effects of motivation type (intrinsic motivation versus extrinsic motivation) and group (controls versus patients). In each group, we obtained Pearson correlations of the acceptance rates for intrinsic motivation and extrinsic motivation with the post-scan ratings (burden and reward intensity), subscale scores of the self-rated scale (autonomy, relatedness, and