NeuroImage: Clinical 9 (2015) 153–163

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function

Karuna Subramaniam [a,*], Christine I. Hooker [c], Bruno Biagianti [a], Melissa Fisher [a], Srikantan Nagarajan [b], Sophia Vinogradov [a]

[a] San Francisco Department of Veterans Affairs Medical Center, Department of Psychiatry, University of California, San Francisco, CA 94121, USA
[b] Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA 94123, USA
[c] Department of Psychology, Harvard University, Cambridge, MA 02138, USA

ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 4 August 2015
Accepted 7 August 2015
Available online 20 August 2015

Keywords:
fMRI
Reward
Punishment
Motivation
Schizophrenia

ABSTRACT

Amotivation in schizophrenia is a central predictor of poor functioning, and is thought to occur due to deficits in anticipating future rewards, suggesting that impairments in anticipating pleasure can contribute to functional disability in schizophrenia. In healthy comparison (HC) participants, reward anticipation is associated with activity in frontal–striatal networks. By contrast, schizophrenia (SZ) participants show hypoactivation within these frontal–striatal networks during this motivated anticipatory brain state. Here, we examined neural activation in SZ and HC participants during the anticipatory phase of stimuli that predicted immediate upcoming reward and punishment, and during the feedback/outcome phase, in relation to trait measures of hedonic pleasure and real-world functional capacity. SZ patients showed hypoactivation in ventral striatum during reward anticipation. Additionally, we found distinct differences between HC and SZ groups in their association between reward-related immediate anticipatory neural activity and their reported experience of pleasure. HC participants recruited reward-related regions in striatum that significantly correlated with subjective consummatory pleasure, while SZ patients revealed activation in attention-related regions, such as the IPL, which correlated with consummatory pleasure and functional capacity. These findings may suggest that SZ patients activate compensatory attention processes during anticipation of immediate upcoming rewards, which likely contribute to their functional capacity in daily life.

1. Introduction

Motivation is the process that drives a person to act towards a desired outcome. Motivational impairments are a cardinal feature of schizophrenia, are present in the earliest phases of the illness and are a significant predictor of impaired real-world functioning (Foussias and Remington, 2010; Schlosser et al., 2014). Current clinical and neuroimaging data indicate that these motivational impairments may be related to neural and behavioral deficits in anticipating future rewards (Juckel et al., 2006; Simon et al., 2010). Specifically, growing evidence indicates that schizophrenia patients may not be able to use anticipation of future rewards to modulate subsequent goal-directed behavior, suggesting impairments in frontal–striatal interactions and dopaminergic transmission between these regions (Abi-Dargham, 2003; Barch and Dowd, 2010; Gold et al., 2008; Strauss et al., 2015). Thus, the question remains as to whether recruitment of impaired frontal–striatal systems may enhance motivation and goal-directed behavior in schizophrenia patients or whether recruitment of other intact networks may be more useful targets for potentiating goal-directed functions in the real-world. The present fMRI study investigates this question.

The reward circuitry is well established in healthy participants (HC). Abundant neuroimaging evidence indicate that, in healthy participants, the motivation to receive upcoming monetary rewards is associated with anticipatory activity in frontal–striatal networks, including the medial prefrontal cortex (extending to the anterior cingulate cortex, mPFC/ACC), caudate, putamen, ventral striatum and nucleus accumbens (Barch and Dowd, 2010; Knutson et al., 2001; Murray et al., 2008). Specifically, data suggest that activity in the ventral striatum (VS), particularly within the nucleus accumbens, during immediate reward anticipation on a Monetary Incentive Delay (MID) task (Knutson et al., 2000) predicts arousal, positive affect, and, most importantly, real-world goal oriented consummatory behavior (e.g. products purchased and money spent at a shopping mall) (Knutson et al., 2001, 2003, 2007).

By contrast, when schizophrenia patients perform the MID task, several studies have consistently revealed reduced ventral striatum

* Corresponding author at: San Francisco Department of Veteran Affairs Medical Center, Department of Psychiatry, University of California, San Francisco, 513 Parnassus Avenue, S362, San Francisco, CA 94143, USA
E-mail address: karuna.subramaniam@ucsf.edu (K. Subramaniam).

http://dx.doi.org/10.1016/j.nicl.2015.08.001

(VS) activity during reward anticipation (Juckel et al., 2006; Kirsch et al., 2007; Schlagenhauf et al., 2008). Yet, prior behavioral research indicate that while patients with schizophrenia reveal specific deficits in anticipating signals leading to future rewarding outcomes, they experience similar levels of consummatory (in the moment) pleasure to HC participants (Gard et al., 2007; Herbener et al., 2008; Kring and Moran, 2008). However, it must also be noted that not all studies have found trait differences between schizophrenia and HC participants in self-reported anticipatory pleasure ratings (assayed with the TEPS anticipatory scale) (Strauss et al., 2011); indeed some behavioral studies have shown that deficits in schizophrenia patients' ability to respond to future rewarding stimuli occur only when the stimuli are not presently available compared to when the rewarding cues are more immediately present (Heerey et al., 2011). Together, these findings suggest that additional studies are needed that use anticipatory pleasure ratings from the TEPS anticipatory scale with neuroimaging measures of immediate reward anticipation, to determine the precise neural underpinnings of amotivation in schizophrenia. To this end, the purpose of this study is to use fMRI in schizophrenia to explicitly examine the relationship between neural activity during the anticipation of an immediate reward (assayed when participants anticipate winning money in response to a WIN $ cue) in relation to self-reports of real world motivated behavior (both in-the-moment pleasure as represented by the TEPS consummatory scale, and future representations of pleasure, as measured by the TEPS anticipatory scale). Therefore, it is possible that neural activation patterns during current representation of rewarding cues in schizophrenia may not directly be associated with future representations of reward (measured with the TEPS-Anticipatory Scale), but rather with more intact consummatory pleasure levels (assayed here with the TEPS-Consummatory Scale), as is shown in healthy participants (Knutson et al., 2007). It also must be noted that while the process of anticipating pleasure can enhance motivation and preparation for upcoming future rewarding events, high levels of consummatory (in the moment) pleasure can also increase neural reward motivational processes to repeat a rewarding activity (Trémeau et al., 2010). In the present study, we therefore hypothesized that it was possible for neural signal during immediate reward anticipation on the MID task to be correlated with either the TEPS-Anticipatory scale, the TEPS-Consummatory scale or with both scales.

Since deficits in anticipatory pleasure are related to deficits in motivation and functional outcome (Gard et al., 2007), and since amotivation in schizophrenia has been shown to be a central predictor of poor functioning, these findings suggest that deficits in anticipating pleasure can contribute to functional disability in schizophrenia (Foussias and Remington, 2010; Gard et al., 2009). However, thus far, no one has investigated the explicit link between deficits during anticipation of immediate rewards, real world motivated behavior (both in-the-moment and the future), and real-world functioning, and whether and how additional intact neural networks (rather than impaired frontal–striatal circuits) may mediate motivated behavior in schizophrenia.

To this end, we examined whole-brain activation in SZ patients and HC participants during the *anticipatory phase* of presentation of stimuli that predicted immediate monetary gain (reward) and loss (punishment), as well as during the *outcome phase* when participants were notified as to whether they had won money or lost money (Knutson et al., 2000). Previous research has shown that activation within the ventral striatum during anticipation of an immediate reward is negatively correlated with negative symptoms, such as apathy (i.e., lack of motivation), as well as with positive symptoms, while striatal activation during reward outcome is negatively correlated with depressive symptoms (Juckel et al., 2006; Nielsen et al., 2012; Simon et al., 2010). These findings suggest that lower striatal activation during anticipation of an immediate reward may contribute to patients' lack of motivation as well as to the development of psychotic symptoms while lower striatal activation during reward outcome may contribute to depressive symptoms (Simon et al., 2010).

In the present study, we examine whole-brain neural activation in relation to clinical symptoms (assayed with the Positive and Negative Symptom Scale), motivation (assayed with the Behavioral Activation Scale); both anticipatory pleasure ratings of future representations of reward and in the moment consummatory pleasure ratings (assayed with the TEPS) (Gard et al., 2007) and with real-world functional capacity (UCSD Performance-based Skills Assessment) (Patterson et al., 2001). Given that prior meta-analyses have indicated that SZ patients do not reveal deficits during "in the moment" emotional experiences (Cohen and Minor, 2010), we predicted that we would not observe overall group differences in neural activation when SZ patients were notified that they had won money. However, in view of the previous studies mentioned above, we hypothesized that SZ patients would reveal hypoactivation in VS specifically during immediate reward anticipation. To our knowledge, this is the first study to investigate whether frontal–striatal dysregulation during immediate reward anticipation may require recruitment of additional intact networks such as those within parietal regions in schizophrenia, that may predict better motivation (assayed with BAS-Drive scale), consummatory pleasure (TEPS) and real-world functioning (assayed with the UCSD Performance-based Skills Assessment).

2. Materials and methods

2.1. Participants and procedures

This study represents the baseline imaging data from the imaging component of our NIMH-funded RO1 of a double-blind randomized clinical trial of cognitive training in schizophrenia (ClinicalTrials.gov NCT02105779). Thirty-seven clinically stable volunteer schizophrenia patients (SZ: mean age = 45.14; mean education = 14.55 years; mean IQ = 102.11; mean illness duration = 25.40 years), who were willing to undergo two imaging sessions, were recruited from the parent study. All patients were stratified by age, education, gender, and symptom severity and then randomly assigned to either social computerized cognitive training, or to a control computerized cognitive training condition without the social training, performed for 80 h. Informed consent was obtained from all subjects. Schizophrenia patients were scanned using fMRI while they performed the Monetary Incentive Delay Task (used to assay reward/punishment processing) at baseline and after 80 h of intervention. We report here the results at baseline of our reward/punishment fMRI experiment investigating frontal–striatal cortical systems in schizophrenia patients when compared to 20 healthy comparison participants (HC), matched at a group level on age, gender, and education (Table 1). SZ participants also underwent clinical and neuropsychological assessments (Table 2). fMRI data from two SZ participants were later excluded due to very poor signal to noise ratio, resulting from excessive motion during the scan.

2.2. Clinical and neuropsychological assessments

Eligibility diagnosis for schizophrenia was determined using the Structured Interview for the DSM (SCID) (First et al., 2002). Symptom

Table 1
Demographics and behavioral measures (mean, SD) of healthy comparison (HC) and schizophrenia (SZ) participants.

Baseline	HC (N = 20)	SZ (N = 37)
Age	43.72 (SD = 13.32)	45.14 (SD = 9.97)
Education	13.63 (SD = 2.11)	14.55 (SD = 1.58)
Gender	14M, 6F	25M, 12F
TEPS Anticipatory pleasure	46.00 (SD = 4.55)	43.09 (SD = 7.85)
TEPS Consummatory pleasure	39.65 (SD = 4.74)	38.74 (SD = 7.78)
MID total accuracy	25.95 (SD = 4.95)	22.42 (SD = 6.93)
MID win accuracy	13.18 (SD = 2.63)	11.56 (SD = 3.51)
MID no lose accuracy	12.77 (SD = 2.43)	10.86 (SD = 3.67)