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Differential reward network functional connectivity in cannabis dependent and non-dependent users☆

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ABSTRACT

Background: Emergent studies show that similar to other substances of abuse, cue-reactivity to cannabis is also associated with neural response in the brain's reward pathway (Filbey et al., 2009). However, the inter-relatedness of brain regions during cue-reactivity in cannabis users remains unknown.
Methods: In this study, we conducted a series of investigations to determine functional connectivity during cue-reactivity in 71 cannabis users. First, we used psychophysiological interaction (PPI) analysis to examine coherent neural response to cannabis cues. Second, we evaluated whether these patterns of network functional connectivity differentiated dependent and non-dependent users. Finally, as an exploratory analysis, we determined the directionality of these connections via Granger connectivity analyses.
Results: PPI analyses showed reward network functional connectivity with the nucleus accumbens (NAc) seed region during cue exposure. Between-group contrasts found differential effects of dependence status. Dependent users ($N = 31$) had greater functional connectivity with amygdala and anterior cingulate gyrus (ACG) seeds while the non-dependent users ($N = 24$) had greater functional connectivity with the NAc, orbitofrontal cortex (OFC) and hippocampus seeds. Granger analyses showed that hippocampal and ACG activation preceded neural response in reward areas.
Conclusions: Both PPI and Granger analyses demonstrated strong functional coherence in reward regions during exposure to cannabis cues in current cannabis users. Functional connectivity (but not regional activation) in the reward network differentiated dependent from non-dependent cannabis users. Our findings suggest that repeated cannabis exposure causes observable changes in functional connectivity in the reward network and should be considered in intervention strategies.

1. Introduction

The mesocorticolimbic reward system is important in evaluating salient and rewarding stimuli and regulating appetitive behavior, and, as such, is an intense area of focus in studies of substance use disorders (SUDs). The reward system has primary dopaminergic projections from the ventral tegmental area (VTA) that innervate limbic (amygdala, hippocampus), dorsal and ventral striatum and prefrontal regions (orbitofrontal cortex, anterior cingulate gyrus; O'Connell and Hofmann, 2011). Functional imaging studies combined with cue exposure paradigms have provided strong evidence for the role of the reward system during craving (Hommer, 1999; Volkow et al., 2002), one of the primary behavioral symptoms of SUDs. Enhanced response in the reward system during cue-elicited craving has been reported in the common substances of abuse such as alcohol (Filbey et al., 2007), nicotine (Claus et al., 2013), and cocaine (Wilcox et al., 2011). To date, two studies have reported concordant findings of enhanced neural response to cues for the most widely used illicit drug in the world – cannabis – as in other drugs of abuse. For example, in response to tactile and visual cannabis cues (relative to neutral cues), Filbey et al. (2009) reported greater neural response in the ventral tegmental area (VTA), thalamus, anterior cingulate gyrus (ACG), insula, and amygdala in heavy cannabis users (Filbey et al., 2012). Relative to non-using controls, Cousijn et al. (2012) showed that in response to images of cannabis cues, cannabis users had greater neural response in the VTA. Among the cannabis users, those with higher cannabis related problems had greater activity in the orbitofrontal cortex (OFC), ACG and striatum compared to those with fewer cannabis-related problems, which also overlaps with findings from Filbey et al. (2009). Taken

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together, the existing literature suggests that alterations in reward system function underlie response to cannabis cues and may drive drug-seeking behavior in cannabis users (Cousijn et al., 2012; Filbey and DeWitt, 2012; Filbey et al., 2009). Notably, response in these areas was found to be associated with pathology related to cannabis use (e.g., craving, problem severity) but not with measures of cannabis use.

A framework proposed by Filbey et al. (2012) suggests that cannabis cues trigger activation in several areas including (1) the ACG that detects salience of the cue, (2) the amygdala that evaluates the emotional content, (3) the insula that engages interoceptive processes, and, (4) the hippocampus that incorporates memory information. These events trigger dopamine release from the VTA to the striatum and OFC, which is necessary for the encoding of learned association of the drug with its relevant cues. While this model proposes associations (and directionality) between these regions, how these regions are functionally organized has not yet been directly examined. Moreover, existing regional activation findings through traditional general linear modeling (GLM)-based analyses may fail to completely characterize dysfunction in the reward system.

In other SUDs, altered functional connectivity has been reported in the reward system. For example, tobacco smokers (Claus et al., 2013) have been shown to have greater functional connectivity with two seed regions (OFC, insula) across several areas (somatosensory areas and parietal lobe, striatum) during tobacco cues compared to food cues. Notably, this connectivity was positively correlated with severity of nicotine dependence. Similarly enhanced functional connectivity between OFC and striatum was also reported in other populations characterized with heightened reward-sensitivity or increased ability to derive pleasure from reinforcers, such as in obese individuals (Stoeckel et al., 2009). These findings suggest that the interaction between reward regions may be accountable for the increased reward salience/motivation in substance abusing individuals. Inversely, in a study that looked at the opposing process of hypo-responsivity to reward, namely, anhedonia or the inability to experience pleasure, it was found that attenuated functional connectivity within reward areas (NAc, paralimbic areas) was associated with trait anhedonia (Keller et al., 2013). In summary, sensitivity to rewards appears to be associated with greater functional coherence or integration of the reward network. To date, however, functional connectivity in the reward network in cannabis users has yet to be determined.

In this report, we expand the growing literature on reward network functioning in cannabis users by examining functional connectivity or the temporal correlation of activity within this network in response to cannabis cues. To that end, we carried out three series of analyses: (1) psychophysiological interaction (PPI) analysis to examine functional connectivity, (2) *t*-tests to determine functional connectivity differences between severity of cannabis use disorder (CUD), and, (3) exploratory Granger connectivity analyses to evaluate the effective functional connectivity or the influential relationship between reward network areas.

2. Methods

This study was approved by the University of New Mexico and University of Texas at Dallas Institutional Review Boards.

2.1. Participants

We scanned 99 regular cannabis users with some having been previously described (see Table 1; Filbey et al., 2009, 2010; Schacht et al., 2012). The study's inclusion criteria were: (1) self-reported regular use of cannabis defined as cannabis use for a minimum of six months prior to study participation at a rate of at least four occasions per week (presence of THC metabolites was verified via urinalysis at study entry to confirm cannabis use), (2) right-handedness, and, (3) English as the primary language. The participants were excluded from the study if: (1) they had a positive urinalysis for other drugs of abuse other than cannabis at study entry, (2) reported current or history of psychosis, traumatic brain injury, or MRI contraindications (e.g., pregnancy, non-removal metallic implants, claustrophobia) and (3) had a current diagnosis of non-cannabis abuse/dependence (past diagnosis was acceptable). Of note, any other Axis I disorder besides psychosis was not an exclusion criterion. Further, there was no IQ requirement for inclusion in the study.

Of the 99 participants who met our eligibility criteria, 28 had motion exceeding 3 mm (in translation) or 3 degrees (in rotation) between TRs during the fMRI task (described below) and were subsequently excluded from further analyses, leaving a total of 71 participants.

2.2. Procedure

Those who met the study's inclusion criteria were scheduled for two separate study visits. The first visit consisted of obtaining informed consent as well as completing behavioral measures. Recent use of marijuana and other substances was assessed with a Time Line Follow Back interview (TLFB; Sobell et al., 1979), drug use questionnaire, marijuana use questionnaire, smoking history questionnaire, cannabis history questionnaire, and the Marijuana Problem Survey (MPS; Stephens et al., 2002). Lifetime and current symptoms of drug dependence were assessed with the SCID for DSM IV Research Version (First et al., 1997).

The participants were then instructed to abstain from cannabis use until their second visit, which consisted of an MRI scan. This was scheduled ~72 h after the first visit. Similar to our previous studies (Filbey et al., 2009, 2010; Schacht et al., 2012), we followed a bogus pipeline whereby participants were informed that a urinalysis would be performed for verification of their compliance to the abstinence instructions. Although THC urinalysis for short abstinence periods is unreliable, use of this bogus pipeline has been shown to improve compliance (Roese and Jamieson, 1993). The participants were also instructed to refrain from alcohol for 24 h, and, from caffeine and cigarettes for the preceding 2 h prior to their scan. Compliance with these instructions was confirmed by self-report (cannabis, alcohol, caffeine and cigarettes) and by breath alcohol level of 0.000 (alcohol) at the start of their MRI session. Participants with positive self-reported cannabis, alcohol, caffeine and cigarette, and/or breath alcohol levels > 0.000 were excluded from the MRI session. Immediately prior to their scan, participants completed a Marijuana Craving Questionnaire (MCQ; Heishman et al., 2001) as well as the Marijuana Withdrawal Checklist (MWC; Budney and Moore, 2002; Budney et al., 2003).

MRI images were collected using a 3T Siemens Trio whole body scanner equipped with Sonata gradient subsystem (40 mT/m amplitude, 200 μs rise time, 100% duty cycle) with a 12-channel coil combined with body coil transmission to achieve greater sensitivity in cortical areas. A high resolution whole brain anatomical MRI scan was also collected with a T1-weighted multi-echo Magnetization Prepared Rapid Gradient Echo or MPRAGE (MEMPR) sequence with the following parameters: TR/TE/TI = 2300/2.74/900 ms, flip angle = 8°, 192 sagittal slices, FOV = 256 × 256 mm, Slab thickness = 176 mm, Matrix = 256 × 256 × 176, Voxel size = 1 × 1 × 1 mm, Number of echos = 4, Pixel bandwidth = 650 Hz. Whole brain fMRI scans were collected using a gradient echo, echoplanar (EPI) sequence with ramp sampling correction using the intercomissural line (AC-PC) as a reference (TR: 2.0 s, TE: 27 ms (39 ms for 1.5 T), : 70o, matrix size: 64 64, 32 slices, voxel size: 3 3 4 mm3) ventral to the surface of the OFC. A tilting acquisition previously described in

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