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Neural mechanisms of risky decision-making and reward response in adolescent onset cannabis use disorder☆

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ABSTRACT

Background: Neural mechanisms of decision-making and reward response in adolescent cannabis use disorder (CUD) are underexplored.
Methods: Three groups of male adolescents were studied: CUD in full remission ($n = 15$); controls with psychopathology without substance use disorder history ($n = 23$); and healthy controls ($n = 18$). We investigated neural processing of decision-making and reward under conditions of varying risk and uncertainty with the Decision-Reward Uncertainty Task while participants were scanned using functional magnetic resonance imaging.
Results: Abstinent adolescents with CUD compared to controls with psychopathology showed hyperactivation in one cluster that spanned left superior parietal lobule/left lateral occipital cortex/precuneus while making risky decisions that involved uncertainty, and hypoactivation in left orbitofrontal cortex to rewarded outcomes compared to no-reward after making risky decisions. Post hoc region of interest analyses revealed that both control groups significantly differed from the CUD group (but not from each other) during both the decision-making and reward outcome phase of the Decision-Reward Uncertainty Task. In the CUD group, orbitofrontal activations to reward significantly and negatively correlated with total number of individual drug classes the CUD patients experimented with prior to treatment. CUD duration significantly and negatively correlated with orbitofrontal activations to no-reward.
Conclusions: The adolescent CUD group demonstrated distinctly different activation patterns during risky decision-making and reward processing (after risky decision-making) compared to both the controls with psychopathology and healthy control groups. These findings suggest that neural differences in risky decision-making and reward processes are present in adolescent addiction, persist after remission from first CUD treatment, and may contribute to vulnerability for adolescent addiction.

1. Introduction

Marijuana, whose active component is delta-9 tetrahydrocannabinol (THC; Ashton, 2001), is the most commonly used illicit drug in the United States (Substance Abuse and Mental Health Services Administration, 2010). Cannabis is an addictive drug (Budney et al., 2001; Gardner, 2005) that leads to cannabis use disorders (CUDs; defined as DSM-IV cannabis dependence or abuse). Substance use disorders (SUDs; defined as DSM-IV substance dependence or abuse) such as CUD can alter the neurobiology of decision-making and reward evaluation (Bechara, 2005; Ernst and Paulus, 2005; Volkow et al., 2003). THC acts directly as an exogenous agonist for cannabinoid 1 receptors located in the brain's decision-making and reward circuits by enhancing dopamine tone and causing psychoactive effects (Iversen, 2003). In adults with CUD these processes are further complicated by lower IQ (Fried et al., 2002), poorer executive functions, visual–spatial deficits, and psychomotor slowing (Jacobus et al., 2009; Meier et al., 2012; Schweinsburg et al., 2008).

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The cognitive and neural effects of CUD in abstinent adolescents and adults are understudied (Crean et al., 2011; Jacobus et al., 2009). Further, some cognitive and imaging studies have not controlled for drug abstinence. The few neuroimaging investigations of decision-making in abstinent adults with CUD compared with controls without substance use disorders (SUDs) have demonstrated dysregulation of the brain regions involved in decision-making and inhibition (Bolla et al., 2005; Eldreth et al., 2004). Studies of adolescent offspring at familial risk for SUD suggest pre-existing vulnerabilities in decision-making, reward evaluation, and inhibition (Andrews et al., 2011; Dawe et al., 2004; Tarter et al., 2004). However, it is unknown if the existing cognitive and neuro-imaging findings are related to vulnerabilities that predate CUD (Macleod et al., 2004; Pope et al., 2003), active cannabis or other substance use during data collection (Fried et al., 2005; Gonzalez and Swanson, 2012; Pope et al., 2001), or the neurobiological consequences of adolescent onset CUD.

CUD is an extremely difficult to treat, persistent, and long-lasting health problem. Therefore, to develop effective early identification, treatment and prevention strategies for youth with CUD, it is important to better characterize brain responses to specific types of decisions and reward in abstinent adolescents with CUD. Immaturity in decision-making and reward circuits (Bjork et al., 2007; Eshel et al., 2007; Galvan et al., 2006; Geier et al., 2010), along with reorganization of dopamine and endocannabinoid circuits during adolescence (Crews et al., 2007; Realini et al., 2009; Wahlstrom et al., 2010), may be responsible for the increased risk for adolescent-onset CUD (Johnston et al., 2008).

Adolescents begin making life decisions that involve uncertainty and experiencing unpredictable outcomes that may involve loss, such as in dating or career choices. The neural circuits recruited for decision-making and reward processing within the context of uncertainty may be altered in adolescent-onset CUD. Decision-making circuits involve a core set of brain structures: the prefrontal cortex; dorsolateral prefrontal cortex; parietal cortex; insular cortex; and anterior and posterior cingulate (Mohr et al., 2010). Reward-related brain circuits include the nucleus accumbens, caudate, putamen, thalamus, orbitofrontal cortex (OFC), bilateral anterior insula, anterior cingulate cortex, and posterior cingulate cortex (Liu et al., 2011). Reward circuits involve structures that receive dopaminergic input from the midbrain and include the ventral striatum (i.e., the nucleus accumbens), and ventromedial prefrontal cortex (Schott et al., 2008).

To address this issue, the Decision-Reward Uncertainty Task (Huettel, 2006) builds on the fact that abstract rewards, such as winning money, are associated with the same neural substrates that respond to primary reinforcers (e.g., food, love) in animals (Schultz, 2000) and humans (Fisher et al., 2010; Gottfried et al., 2003). As such, the Decision-Reward Uncertainty Task is a monetary reward task designed to examine decision-making and reward circuits separately in one task (Huettel, 2006). This methodological feature of the task is important because most previous research has failed to differentiate decisions into risk types and reward evaluation. Thus, in most studies, decision-making was contingent in time upon reward and not separated from reward evaluation (Xiangrui et al., 2010). To address these methodological issues, the Decision-Reward Uncertainty Task examines three types of risk: reward risk; behavioral risk; and no risk. Reward risk is defined as certainty about what decision to make but uncertainty about reward outcomes. In other words, one knows what actions to take for a reward but the reward is probabilistically determined. Reward risk activates decision-making circuits in the parietal cortex, dorsolateral prefrontal cortex, medial frontal lobe, basal ganglia, thalamus, and insula in adults (Huettel, 2006) and adolescents (Yaxley et al., 2011). Behavioral risk is defined as uncertainty about which decisions should be taken to earn a reward or achieve a desired goal. Under these conditions, one is uncertain about what decision to make for a reward. Behavioral risk activates decision-making circuits in additional decision-making circuits in prefrontal, parietal, and insular regions in adults (Huettel, 2006) and adolescents (Yaxley et al., 2011). In this task, behavioral risk and reward risk conditions are matched on probability and expected value, in that each contain a 50% chance of receiving a constant-size reward. The only difference between these conditions is in whether the participant knows what decision to make (reward risk) or not (behavioral risk). Decision-making under both reward risk and behavioral risk conditions is considered risky because reward is not certain. The Decision-Reward Uncertainty Task includes a no-risk or certainty condition as a control, where the decision required to earn a reward is known and reward is certain.

Since most addiction imaging studies do not control for risk factors such as co-morbid mental illness, co-morbid substance use disorder, or active substance use, we designed this study to control for co-morbid substance use disorder, psychopathology, active substance use, and prenatal factors that may influence adolescent SUD outcomes. Psychopathology is common in adolescent-onset CUD. Co-morbidity may contribute to the neuro-mechanisms leading to addiction and the high relapse rates in adolescents seeking treatment (Kaminer and Bukstein, 2008; Spear et al., 1999). Adolescent CUD is frequently co-morbid with alcoholism (Clark, 2004; Lynskey et al., 2003), conduct disorder (Armstrong and Costello, 2002; Clark et al., 1998; Costello et al., 2003), attention deficit hyperactivity disorder (ADHD; Armstrong and Costello, 2002), major depression (Degenhardt et al., 2003), trauma history (Dembo et al., 1988), and posttraumatic stress disorder (PTSD; Clark et al., 1997). Decision-making and reward deficits are seen in conduct disorder (Rubia, 2011; Rubia et al., 2009), ADHD (Rubia, 2011; Volkow et al., 2009), major depression (Rao, 2006), anxiety disorders (Miu et al., 2008), trauma history (Dillon et al., 2009), and PTSD (Admon et al., 2012; Elman et al., 2009; Sailer et al., 2008). Psychopathology may either contribute to or confound the results of previous imaging investigations of decision-making and reward circuits in adolescents with SUD (Clark, 2004; De Bellis, 2002).

In this investigation, we compared three groups of adolescent males using the Decision-Reward Uncertainty Task: (1) CUD in remission, after successful first-time treatment for CUD; (2) controls with psychopathology similar to the CUD group but without SUD history; and (3) healthy controls. Although there are many youth with psychiatric disorders, most do not suffer from addictions. Thus, we examined decision-making and reward circuits under uncertainty using functional magnetic resonance imaging to examine these neurobiological circuits in healthy adolescents, adolescent with psychiatric disorders, and those with CUD in remission.

We hypothesized that there would be dysregulation in decision-making and reward circuits during risky decision-making in abstinent adolescents with CUD, compared to adolescents with psychopathology and healthy controls. We hypothesized that abstinent adolescents with CUD would show altered brain activations in the key structures described above that are associated with behavioral risk during decision-making and reward processing after making risky decisions compared to both adolescent control groups.

2. Methods

2.1. Participants

Fifteen adolescents with recent outpatient treatment for CUD, in full remission; 23 adolescent control outpatients with psychopathology similar to the CUD group, but without any SUD history; and 18 healthy control adolescent males participated (Table 1). The adolescent controls with psychopathology and CUD group had similar psychopathology and number of biological parents with lifetime SUD, and were recruited through the same outpatient university clinics, where core treatments