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Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: An exploratory study of relationships with abstinence during behavioral treatment[1]

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ABSTRACT

Background: Cannabis is widely abused, and efficacies of therapeutics for cannabis dependence remain suboptimal. Magnetic resonance imaging (MRI) may aid in the identification of biological markers for successful treatment outcomes (i.e., abstinence).
Methods: Twenty men with cannabis dependence and twenty non-substance-using healthy comparison (HC) men underwent MRI scanning. Cannabis-dependent individuals then participated in a 12-week randomized clinical trial of behavioral treatments (contingency management (CM), cognitive behavioral therapy (CBT) or both). Pretreatment functional and structural data were compared between the cannabis-dependent and HC participants. In addition, individuals with cannabis dependence were subdivided based on the successful achievement of 21 days of consecutive abstinence during treatment to assess whether abstinent versus non-abstinent cannabis-dependent participants displayed different pretreatment functional and structural characteristics when compared to HC participants.
Results: In comparison to HC participants, cannabis-dependent participants demonstrated greater ventral striatal activation during the receipt of losing outcomes and smaller putamenal volumes. Cannabis-dependent participants who did not subsequently achieve 21 days of consecutive abstinence had increased activity within the striatum during the receipt of losing outcomes, relative to HC participants. Cannabis-dependent participants who did not achieve 21 days of abstinence had decreased bilateral putamen volumes prior to treatment, relative to HC participants.
Conclusions: Individual differences in pretreatment striatal function and structure may relate to individual differences in treatment responses for cannabis dependence. While mechanisms underlying these associations require further exploration, the striatum might mediate treatment responses via its role in associative reward-learning (e.g., through skills training in CBT or reinforcement of abstinence in CM).

1. Introduction

Cannabis is widely abused worldwide (Hall and Degenhardt, 2009; Degenhardt and Hall, 2012). Long-term heavy cannabis use is associated with increased rates of mood, anxiety and psychotic disorders, risky sexual behaviors, and other measures of poor health (Kingree and Betz, 2003; Moore et al., 2007; Degenhardt et al., 2009, 2013; Mathews et al., 2011; Andrade et al., 2013). Specific neurocognitive effects of long-term cannabis use may include alterations in IQ, executive functioning and verbal and visual memory (Bolla et al., 2002; Gruber et al., 2012; Meier et al., 2012). Despite the prevalence and negative consequences of cannabis use, the efficacy of current treatment options for cannabis dependence remains limited (Kadden et al., 2007; Carroll et al., 2012).

Current treatment options for cannabis dependence are predominantly non-pharmacological and include cognitive behavioral therapy (CBT; Denis et al., 2006) and contingency management (CM; Carroll et al., 2006). These treatments appear effective for some individuals with cannabis dependence; however, overall

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rates of abstinence during and subsequent to treatment remain suboptimal (Denis et al., 2006; Kadden et al., 2007; Carroll et al., 2012; Danovitch and Gorelick, 2012). While further research into how best to improve treatment interventions is needed (Danovitch and Gorelick, 2012), a complementary line of research involves the identification of behavioral and/or biological factors that might characterize treatment responders and which could predict optimal treatment responses on an individual basis (Potenza et al., 2011; Feldstein Ewing and Chung, 2013). Such factors may shed light on the mechanisms of action of existing treatments, which could inform treatment adaptations to enhance efficacy or guide individually-tailored treatment-assignment approaches.

Despite behavioral literature suggesting complex and relatively subtle neuropsychological alterations associated with long-term cannabis use (Rogers and Robbins, 2001; Bolla et al., 2002; van Holst and Schilt, 2011), relatively few studies have examined the relationship between neural function and treatment outcomes in cannabis dependence. However, pretreatment individual differences in functional neurocircuitry might impact treatment responses in cannabis-using youth (Feldstein Ewing and Chung, 2013), and less is known about such relationships among adults with cannabis dependence.

As with brain function, brain structure may also relate to substance-use-treatment outcomes (Xu et al., 2010; Froeliger et al., 2010). While the precise mechanism behind these associations remains unclear, it is possible that specific structural alterations might negatively impact individuals' successful engagement in treatment (Chung et al., 2013). For example, preclinical data have demonstrated that structural damage to the putamen disrupts habit formation or the learning of new action-outcome contingencies (Yin et al., 2004). Thus, structural alterations within this region might impair an individual's ability to modify previously-learned stimulus-response relationships (such as those relating to the reinforcing properties of cannabis) as is required for the development of new adaptive behaviors (e.g., skills training to deal with craving) aimed at reducing substance use. However, further research is needed to confirm this hypothesis, and to explore the relationship between pretreatment brain structure and function and treatment outcomes in cannabis dependence.

In particular, investigating how structure and function of brain regions involved in reward processing (e.g., ventral striatum; VS; Knutson et al., 2001a,b) may relate to treatment outcomes is important in the study of addictions and their treatment (Thayer and Hutchison, 2013). To our knowledge, no studies have explored the relationship between pretreatment brain structure and responses to treatment in cannabis dependence. Such research may aid in the identification of biological markers which might eventually guide the selection of appropriate treatment interventions (Feldstein Ewing and Chung, 2013).

The ventral and dorsal striatum are involved in multiple aspects of reward processing (e.g., craving, anticipatory and outcome processing; Roitman et al., 2005; Liu et al., 2011; Everitt and Robbins, 2013; Goldman et al., 2013). Thus, the striatum may relate to important aspects of the pathophysiology of substance-use disorders and their treatment (Brewer et al., 2008).

In this study, we explored the relationship between pretreatment striatal function and brain structure and short-term abstinence in response to behavioral treatments for cannabis dependence. VS activity was examined using a monetary incentive delay (MID) task (Andrews et al., 2011) which is a well-established probe of reward-related neurocircuitry (Knutson et al., 2001a,b; Andrews et al., 2011) previously used to study aspects of reward processing across a range of substance- and addiction-related disorders (Goldstein et al., 2007; Wrase et al., 2007; Beck et al., 2009; Peters et al., 2011; Balodis et al., 2012; Donovan et al., 2012). In particular, amongst cocaine-dependent individuals performing the MID task, greater bilateral VS activation was observed (relative to non-substance-using comparison participants) when participants were presented with winning outcomes (e.g., WON $5), and greater right VS activation was related to poorer treatment outcome (less abstinence; Jia et al., 2011). These findings suggest that MID performance successfully recruits brain regions related to real-world clinical outcomes, although such relationships may differ across addictions (e.g., to cannabis versus cocaine). To investigate striatal volume, bilateral caudate and putamen volumes were compared using FSL's FIRST, an automated segmentation tool for subcortical structures (Patenaude et al., 2011).

Two previously published fMRI studies employing MID tasks have studied reward processing among cannabis users, and both have reported increases in VS activity during reward anticipation (Nestor et al., 2010; Jager et al., 2013); however, neither study included treatment-seeking individuals or a formal assessment (e.g., SCID) of cannabis dependence. Based on these findings (Nestor et al., 2010; Jager et al., 2013), we hypothesized that, relative to non-substance-using HC participants, individuals with cannabis dependence would: (i) exhibit greater brain activity within the VS during reward processing (i.e., reward anticipation and reward receipt) during MID task performance; and (ii) have lower gray matter (GM) volumes within the caudate and putamen. We also explored the hypothesis that, among individuals with cannabis dependence, individual differences in GM volumes and brain activations within the striatum would relate to treatment responses, as has been observed functionally in studies of cocaine dependence (Jia et al., 2011) and structurally in studies of tobacco smoking (Froeliger et al., 2010).

2. Methods

2.1. Participants and recruitment

Cannabis-dependent participants were recruited from a randomized clinical trial (RCT) of community-based, outpatient treatments for cannabis dependence exploring the relative efficacy of CM, CBT or combined CM and CBT (Carroll et al., 2012). Two-hundred-and-six individuals were screened for eligibility for participation in the trial. Forty-four individuals did not complete screening and a further 35 individuals were deemed ineligible for trial participation (Carroll et al., 2012). Exclusion criteria for the RCT included likely and imminent incarceration and physical dependence on any substance other than cannabis or nicotine. Participants with cannabis dependence were not excluded for co-occurring disorders (see Carroll et al., 2012 for further details). While both men and women were recruited for the RCT, the study sample was largely male (>80%; Carroll et al., 2012). The participants from the RCT who also participated in pretreatment neuroimaging consisted of 20 men and 1 woman with cannabis dependence. Given the possibility of gender-related differences in neural responses, the female participant was excluded from subsequent analyses. Thus, the final sample included 20 men with cannabis dependence (mean age = 26.7 years; standard error = 2.2) and 20 male HC participants (mean age = 29.2; standard error = 2.3) recruited from the community via advertisement. Exclusion criteria for HC participants included any past or current psychotropic medication (e.g., antidepressants, anxiolytics, antipsychotics, mood stabilizers), any Axis-I disorder, including lifetime alcohol or other substance-use disorder other than nicotine dependence, as assessed using a Structured Clinical Interview (SCID; First et al., 1995). Exclusion criteria for all participants additionally included claustrophobia, head trauma resulting in loss of consciousness or other contraindication to MRI scanning.

Demographic and clinical characteristics of cannabis-dependent and HC participants are shown in Tables 1A and 1B. The cannabis-dependent and HC groups did not differ in age ($F = 0.66$, $p = 0.42$); but differed in race ($\chi 2 = 7.87$, $p = 0.05$) and the cannabis-dependent group had lower IQ, on average ($F = 16.85$, $p < 0.001$).

2.2. Abstinence

Given the difficulty many cannabis users have in achieving abstinence (rather than reducing the frequency of their use) a sustained period of continuous abstinence – as opposed to proportion of (non-continuous) days of abstinence during treatment – is considered a clinically-relevant outcome (Kadden et al., 2007). Thus, abstinence was defined based on the total number of consecutive days of self-reported abstinence during treatment. A threshold of 21 or more consecutive days of abstinence was selected, as this has been found to be a significant predictor of

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