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Understanding marijuana's effects on functional connectivity of the default mode network in patients with schizophrenia and co-occurring cannabis use disorder: A pilot investigation

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ABSTRACT

Nearly half of patients with schizophrenia (SCZ) have co-occurring cannabis use disorder (CUD), which has been associated with decreased treatment efficacy, increased risk of psychotic relapse, and poor global functioning. While reports on the effects of cannabis on cognitive performance in patients with SCZ have been mixed, study of brain networks related to executive function may clarify the relationship between cannabis use and cognition in these dual-diagnosis patients. In the present pilot study, patients with SCZ and CUD ($n = 12$) and healthy controls ($n = 12$) completed two functional magnetic resonance imaging (fMRI) resting scans. Prior to the second scan, patients smoked a 3.6% tetrahydrocannabinol (THC) cannabis cigarette or ingested a 15 mg delta-9-tetrahydrocannabinol (THC) pill. We used resting-state functional connectivity to examine the default mode network (DMN) during both scans, as connectivity/activity within this network is negatively correlated with connectivity of the network involved in executive control and shows reduced activity during task performance in normal individuals. At baseline, relative to controls, patients exhibited DMN hyperconnectivity that correlated with positive symptom severity, and reduced anticorrelation between the DMN and the executive control network (ECN). Cannabinoid administration reduced DMN hyperconnectivity and increased DMN-ECN anticorrelation. Moreover, the magnitude of anticorrelation in the controls, and in the patients after cannabinoid administration, positively correlated with WM performance. The finding that DMN brain connectivity is plastic may have implications for future pharmacotherapeutic development, as treatment efficacy could be assessed through the ability of therapies to normalize underlying circuit-level dysfunction.

1. Introduction

Cannabis is the most commonly used illicit drug in patients with schizophrenia (SCZ), with up to 43% of patients meeting criteria for cannabis use disorder (CUD) (Green et al., 2008; Henquet et al., 2005; Koskinen et al., 2010; Peralta and Cuesta, 1992; Regier et al., 1990) as compared to approximately 3% in US general population (Grant et al., 2016). Long-term cannabis use substantially worsens outcomes of patients with SCZ, resulting in symptom exacerbation (Buckley et al., 2009), increased risk of psychotic relapse, and decreased response to antipsychotic medication (Henquet et al., 2010; Swendsen et al., 2011; Zammit et al., 2008). While cannabis use has been associated with detrimental effects on cognition in healthy participants (Jacobsen et al., 2004; Rabin et al., 2013; Solowij et al., 2002), its effects on cognition in SCZ are debated, and several studies and two meta analyses have shown that cannabis use in schizophrenia is associated with improved cognitive function compared to non-cannabis using patients (Loberg and Hugdahl, 2009; Meijer et al., 2012; Rabin et al., 2011; Yucel et al., 2012) on measures of working memory, attention, processing speed, and verbal fluency (DeRosse et al., 2010; Rabin et al., 2013; Schnell et al., 2009; Yucel et al., 2012). Thus, understanding the basis of cannabis' effects on the brain in patients with SCZ could potentially lead to new treatments that decrease use and increase cognitive function in these patients.

Resting-state functional connectivity (rs-fc) elucidates the intrinsic functional architecture of the human brain through the examination

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of positive and negative temporal correlations between different brain regions (Biswal et al., 1995; Fox et al., 2005). It is a method that is gaining increasing focus for investigating the underlying pathophysiology of clinical disorders because it can be obtained over a short period of time (Van Dijk et al., 2010), is not confounded with task performance, and has been shown to be robust and reliable (Damoiseaux et al., 2006; Shehzad et al., 2009). Through detecting functional correlation of blood oxygen level-dependent signals across the brain, rs-fc detects intrinsic functional brain networks. One such network is the default mode network (DMN), which is comprised of brain regions typically more activated during rest than during task performance (Gusnard et al., 2001). Regions in the DMN also exhibit negative correlations (anticorrelations) with other brain regions that are activated during executive function (e.g., the executive control network [ECN]), including the dorsolateral prefrontal cortex (DLPFC) (Fox et al., 2005). Collectively, we refer to the positive as well as the negative (i.e., anti) correlations of a particular network as 'functional connectivity.' Investigating the effects of cannabis on functional connectivity of the DMN may shed light on its interaction with the ECN, as well as on the effects of cannabis use in SCZ.

The DMN, which includes the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and inferior parietal lobes (IPL), is associated with spontaneous task-independent mentation (Buckner et al., 2008; Raichle et al., 2001). When compared to healthy control participants, patients with SCZ as well as their first-degree relatives demonstrate DMN hyperconnectivity (Anticevic et al., 2015; Liu et al., 2010; Shim et al., 2010; Whitfield-Gabrieli et al., 2009). Hyperconnectivity of this network has been theorized to result in a blurring of boundaries between internally derived thoughts and external events (Anselmetti et al., 2007; Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009), thereby contributing to altered perceptions of reality manifesting as the characteristic positive symptoms of SCZ.

Negative correlation (anticorrelation) of the DMN and the executive control network (ECN), implicated in externally focused goal-oriented attention, is thought to reflect a competitive relationship that underlies the ability to appropriately shift between internally directed thought and externally focused attention (Corbetta and Shulman, 2002; Fox et al., 2005; Whitfield-Gabrieli and Ford, 2012). Chronic as well as first-episode (medication naïve) patients with SCZ, first degree relatives and individuals with high risk for psychosis have shown reduced anticorrelation between the MPFC region of the DMN and the DLPFC component of the ECN (Chai et al., 2011; Shim et al., 2010; Whitfield-Gabrieli et al., 2009). While its relationship to working memory has not yet been investigated in patients with SCZ, the strength of the anticorrelation between the MPFC and the DLPFC has been shown to directly correlate with working memory performance in healthy controls (Hampson et al., 2010; Keller et al., 2015).

In this pilot study, we assessed resting state functional connectivity of the DMN in patients with SCZ and cannabis use disorder (CUD) relative to healthy controls. In line with previous findings in non-cannabis using patients with SCZ, we predicted that patients with SCZ and co-occurring CUD would show DMN hyperconnectivity and reduced anticorrelation with regions of the ECN. We also explored the effects of cannabinoids, (smoked cannabis and oral delta-9-tetrahydrocannabinol [THC; the primary psychoactive constituent within cannabis]), on functional connectivity of the DMN in these patients. We administered both smoked cannabis and oral THC to begin to assess whether THC per se affected the DMN in a manner consistent with that produced by smoked cannabis, given that cannabis has multiple pharmacologically active components in addition to THC. Lastly, we assessed the relationship between positive symptom severity and DMN hyperconnectivity, and between working memory performance and the strength of the MPFC-DLPFC anticorrelation in both patients and controls. We predicted that positive symptoms in patients would directly correlate with hyperconnectivity of the DMN, and that working memory performance would relate to strength of anticorrelation in controls and in patients after cannabinoid treatment (Whitfield-Gabrieli et al., 2009).

2. Experimental materials and methods

2.1. Subjects

Twelve patients with SCZ and CUD and twelve healthy control subjects participated in this study. As previously described in Fischer et al. (2014) all patients were recruited from community mental health centers and met criteria for SCZ and CUD, defined as either current cannabis abuse or dependence with use within the past month prior to study enrollment, as determined by the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2012). While a history of alcohol or substance use (other than cannabis) was permitted in the patient group, they were required to be alcohol and substance free for a minimum of seven days prior to testing and scanning. Tobacco users were included in the study, since up to 90% of patients with SCZ smoke cigarettes (Kalman et al., 2005). All patients were on a stable dose of antipsychotic medication for a minimum of one month prior to study participation. Patients taking clozapine were excluded given its proposed ability to decrease alcohol and cannabis use in patients with SCZ (Green et al., 2008). Pharmacotherapies for addiction, mental retardation, a history of head injury, or factors that contraindicate the use of fMRI served as exclusion criteria. The healthy control group was matched to the patient sample on age, gender and handedness. In addition to the exclusion criteria noted above, controls were excluded if they had any current or history of Axis I or II disorders, including any substance use disorder. A signed informed consent was obtained from participants prior to initiation of the study. The protocol was approved by the Committee for the Protection of Human Subjects (IRB) at Dartmouth College. Further details of the study design were reviewed in Fischer et al. (2014).

2.2. Study design and procedure

Participants refrained from substance use (except for tobacco or caffeine) for the duration of the study. Subjects completed a 'baseline' session (T1), and then returned one week later for a second scan session (T2) during which patients were randomized to one of two double-blinded cannabinoid intervention groups: an oral THC group ($N = 6$) or an active cannabis cigarette (3.6% THC) group ($N = 6$). Those in the THC group were given a 15 mg THC pill (3 h prior to scanning) and then smoked a placebo cannabis cigarette immediately prior to scanning. Those in the cannabis group were given a placebo pill (3 h prior to scanning) and then smoked an active 3.6% THC cannabis cigarette immediately before scanning. Smoking took place in a smoking chamber within the scanner bay, immediately prior to scanning (Fig. 1a). Patients who were tobacco smokers were asked to smoke a cigarette 90 min prior to scanning, based upon pharmacokinetics of smoked tobacco. Further details can be found in Fischer et al., 2014. Healthy control participants followed the same study protocol, but did not receive any pharmacologic intervention during T2.

In order to assist patients in remaining abstinent from substance use for the duration of the study, they were assessed three times in the week prior to each scan session. Each time, they were screened for substance use with an alcohol breathalyzer, a Timeline Follow-Back interview (Sobell et al., 1996), and a urine toxicology screen (ToxCup Drug Screen cup; CLIAwaived, Sand Diego, CA). Patients were discontinued from the study if screening suggested substance use during study participation.

2.3. THC and symptom measures

Venous blood samples were collected from patients at T1, in the morning of the T2 session, immediately prior to fMRI scanning, and before cognitive testing (Fig. 1b). The Marijuana Craving Questionnaire

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