Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users

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ARTICLE INFO

ABSTRACT

Background: Recreational drugs are generally used to intentionally alter conscious experience. Long-lasting cannabis users frequently seek this effect as a means to relieve negative affect states. As with conventional anxiolytic drugs, however, changes in subjective feelings may be associated with memory impairment. We have tested whether the use of cannabis, as a psychoactive compound, is associated with alterations in spontaneous activity in brain networks relevant to self-awareness, and whether such potential changes are related to perceived anxiety and memory performance.
Methods: Functional connectivity was assessed in the Default and Insula networks during resting state using fMRI in 28 heavy cannabis users and 29 control subjects. Imaging assessments were conducted during cannabis use in the unintoxicated state and repeated after one month of controlled abstinence.
Results: Cannabis users showed increased functional connectivity in the core of the Default and Insula networks and selective enhancement of functional anticorrelation between both. Reduced functional connectivity was observed in areas overlapping with other brain networks. Observed alterations were associated with behavioral measurements in a direction suggesting anxiety score reduction and interference with memory performance. Alterations were also related to the amount of cannabis used and partially persisted after one month of abstinence.
Conclusions: Chronic cannabis use was associated with significant effects on the tuning and coupling of brain networks relevant to self-awareness, which in turn are integrated into brain systems supporting the storage of personal experience and motivated behavior. The results suggest potential mechanisms for recreational drugs to interfere with higher-order network interactions generating conscious experience.

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1. Introduction

Individuals may use recreational drugs altering conscious experience because of a variety of reasons including being adventurous and curious, and peer pressure. Nevertheless, the most common

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reason given for long-lasting cannabis use is relief from tension or to attenuate negative affect states such as anxiety (Buckner et al., 2007; Crippa et al., 2009; Ogborne et al., 2000; Reilly et al., 1998). Like other psychoactive drugs, however, cannabis has potential side effects. Apart from the possibility of generating drug dependence and the potentially deleterious effect in subjects at risk of developing psychosis (Large et al., 2011), continued cannabis use may impair cognition. Memory is the cognitive domain that has been most consistently reported as impaired in cannabis users (Solowij and Battisti, 2008), although such impairment tends to be mild when no other substances of abuse are implicated (Hall and Solowij, 1998; Solowij and Battisti, 2008).

Neuroimaging research is contributing uniquely to understand the biological bases of mental states. Functional magnetic resonance imaging (fMRI) of spontaneous brain activity permits the identification of a range of functional networks on the basis of region synchrony, defined as functional connectivity. Of relevance are recent studies suggesting the contribution of particular networks to conscious awareness of self. The "Default" network is perhaps the network most extensively investigated. Its main elements are the posterior cingulate cortex (PCC) and adjacent precuneus, angular gyri and medial frontal cortex (Buckner et al., 2008; Harrison et al., 2008). Default network contribution to self-referential mental processes is thought to be related to awareness of the (somatic) body and its relationship to the external environment (Buckner and Carroll, 2007; Buckner et al., 2008; Shulman et al., 1997; Small et al., 2003). In the temporal dimension, the Default network may assist autobiographical memory retrieval, but may also modulate working memory processes (Bluhm et al., 2011; Buckner et al., 2008; Leech et al., 2011). On the other hand, the insula cortex and functionally connected regions are known to be relevant for interoceptive awareness (Caseras et al., 2011; Craig, 2009; Critchley et al., 2004). Activity in the Insula network is associated with conscious perception of the physiological conditions of the (visceral) body (e.g., cardiovascular, airway, gut and sexual sensations) that jointly give rise to an internal representation of oneself, and provide a foundation for subjective feeling states that color emotional experience (Craig, 2002, 2009; Critchley et al., 2004).

Although the Default and Insula networks underlie distinct aspects of self-awareness, there is relevant function overlap, which concerns the contribution of Default network anterior areas to the cognitive control of interoception (Bishop et al., 2004; Ochsner and Gross, 2005; Sylvester et al., 2012), and Insula network posterior areas to the somatic representation of the body (Augustine, 1996; Eickhoff et al., 2006; Ruben et al., 2001). Moreover, activity in these networks seems to be closely coordinated, as their fMRI signal fluctuations show a strong negative correlation during resting state, with periods of high activity in one network often corresponding to low activity in the other network (Fox et al., 2005; Harrison et al., 2011). These functionally "anticorrelated" networks, however, may synchronically deactivate during highly-demanding goal-directed behavior suggesting the attenuation of both somatic and visceral awareness when attention is focused on external targets (Harrison et al., 2011).

In the current study, we have assessed spontaneous activity in the Default and Insula networks in chronic cannabis users. Our hypothesis was that cannabis, as a psychoactive compound, would modulate activity in networks relevant to self-awareness and that this effect would be related to both anxiety levels and cognitive performance. Specifically, we have investigated whether resting-state functional connectivity alterations exist in early onset and heavy cannabis users without comorbid psychiatric disorders compared with control subjects, and whether such potential alterations are associated with variations in anxiety and memory measurements. Resting-state fMRI was initially acquired during cannabis chronic use in the unintoxicated state. The assessment was repeated after one month of abstinence with the prediction that functional alterations may show long-lasting effects, as suggested in a recent review by our group (Batalla et al., 2013).

2. Methods

2.1. Participants

A total of 28 chronic cannabis user men (mean ± SD age, 21 ± 2 years) were assessed and compared with a reference control group of 29 men (age, 22 ± 3 years, ns). One cannabis user was excluded from an original sample of 29 subjects due to non-optimal data acquisition. All participants were followed-up during one month of controlled abstinence, and 27 cannabis users and 28 control subjects were available to repeat fMRI with identical procedures. Written informed consent was obtained from all participants. The study was approved by the local ethics committee (CEIC-IMAS, Barcelona) and was in compliance with the Declaration of Helsinki.

Participants were recruited via a web page and distribution of flyers and ads. To evaluate study eligibility, a comprehensive telephone screening was carried out. When eligible, participants were assessed using a detailed medical history, physical examination, a structured psychiatric interview (PRISM; Torrens et al., 2004), blood biochemical analyses and urine toxicology analyses. To facilitate open disclosure, confidentiality was guaranteed within ethical and legal limits.

Inclusion to the cannabis group required participants to be male, aged between 18 and 30 years, with at least 10 years of education (mean ± SD, 14 ± 2 years), cannabis use onset before age 16, cannabis consumption (smoking) more than 14 times a week at the time of selection and during at least 2 years prior to the study, positive urine test for cannabinoids and negative for opiates, cocaine, amphetamines and benzodiazepines (immunometric assay kits, Instant-View, ASD Inc, Poway, California). Exclusion criteria were: Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Association, 2000) Axis I disorder, relevant medical or neurological disorders, learning disabilities, use of psychoactive medications, previous use of any other recreational drug for more than 5 occasions lifetime except alcohol and nicotine, lifetime criteria for alcohol abuse or dependence and relevant current alcohol consumption. Current alcohol intake was very low in both study groups, showing a mean ± SD of 5.3 ± 4 units a week in users and 3.1 ± 2.6 units a week in control subjects. On average, cannabis users smoked a mean ± SD of 5.9 ± 5.2 cigarettes a day and control subjects, 2.4 ± 5.9 cigarettes a day. Only three participants (two users and one control subject) smoked more than 10 cigarettes per day. All subjects were right-handed.

Control subjects were required to be male, aged between 18 and 30 years, with at least 10 years of education (15 ± 1 years), showing less than 15 lifetime experiences with cannabis (none in the past month) and negative urine drug screen. Exclusion criteria were identical to the cannabis group. Cannabis users and control subjects showed a mean difference of one year in education ($t = 2.2$, $P = 0.032$).

Participants were required to refrain from smoking and caffeine 6 h, and alcohol and cannabis 12 h before fMRI. The study consisted of two fMRI assessments. The second fMRI session was carried out in all available participants after a period of 28 days of controlled cannabis abstinence.

2.2. Behavioral assessment

Primary assessments were the State–Trait Anxiety Inventory (STAI; Spielberger et al., 1983) and Rey Auditory-Verbal Learning