Review

Biological Psychiatry

The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users

Valentina Lorenzetti, Nadia Solowij, and Murat Yücel

ABSTRACT

The past few decades have seen a marked change in the composition of commonly smoked cannabis. These changes primarily involve an increase of the psychoactive compound Δ^9-tetrahydrocannabinol (THC) and a decrease of the potentially therapeutic compound cannabidiol (CBD). This altered composition of cannabis may be linked to persistent neuroanatomic alterations typically seen in regular cannabis users. In this review, we summarize recent findings from human structural neuroimaging investigations. We examine whether neuroanatomic alterations are 1) consistently observed in samples of regular cannabis users, particularly in cannabinoid receptor–high areas, which are vulnerable to the effects of high circulating levels of THC, and 2) associated either with greater levels of cannabis use (e.g., higher dosage, longer duration, and earlier age of onset) or with distinct cannabinoid compounds (i.e., THC and CBD). Across the 31 studies selected for inclusion in this review, neuroanatomic alterations emerged across regions that are high in cannabinoid receptors (i.e., hippocampus, prefrontal cortex, amygdala, cerebellum). Greater dose and earlier age of onset were associated with these alterations. Preliminary evidence shows that THC exacerbates, whereas CBD protects from, such harmful effects. Methodologic differences in the quantification of levels of cannabis use prevent accurate assessment of cannabis exposure and direct comparison of findings across studies. Consequently, the field lacks large "consortium-style" data sets that can be used to develop reliable neurobiological models of cannabis-related harm, recovery, and protection. To move the field forward, we encourage a coordinated approach and suggest the urgent development of consensus-based guidelines to accurately and comprehensively quantify cannabis use and exposure in human studies.

Keywords: Cannabidiol, Cannabinoids, Cannabis, CBD, Hippocampus, Prefrontal, THC

http://dx.doi.org/10.1016/j.biopsych.2015.11.013

Although cannabis has existed for thousands of years, the past few decades have seen a marked increase in the prevalence of highly potent cannabis strains (1). These strains have a high proportion of the psychoactive constituent Δ^9-tetrahydrocannabinol (THC) (2), which exerts persistent adverse effects on cognition, mental health, and the brain (3,4). In parallel, there are decreasing levels of other constituent cannabis compounds, such as cannabidiol (CBD), which has been touted as a potential therapeutic agent for conditions ranging from chronic pain and seizures to psychiatric symptoms (5–7). These recent changes in the composition of "street" cannabis create a new and complex landscape for investigators endeavoring to understand the neurobiological harm and the therapeutic potential of cannabis products.

Specific cannabinoid compounds have distinct effects on mental health and brain function. The psychoactive and addictive properties of cannabis are primarily due to THC (8). Increased availability of cannabis varieties that are high in THC (e.g., "skunk") have been consistently linked to accelerated onset of psychosis (9,10), increased cannabis-related hospital admissions (11), and increased anxiety symptoms and psychotic-like experiences (12–15). Preclinical studies showed that THC is neurotoxic to brain areas rich in cannabinoid type 1 receptors, including the hippocampus (16–20), amygdala (20), striatum (21), and prefrontal cortex (PFC) (21–23). In contrast, CBD has been found to have anxiolytic, antipsychotic, and therapeutic properties (24–27). There is evidence suggesting that CBD is neuroprotective, mitigating the neurotoxic effects of THC (28–30).

The compounds THC and CBD have also been shown to have opposing effects on the functional activity and connectivity between brain regions that are high in cannabinoid receptors, such as the hippocampus, amygdala, striatum, cerebellum, and PFC (12–14,31–36). These changes in brain function, documented using functional magnetic resonance imaging (MRI), may modulate the effects of THC on anxiety and psychotic-like experiences in humans (5,32,37). Similar processes may underpin the protective effects of CBD on such experiences (5,6,27,32,37). Participants pretreated with CBD do not experience the psychotogenic and anxiogenic effects of THC (12–14,32–37).

The recent changes in the relative composition of cannabinoids found within commonly available cannabis increase the potential for psychological and neurobiological harm in the current generation of cannabis users. However, the relative contribution of the two major compounds of cannabis (i.e.,

THC and CBD) to such damage is unclear (37). In this review, we summarize the current literature on neuroanatomic alterations reported in regular cannabis users, which includes nine additional studies relative to the most recent review on the topic, reflecting an increased focus on this field of research and warranting a need to integrate the most recent findings (38–46). We present a novel focus on the emerging evidence for differential roles of specific cannabinoids in neuroanatomic abnormalities (41,43,47,48). First, we provide an overview of findings and stratify them according to brain regions. Second, we examine the link between neuroanatomic alterations and levels of cannabis use, with a specific focus on the cannabinoid compounds THC and CBD. Finally, we identify major limitations of current research, particularly in relation to the measurement of cannabis use and cannabinoid compounds. These methodologic inadequacies limit the ability to develop evidence-based models of the effects of cannabis on neuroanatomy, whereby specific patterns (and types) of cannabis use are associated with discrete alterations in defined neural circuits. We suggest that a coordinated approach is required to move the field forward, and we offer preliminary guidelines to develop a standardized protocol to measure levels of cannabis use.

METHODS AND MATERIALS

We performed a PubMed search on April 7, 2015, using the keywords "Cannabis OR Marijuana" AND "MRI OR Computed Tomography OR Neuroimaging" and identified 492 articles. We screened these studies according to the following inclusion criteria: 1) use of structural neuroimaging techniques and 2) examination of regular cannabis users (as defined by each study protocol). We excluded nonempirical studies and samples including any other regular substance use or major psychopathologies. We included 32 studies in this review for further inspection (30,38–46,49–70), of which 23 were described previously (47). Nine additional studies conducted since 2012 were identified (38–46). The newest studies add to the literature five investigations of the PFC (38–42,44) and of the hippocampus (39,40,44–46); four investigations of the amygdala (39,41,44,46); three investigations of the striatum (39,41,43); two investigations of the insula (40,41); and single investigations of the parietal and occipital cortices (41), cerebellum (39), and pituitary gland (38).

RESULTS

Characteristics of Samples Included in Structural MRI Studies

Key characteristics of the reviewed samples are summarized in Table 1 and Figure 1. The total sample sizes included between 15 and 30 participants [range, 8 (63) to 62 (42) control subjects and 10 (70) to 57 (65) cannabis users]. Mean ages of cannabis users were between 17 years (49,54) and 40 years (38,45,50,58). The age distribution varied within samples, ranging from 16 years (49,54) to 60 years (38,45,50,58).

All samples of cannabis users smoked cannabis regularly, on a daily (30,39,40,42–44,49,51,62,68–70) or almost daily (38,41,45,50,53,55,58,61,63) basis. Some studies did not provide information on frequency of use but estimated the number of smoking episodes (52,54,56,57,60,64) and joints (38,45,50,58,59,65–67). Most cannabis users started smoking between age 15 and 17 years. Participants in a few samples started smoking 1 or 2 years earlier [14 years (43,52)] or later [18–20 years (38,42,45,50,53,58,64)]. Duration of use varied greatly across all examined samples and ranged from 2 years (54,60) to 23 years (62,69) of regular use. Lifetime exposure to cannabis was computed in cumulative number of joints, cones (standard cannabis unit, with 1 joint = 3 cones, 1 g = 12 cones; for other conversions, see guidelines from the National Cannabis Prevention and Information Centre at https://ncpic.org.au/media/1593/timeline-followback.pdf) (red triangles in Figure 2), or smoking episodes (blue squares in Figure 2), which was available for all but a few studies (39,43,64,66,67,69,70).

Lifetime episodes of cannabis use ranged from 402 (60) to 5625 (42). Lifetime cumulative cannabis dosage (dosage × smoking days × duration of regular use) ranged from 5322 cones (30) to 68,000 cones (68). Most studies measured cannabinoid compounds, with three exceptions (39,55,62). In 20 studies, urinalysis was used to detect cannabinoid compounds. Eight studies reported the levels of cannabinoid metabolites. Mean values for 11-nor-9-carboxy-THC (THC-COOH) (green circles in Figure 2) were reported from toxicology analyses of urine samples in eight studies (38,40,45,49,50,54,58) and analyses of hair samples in one study (30). In 11 studies, positive [three studies (44,53,63,64)] or negative [eight studies (51,56,57,59–61,65)] returns were reported from toxicologic analysis of urine samples without quantification.

The reviewed studies used various specimens to detect cannabinoids or their metabolites, including urine samples in 19 studies (30,38,40–43,45,49,50,52,54,56–60,63,64,71), oral fluid (40) and blood samples (40) in single studies, and hair in 2 studies (30,44), only one of which reported the outcome of the assessment (30) (Table 1). Some studies used several specimens [i.e., hair and urine (30,44), blood and oral fluid (40)]. Breathalyzers were used in five studies to screen for acute intoxication (52,56,57,59,60). Several studies controlled for the confounding effects of alcohol (n = 18) and tobacco use (n = 13) (Table 1) by covarying for their influence in group comparisons or reanalyzing the data after excluding participants with concurrent alcohol and tobacco use.

Neuroanatomic Alterations in Regular Cannabis Users Relative to Control Subjects

Neuroanatomic alterations were reported in several brain regions (Table 2 and Figure 3A). Abnormalities in cannabis users, relative to control subjects, emerged most consistently in the hippocampus [seven studies (30,40,45,51,58,63)]. Several studies reported alterations in the volume (i.e., sum of all voxels that are included within the boundaries of the region of interest) and gray matter density (i.e., amounts of gray or white matter concentration in each voxel) within the amygdala and striatum (41,43,52,58,63), PFC (40–42,49,55,70), parietal cortex (41,49,55), insular cortex (40,41,49), and cerebellum (50,53,56). Single studies reported alterations within the fusiform gyrus (63), temporal pole, superior temporal gyrus, and occipital cortex (41).