Dopaminergic Function in Cannabis Users and Its Relationship to Cannabis-Induced Psychotic Symptoms

Michael A.P. Bloomfield, Celia J.A. Morgan, Alice Egerton, Shitij Kapur, H. Valerie Curran, and Oliver D. Howes

Background: Cannabis is the most widely used illicit drug globally, and users are at increased risk of mental illnesses including psychotic disorders such as schizophrenia. Substance dependence and schizophrenia are both associated with dopaminergic dysfunction. It has been proposed, although never directly tested, that the link between cannabis use and schizophrenia is mediated by altered dopaminergic function.

Methods: We compared dopamine synthesis capacity in 19 regular cannabis users who experienced psychotic-like symptoms when they consumed cannabis with 19 nonuser sex- and age-matched control subjects. Dopamine synthesis capacity (indexed as the influx rate constant K_i^{cer}) was measured with positron emission tomography and 3,4-dihydroxy-6-[^{18}F]-fluoro-*l*-phenylalanine ([^{18}F]-DOPA).

Results: Cannabis users had reduced dopamine synthesis capacity in the striatum (effect size: .85; $t_{36} = 2.54$, $p = .016$) and its associative (effect size: .85; $t_{36} = 2.54$, $p = .015$) and limbic subdivisions (effect size: .74; $t_{36} = 2.23$, $p = .032$) compared with control subjects. The group difference in dopamine synthesis capacity in cannabis users compared with control subjects was driven by those users meeting cannabis abuse or dependence criteria. Dopamine synthesis capacity was negatively associated with higher levels of cannabis use ($r = -.77$, $p < .001$) and positively associated with age of onset of cannabis use ($r = .51$, $p = .027$) but was not associated with cannabis-induced psychotic-like symptoms ($r = .32$, $p = .19$).

Conclusions: These findings indicate that chronic cannabis use is associated with reduced dopamine synthesis capacity and question the hypothesis that cannabis increases the risk of psychotic disorders by inducing the same dopaminergic alterations seen in schizophrenia.

Key Words: Addiction, dependence, dopamine, drugs, imaging, psychosis

Cannabis is the most widely used illicit drug globally (1), and the prevalence of cannabis abuse or dependence in the United States is 4.4% (2). Cannabis can induce transient psychotic symptoms in healthy individuals (3,4), and there is consistent epidemiologic evidence that cannabis dose-dependently increases the risk of psychotic disorders (5,6).

Dopaminergic dysfunction is linked to drug dependence (7–11) and psychosis (12–17). Increased dopamine synthesis capacity and release have been reported in psychotic patients (18–26), drugs that increase dopamine release can induce or worsen psychosis (15,27,28), and elevated dopamine synthesis capacity has been reported in people who subsequently develop a frank psychotic disorder (29–32). Patients with cannabis-induced psychosis have elevated peripheral dopamine metabolites (33), and a case report found striatal dopamine release and symptom exacerbation in a schizophrenic patient following cannabis use (34). Thus, cannabis has been proposed to increase psychosis risk by causing striatal hyperdopaminergia (32).

Supporting this, preclinical studies indicate acute administration of Δ9-tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis (35), increases mesolimbic dopaminergic neuron firing rates via endocannabinoid CB_1 receptor agonism (36). CB_1 agonists inhibit striatal dopamine reuptake (37), selectively increase tyrosine hydroxylase expression (38), and increase dopamine release (39) and synthesis (40) in the majority of, although not all, studies (41).

Dopaminergic sensitisation to THC occurs in animals (42), suggesting that dopaminergic effects are greater with regular cannabis exposures. Studies in recently abstinent and ex-cannabis users have not found abnormal striatal dopamine release (43) or $D_{2/3}$ receptor availability (44,45), but this may be due to normalization of dopaminergic function with abstinence, as has been observed with alcohol (46). One study reported reduced dopamine transporter availability in cannabis users (47), although this was related to concurrent tobacco use, rather than cannabis. However, to our knowledge, no study has examined dopamine synthesis capacity in cannabis users or whether acute psychotic response to cannabis is related to dopaminergic function.

We therefore sought to study presynaptic dopaminergic function in active cannabis users who experienced cannabis-induced psychotic-like symptoms because these individuals are most at risk of psychosis (48). We hypothesized that regular cannabis users sensitive to cannabis' psychotogenic effects would exhibit elevated dopamine synthesis capacity compared with nonuser control subjects, and this would be directly related to cannabis-induced psychotic-like symptom severity.

From the Psychiatric Imaging Group (MAPB, AE, ODH), Medical Research Council Clinical Sciences Centre, Institute of Clinical Sciences, Hammersmith Hospital, Imperial College London; Clinical Psychopharmacology Unit (CJAM, HVC), Division of Psychology and Language Sciences, University College London; and Department of Psychosis Studies (MAPB, AE, SK, ODH), Institute of Psychiatry, King's College London (King's Health Partners), London, United Kingdom.

Address correspondence to Oliver D. Howes, D.M., Ph.D., M.A., B.M., B.Ch., M.R.C.Psych., Psychiatric Imaging Group, Francis Fraser Laboratories, MRC Clinical Sciences Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN United Kingdom; E-mail: oliver.howes@csc.mrc.ac.uk.

Received Nov 15, 2012; revised May 17, 2013; accepted May 23, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.05.027

Methods and Materials

The study was approved by the National Research Ethics Service and the Administration of Radioactive Substances Advisory Committee. The study was conducted in accordance with the Declaration of Helsinki. All subjects provided informed written consent to participate.

Study Population

Inclusion criteria for all subjects were as follows: minimum age 18 years, good physical health with no history of major medical condition, and capacity to give written informed consent. Exclusion criteria for all subjects were current or past psychiatric illness (except cannabis use disorders in the cannabis user group and nicotine use disorder in all subjects) using the Structured Clinical Interview for DSM-IV (49), history of serious mental illness (including psychosis) in a first-degree relative determined via the Family Interview for Genetic Studies (50), evidence of an At Risk Mental State for psychosis (51), DSM-IV-TR (52) substance dependency or abuse (other than cannabis in the cannabis user group and tobacco for all subjects), and contraindications to positron emission tomography (PET; including pregnancy and breast-feeding). None of the subjects were taking psychotropic medication at the time of study participation.

Detailed drug histories were obtained from all subjects using the Cannabis Experience Questionnaire (53), structured interview and timeline follow-back. Lifetime cannabis use was estimated as the total number of "spliffs" (cannabis cigarettes; "joints") consumed. The time taken to smoke an "eighth" of cannabis (one-eighth ounce; approximately 3.5 g, representing the standard unit of sale in Britain) was chosen as the primary index of cannabis use because this provides a measure of the amount of current drug consumption (shorter time indicating greater consumption). This is likely to be more accurate than subjective recall of the number of spliffs consumed because of variability in cannabis dose between spliffs and inconsistencies in self-reported cannabis use (54).

Cannabis User Group

We recruited cases from an ongoing cohort study in which more than 400 cannabis users were tested when intoxicated with cannabis and when not intoxicated (55). Subjects met the following criteria: current, at least weekly use of cannabis and the induction of psychotic-like symptoms in response to smoking cannabis, which was defined as a positive change on the psychotic items score of the Psychotomimetic States Inventory (PSI) (56) measured 5 minutes after smoking their usual amount of cannabis (i.e., when acutely intoxicated) compared with when not intoxicated with the drug. Cannabis users consumed their own cannabis, and testing occurred in the presence of a researcher in the environment where users habitually consumed cannabis in their usual drug-taking context (e.g., at home) because drug effects are typically larger in naturalistic as opposed to laboratory environments (53). Cannabis-induced psychotic-like symptoms abated within 2 hours of consumption, and no subject met the DSM-IV TR criteria for a diagnosis of a psychotic disorder. The psychotic items from the PSI covered "Delusional Thinking," "Perceptual Distortions," "Cognitive Disorganization" (thought disorder), and "Paranoia." Each item is rated on a 4-point scale from "not at all" (score = 0) to "strongly" (score = 3). Examples of items include "People can put thoughts into your mind" and "You can sense an evil presence around you, even though you cannot see it." A sample of the cannabis that each participant smoked was taken on the day of testing and analyzed for levels of THC (Forensic Science Service, Birmingham, United Kingdom).

Control Group

Nonuser control subjects were recruited from the same geographic area by public advertisement. Controls were required to have no lifetime history of cannabis dependence or abuse (DSM-IV), no more than 10 total uses of cannabis in their lifetime, no report of the induction of psychotic symptoms by cannabis, and no history of cannabis use in the preceding 3 months. Community surveys indicate that more than 30% of young adults in England report trying cannabis in their lifetime (57). We therefore permitted control subjects to have had a minimal exposure to cannabis to ensure the control group was representative of the same general population from which we recruited the cannabis users.

PET Data Acquisition

All subjects underwent a 3,4-dihydroxy-6-[^{18}F]-fluoro-/-phenylalanine ([^{18}F]-DOPA) scan on an ECAT HR+ 962 PET scanner (CTI/Siemens, Knocksville, Tennessee) in three-dimensional mode, with an axial field of view of 15.5 cm, performed as previously reported (28). Subjects were asked to fast and abstain from cannabis for 12 hours and to refrain from smoking tobacco for 2 hours before imaging. On the day of the PET scan, urine drug screen (Monitect HC12, Branan Medical Corporation, Irvine, California) confirmed no recent drug use (other than cannabis in the user group), and a negative urinary pregnancy test was required in all female subjects. A research clinician assessed psychotic symptoms using the Positive and Negative Syndrome Scale at the time of scanning. No subjects had psychotic symptoms at the time of scanning (mean [SD] Positive and Negative Syndrome Scale positive score cannabis users = 7.3 [.5]; control subjects = 7.2 [.4]). Subjects received carbidopa 150 mg and entacapone 400 mg orally 1 hour before imaging (58) to reduce the formation of radiolabeled [^{18}F]-DOPA metabolites (59,60). Head position was marked and monitored via laser crosshairs and a camera and minimized using a head-strap. A 10-minute transmission scan was performed before radiotracer injection for attenuation and scatter correction. Approximately 180 MBq of [^{18}F]-DOPA was administered by bolus intravenous injection 30 seconds after the start of PET imaging. We acquired emission data in list mode for 95 minutes, rebinned into 26 timeframes (30-second background frame, four 60-second frames, three 120-second frames, three 180-second frames, and fifteen 300-second frames).

Volume of Interest Analysis

To correct for head movement, nonattenuation-corrected dynamic images were denoised using a level 2, order 64 Battle-Lemarie wavelet filter (61), and individual frames were realigned to a single frame acquired 10 minutes after the [^{18}F]-DOPA injection using a mutual information algorithm (62). Transformation parameters were then applied to the corresponding attenuation-corrected frames, and the realigned frames were combined to create a movement-corrected dynamic image (from 6 to 95 minutes following [^{18}F]-DOPA administration) for analysis.

After movement correction, we defined standardized volumes of interest (VOIs) bilaterally in the whole striatum, the limbic (ventral), associative (precommisural dorsal caudate, precommisural dorsal putamen, and postcommisural caudate), and sensorimotor (postcommisural putamen) striatal functional subdivisions and the cerebellar reference region in Montreal Neurologic Institute space (63,64). An [^{18}F]-DOPA template was normalized with the VOI map to each individual PET summation