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 $K_{inc}$) 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 (18–20), 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 CB1 receptor agonism (36). CB1 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.
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-[18F]-fluoro-phénylalanine ([18F]-DOPA) scan on an ECAT HR+ 962 PET scanner (CTI/Siemens, Knoxville, Tennessee) in three-dimensional mode, with an axial field of view of 15.5 cm, performed as previously reported (28). Initially, subjects were told to fast for 6 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 [18F]-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 [18F]-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 [18F]-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 [18F]-DOPA administration) for analysis.

After movement correction, we defined standardized volumes of interest (VOIs) bilaterally in the whole striatum, the limbic (ventral), associative (precomissural dorsal caudate, precommissural dorsal putamen, and postcomissural caudate), and sensorimotor (postcomissural putamen) striatal functional subdivisions and the cerebellar reference region in Montreal Neurologic Institute space (63,64). An [18F]-DOPA template was normalized with the VOI map to each individual PET summation
The parametric image for each participant was then normalized into standard space using the participants PET summation image and the \(^{18}\text{F}\)-DOPA template (29). Statistical parametric mapping was conducted using SPM5 and a striatal mask defined according to previously described criteria (64) to compare groups. Results are presented corrected for multiple comparisons using random field theory as applied in SPM5 \((p < .05, \text{corrected at the family-wise error rate})\).

### Statistical Analysis

We assessed normality of distributions using the one-sample Kolmogorov-Smirnov test. Between-group comparisons were made with two-tailed independent \( t \) tests for normally distributed data and Mann-Whitney \( U \) tests for nonnormally distributed data.

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**Table 1. Sample Characteristics and Scan Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Controls ((n = 19))</th>
<th>Cannabis Users ((n = 19))</th>
<th>( p^{ad} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Characteristic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years, mean (SD))</td>
<td>22.3 (2.8)</td>
<td>20.8 (1.7)</td>
<td>.07</td>
</tr>
<tr>
<td>Sex ((n))</td>
<td>2 female, 17 male</td>
<td>2 female, 17 male</td>
<td>1.00</td>
</tr>
<tr>
<td>Handedness ((n))</td>
<td>2 left, 17 right</td>
<td>4 left, 15 right</td>
<td>.37</td>
</tr>
<tr>
<td>Ethnicity ((n))</td>
<td>4 AB, 3 BB, 1 ME, 11 WB</td>
<td>4 AB, 15 WB</td>
<td>.16</td>
</tr>
<tr>
<td><strong>Current Drug Use(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis users ((n))</td>
<td>0 users, 19 nonusers</td>
<td>19 users, 0 nonusers</td>
<td>1.00</td>
</tr>
<tr>
<td>THC content of cannabis ((%), mean (SD))</td>
<td>—</td>
<td>8.7 (3.8)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Scan Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injected dose ((\text{MBq})), mean (SD)</td>
<td>180.6 (7.2)</td>
<td>184.4 (5.2)</td>
<td>.11</td>
</tr>
<tr>
<td>Specific activity ((\text{MBq/\mu mol})), mean (SD)</td>
<td>31.1 (17.3)</td>
<td>30.5 (14.0)</td>
<td>.92</td>
</tr>
<tr>
<td>Whole striatal volume ((\text{mm}^3)), mean (SD)</td>
<td>17,587.82 (1729.50)</td>
<td>17,942.90 (1286.73)</td>
<td>.48</td>
</tr>
<tr>
<td>Associative striatal volume ((\text{mm}^3)), mean (SD)</td>
<td>10,801.19 (1134.46)</td>
<td>10,772.76 (1161.24)</td>
<td>.94</td>
</tr>
<tr>
<td>Limbic striatal volume ((\text{mm}^3)), mean (SD)</td>
<td>2080.30 (234.77)</td>
<td>2276.51 (977.85)</td>
<td>.40</td>
</tr>
<tr>
<td>Sensorimotor striatal volume ((\text{mm}^3)), mean (SD)</td>
<td>4706 (106.60)</td>
<td>4668.98 (443.16)</td>
<td>.80</td>
</tr>
</tbody>
</table>

\( ^{a} \text{UK alcohol unit = 10 mL (~7.88 g) alcohol.} \)

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**Voxelwise Analysis**

We complemented the VOI analysis with an independent voxelwise analysis using a wavelet-based Patlak method (69) as previously described (29). The parametric image for each sample was calculated from [\(^{18}\text{F}\)]-DOPA uptake, relative to the cerebellum (\(K_{\text{IC}}\) \((\text{min}^{-1})\)), for each VOI using the Patlak graphic analysis adapted for a reference tissue input function (65–68). We have previously demonstrated good test–retest reliability for striatal \(K_{\text{IC}}\) determined this way (64).

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### Notes

- AB, Asian British; BB, black British; IQR, interquartile range; MDMA, 3,4-methylenedioxy-N-methylamphetamine ("Ecstasy"); ME, mixed ethnicity; WB, white British.
- \(^{b}\)Independent-samples \(t\) tests for variables with normal data distributions; Mann-Whitney \(U\) tests for variables with nonnormal data distributions; \(\chi^2\) tests for dichotomous variables.
- \(^{d}\)Groups were compared on a dichotomized ethnicity variable (white British vs. ethnic minority).
- \(^{e}\)Drug use reported in 3 months before scan. Drug user defined as any drug use in the 3 months before scan.
- \(^{f}\)There was no reported lysergic acid diethylamide, benzodiazepine, opiate, or methamphetamine use in the 3 months before scanning.
- \(^{i}\)1 UK alcohol unit = 10 mL (~7.88 g) alcohol.

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**References**

- Bloomfield et al. (2014). Statistical analysis and voxelwise analysis of [\(^{18}\text{F}\)]-DOPA uptake in a sample of volunteers using SPM5.
Relationships among $K_{\text{cter}}^c$, levels of cannabis use, and cannabis-induced psychotic-like symptom severity were tested using Pearson’s product–moment correlation coefficient. Potential confounding effects of other substance use were explored using a single analysis of covariance (ANCOVA) with subject group as the fixed factor; $K_{\text{cter}}^c$ as the dependent variable and levels of use of each substance other than cannabis as separate covariates, and using Pearson’s product–moment correlation coefficient to determine if there was a relationship between $K_{\text{cter}}^c$ and levels of tobacco smoking. Statistical significance was defined as $p < .05$ (two-tailed). Our primary outcome measure was $K_{\text{cter}}^c$ in the whole striatum. Exploratory analyses were conducted in the striatal subdivisions (presented uncorrected for multiple comparisons).

Results

Subject Characteristics and Scan Parameters

Twenty cannabis users were recruited to the study. Owing to tomograph malfunction during one scan, complete data were available on nineteen users. All cannabis users consumed the drug as a spliff. The mean (SD) age of first cannabis use was 15.5 (1.6) years, and the mean (SD) duration of at least weekly use was 4.7 (3.1) years. The median (interquartile range) time taken to smoke an eighth and lifetime exposure to cannabis was 4.0 (3.1) years. The median (interquartile range) time taken to smoke one cannabis was 9.5 (1.6) years and the mean (SD) duration of at least weekly use was 4.7 (3.1) years. The median (interquartile range) time between the scan and the last use was 2340 (6240) spliffs, respectively. Within the user group, the median (interquartile range) time between the scan and the last cannabis exposure was 4.0 (13.5) days and 2340 (6240) spliffs, respectively. Within the user group, the median (interquartile range) time between the scan and the last cannabis exposure and self-reported cannabis-induced psychotic-like symptoms was 14.0 (23.8) hours. Ten users met DSM-IV criteria for cannabis dependence ($n = 5$) or abuse ($n = 5$). Mean (SD) time to smoke an eighth was 2.3 (2.2) days in users who met dependency/abuse criteria and 6.9 (4.7) days in users who did not meet criteria. Mean (SD) age of first cannabis consumption was 14.8 (1.6) years in users who met dependency/abuse criteria, and 16.2 (1.3) years in users who did not meet criteria. Nineteen control subjects were matched to the user group for age ($\pm 5$ years) and sex. Subjects’ characteristics are reported in Table 1. Urine drug screen was positive for THC and negative for all other substances (amphetamine, opiates, cocaine, methamphetamine, benzodiazepines) in every cannabis user and negative for all drugs (including cannabis) in every control subject. There was a significant group difference in current cannabis consumption, as expected, and also in tobacco and ecstasy use (Table 1).

There was no significant group difference in the amount of radioactivity or specific activity injected (Table 1). There was no significant difference in whole striatal or subdivision volumes between the groups. There was no relationship between age and $K_{\text{cter}}^c$ in the striatum or its subdivisions in the whole sample or in either group (data available on request).

Striatal Dopaminergic Function

$K_{\text{cter}}^c$ was significantly reduced in cannabis users relative to controls in the whole striatum (Figure 1). Secondary analysis in each striatal subdivision showed that this reduction reached significance in the limbic and associative subdivisions (Table 2). The finding of reduced $K_{\text{cter}}^c$ in cannabis users remained significant after covarying for other drugs used, with the amount of use of each of the drugs listed in Table 1 included as separate covariates in the ANCOVA, in the whole striatum ($F_{1,37} = 4.65, p = .040$) and its associative ($F_{1,37} = 5.00, p = .034$) and limbic ($F_{1,37} = 7.358, p = .011$) subdivisions.

Voxel-based analysis confirmed reduced $K_{\text{cter}}^c$ in the cannabis user group relative to nonuser control subjects with peak statistical significance in the right putamen (Montreal Neurological Institute coordinates: 28, 6, –8; $p = .048$ [corrected for familywise error]; Figure 2). There were no voxels where there was a significant elevation in $K_{\text{cter}}^c$ in cannabis users relative to control subjects.

The Relationship Between Striatal Dopamine Synthesis Capacity and Cannabis Use

Within the cannabis user group, greater levels of current cannabis use (less time to smoke an eighth of cannabis) were associated with lower $K_{\text{cter}}^c$ in the whole striatum ($r = –.77, p < .001$; Figure 3A). Secondary analysis in each striatal subdivision showed that this pattern reached significance in the associative ($r = –.68, p = .001$) and sensorimotor ($r = –.84, p < .001$) subdivisions but not the limbic subdivision ($r = –.26, p = .290$). In addition, there was a significant correlation between age of onset of cannabis use and $K_{\text{cter}}^c$ in the whole striatum ($r = .51, p = .027$; Figure 3B) and in its associative subdivision ($r = .56, p = .013$), which remained significant after controlling for current age ($r = .49, p = .04$ [whole striatum]; $r = .54, p = .02$ [associative]), with no significant correlation in the sensorimotor ($r = .34, p = .158$) or limbic ($r = .36, p = .126$) subdivisions. There was no significant correlation between age of first cannabis use and current cannabis use ($r = .16, p = .52$).

Table 2. $[^{18}\text{F}]$-DOPA $K_{\text{cter}}^c$ (min$^{-1}$) by Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Control Subjects ($n = 19$)</th>
<th>Cannabis Users ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOI</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>STR</td>
<td>.0134 (.0099)</td>
<td>.0127 (.0007)</td>
</tr>
<tr>
<td>AST</td>
<td>.0127 (.0099)</td>
<td>.0121 (.0007)</td>
</tr>
<tr>
<td>LST</td>
<td>.0138 (.0009)</td>
<td>.0132 (.0008)</td>
</tr>
<tr>
<td>SMST</td>
<td>.0146 (.0014)</td>
<td>.0139 (.0008)</td>
</tr>
</tbody>
</table>

AST, associative striatum; $K_{\text{cter}}^c$, influx rate constant; LST, limbic striatum; SMST, sensorimotor striatum; STR, whole striatum; VOI, volume of interest.

$^a$Independent-samples $t$ tests.
Across the whole sample and within the control group, there was no significant difference between \( K_e \) in tobacco smokers and nontobacco smokers in any of the regions examined (all \( p > .1 \)). Within the whole sample and within each group, there was no relationship between \( K_e \) and daily cigarette use among tobacco cigarette smokers in the whole striatum (\( r = .26, p = .91 \) [whole sample], \( r = .10, p = .81 \) [control subjects]; \( r = .18, p = .52 \) [cannabis users]) and its functional subdivisions (data available on request). Within the whole sample and within each group, there were no significant relationships (all \( p > .1 \)) between whole striatal \( K_e \) and other substances used (listed in Table 1).

To examine whether cannabis dependency/abuse was associated with reduced \( K_e \), we divided the cannabis user group into subjects that met DSM-IV diagnostic criteria for cannabis dependency or abuse (\( n = 10 \)) and those who did not meet criteria (\( n = 9 \)). One-way analysis of variance found a significant effect of group on whole striatal \( K_e \) (\( F_{2,37} = 4.02, p = .027 \), Figure 4). Post hoc \( t \) tests showed significant differences between the cannabis dependency/abuse and nondependency/nonabuse cannabis user subgroups (\( t_{17} = 2.80, p = .012 \)) and between the cannabis dependency/abuse subgroup and control subjects (\( t_{27} = 2.67, p = .013 \), but not between the nondependency/nonabuse subgroup and the control group (\( p = .60 \)). When examining the striatal subdivisions, significant differences in \( K_e \) between the cannabis dependency/abuse and nondependency/nonabuse cannabis user subgroups were observed in the associative subdivision only (\( t_{17} = 2.89, p = .010 \)).

### The Relationship Between Striatal Dopamine Synthesis Capacity and Cannabis-Induced Psychotic Symptoms

Within the cannabis user group, the mean (SD) increase in PSI psychotic symptom subscale score after consuming cannabis was 9.9 (5.1). There was no significant correlation between striatal \( K_e \) and increase in transient psychotic-like symptoms following cannabis use (\( r = .32, p = .19 \); Figure 5).

### Discussion

Our main finding is that striatal dopamine synthesis capacity is lower in current cannabis users than matched nonuser control subjects. In users, lower dopamine synthesis capacity was associated with greater current cannabis use, which explained 59% of variance in striatal dopamine synthesis capacity, and

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Figure 2. Reduced striatal dopamine synthesis capacity in regular cannabis users relative to nonuser controls. The image shows a statistical parametric map of significant reductions (\( p < .05 \)) in dopamine synthesis capacity, relative to healthy comparison subjects (\( n = 19 \)), in regular cannabis users who experienced transient psychotic-like symptoms (\( n = 19 \)). The most significant reduction was in the right putamen (Montreal Neurological Institute coordinates: 28, 6, –8; \( p = .048 \), corrected at the family-wise error rate). The color bar indicates the \( t \) statistic for each voxel.

Figure 3. (A) The correlation between level of cannabis use (time to smoke an “eighth” [\( \sim 3.5 \text{ g} \)] of cannabis; days) and striatal dopamine synthesis capacity, indexed as \( K_e \) (min\(^{-1}\)), in cannabis users (\( r = –.77, p < .001 \)). (B) The correlation between age of onset of cannabis use and \( K_e \) in the whole striatum (\( r = .51, p = .027 \)), which remained significant when controlling for current age (\( r = .49, p = .04 \)).
dopamine dysfunction, our findings suggest a causative relationship between cannabis use and a biphasic dose-dependent dopamine response to THC (71), response to acute THC treatment. However, there is evidence of animal studies indicate increased dopaminergic function in the striatum was associated with earlier age of onset of cannabis use, not with cannabis-induced psychotic-like symptoms.

Importantly, we also found that the lower levels of dopamine synthesis capacity in cannabis users compared with nonusers were driven by users who met diagnostic criteria for abuse and dependence. These findings are inconsistent with our hypothesis that elevated dopamine synthesis capacity underlies the link between cannabis and risk of psychosis.

Our results extend previous findings in current (70) and recently abstinent cannabis users (43), which found reduced dopamine receptor density was associated with higher current cannabis use and lower dopamine release in the associative striatum was associated with earlier age of onset of cannabis. Although these studies (43,44,70) and a further study in ex-users (45) have reported estimates of the number of lifetime uses of cannabis and our sample is comparable to these, measures of the amount or type of cannabis consumed have not been reported, such that direct comparisons of cannabis use across the studies cannot be made. Our findings of reduced dopamine synthesis capacity in dependent subjects may reflect a “blunted” dopamine system, as observed with other drugs of addiction (7). Taken with findings from these and other studies (8–11), there is mounting evidence that dopaminergic dysfunction provides a biomarker of addiction severity.

Although the case–control design of this study is not able to detect a causative relationship between cannabis use and dopamine dysfunction, our findings suggest that dopamine effects warrant further research into potential causative mechanisms. Animal studies indicate increased dopaminergic function in response to acute THC treatment. However, there is evidence of a biphasic dose-dependent dopamine response to THC (71), suggesting higher cannabis exposures may reduce dopamine synthesis capacity, in line with our findings. Furthermore, with the exception of perinatal studies (72), animal data on dopaminergic effects of long-term and high dose cannabis exposures are sparse, and the longest duration of THC administration has been 21 days (42,73–75). Of these, one study (74) in Sprague-Dawley rats reported that long-term treatment with THC was associated with reduced striatal tyrosine hydroxylase gene expression and concurrent supersensitivity of D2 receptors, and a separate study (75) in catechol-O-methyltransferase mutant mice found chronic treatment with THC in adolescence was associated with reduced dopaminergic cell size in the ventral tegmental area.

One explanation for our findings is that chronic cannabis use is associated with dopaminergic down-regulation. This might underlie amotivation and reduced reward sensitivity in chronic cannabis users (76). Alternatively, preclinical evidence suggests that low dopamine neurotransmission may predispose an individual to substance use (77). However, this is inconsistent with findings that recently abstinent and former cannabis users show neither altered dopamine receptor availability (44,45,70) nor altered dopamine release (43), suggesting that altered dopaminergic function during chronic cannabis use is normalized by abstinence, as is observed with amphetamine in vervet monkeys (78).

In this study, we investigated dopaminergic function in cannabis users who experience a transient increase in psychotic-like experiences when acutely intoxicated with cannabis. The lack of relationship between the induction of psychotic-like experiences and dopaminergic function suggests that our findings would generalize to cannabis users in general, but this requires confirmation in future studies.

Our findings suggest that elevated striatal dopamine synthesis capacity is unlikely to be the mechanism underlying the link between cannabis and psychosis. Our study focused on the striatum because dopaminergic changes there have been reliably linked to psychosis (22) but we cannot exclude the possibility that dopaminergic changes in extrastriatal regions underlie...
cannabis-induced psychotic symptoms. A previous study (79) using single photon emission computed tomography reported a significant increase in temporal cortex D2/D3 receptor availability in antipsychotic-naive first-episode patients with psychosis who tested positive for cannabis compared with those who did not. Alternatively, the mechanism may be mediated via non-dopaminergic systems, such as direct effects on cannabinoid receptors (80).

Nevertheless, findings that striatal dopamine release in patients with comorbid schizophrenia and substance dependence is blunted but still associated with amphetamine-induced psychotic symptoms (81) supports the possibility that other aspects of striatal dopaminergic function are altered by cannabis or that cannabis use interacts with other risk factors for schizophrenia to induce hyperdopaminergia. In support of this, early work in Wistar rats (82) found THC decreased striatal dopamine uptake compared with vehicle, but increases in striatal dopamine uptake were observed when THC-treated rats were housed under “stressful” versus “normal” conditions. Earlier age of onset of cannabis use increases psychosis risk and may interfere with normal brain development (83). Another possibility is thus that cannabis use during key developmental periods alters the regulation of dopaminergic function to make it more susceptible to subsequent stressors that could underlie an increased risk of psychosis. Additional prospective studies on the effects of chronic cannabis exposure are therefore warranted.

Study Limitations

One potential limitation of this study is that subjects consumed their own cannabis rather than a standard preparation. However, we tested individuals while intoxicated, measured levels of THC in samples of the cannabis our subjects were using, and confirmed it contained high levels of THC in all subjects (mean THC content = 8.7%). There was no fixed interval between cannabis exposure and PET, meaning that heavier cannabis users may have had a shorter interval between exposure and scan. It therefore remains possible that differences in the time since last cannabis use contribute to the differences between the dependent/abuser and nondependent groups, rather than dependency or abuse per se. In addition, lack of association between cannabis-induced psychotic symptoms may be due to variable interval between cannabis exposure and PET. However, in terms of acute effects of cannabis, only one of three molecular imaging studies of the acute effects of THC in healthy volunteers have found evidence of dopamine release (84–86), suggesting that acute effects of THC on dopaminergic function may not be large or consistent in humans. Given that THC and its metabolites have an elimination half-life of about 7 days (87) and all our cannabis users were regular, long-term users who had consumed cannabis within the past 7 days (median time since last consumption = 14 hours), our subjects were unlikely to be acutely withdrawing.

Our measures of substance use rely on self-report, and we were not able to independently verify substance use histories beyond ongoing cannabis use in the user group and no recent use of other drugs in all participants. As would be expected, higher rates of other substance use were reported in cannabis users, although, with the exception of tobacco, the use of other substances was low in both groups. Our findings remained significant after covarying for all other drug use, suggesting that use of other substances does not underlie our findings, although it should be noted that ANCOVA may be less able to adjust for factors when groups differ significantly in covariates (88) and should be considered exploratory. We therefore cannot exclude the possibility that group differences in other drug use contributed to the results observed.

Although cannabis users in our sample reported higher levels of ecstasy use than control subjects, ecstasy has been associated with increased dopamine synthesis capacity (89), so this is unlikely to explain our findings. More of the cannabis users smoked cigarettes than control subjects. The effects of cigarette smoking on presynaptic dopamine function are unclear; tobacco use has been associated with reduced amphetamine-induced dopamine release (90) but increased dopamine synthesis capacity (91). In addition, tobacco smoking may influence [18F]-DOPA kinetics via cerebral blood flow effects (92), which, if regionally selective, could affect our outcome measure. However, we did not find a relationship between levels of cigarette consumption and dopamine synthesis capacity, suggesting this did not influence our results, although additional research is needed to determine the effect of tobacco smoking on dopaminergic function.

Conclusion

Our results show that regular long-term cannabis use is associated with a dose-dependent reduction in dopamine synthesis capacity in the corpus striatum, particularly in those meeting diagnostic criteria for cannabis abuse or dependence. However, we found no relationship between dopaminergic function and cannabis-induced psychotic-like symptoms. These findings question the prevailing assumption that cannabis increases the risk of schizophrenia by inducing the same dopaminergic alterations seen in schizophrenia.

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