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## Further human evidence for striatal dopamine release induced by administration of 9-tetrahydrocannabinol (THC): selectivity to limbic striatum

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### Abstract

**Rationale**—Elevated dopamine function is thought to play a key role in both the rewarding effects of addictive drugs and the pathophysiology of schizophrenia. Accumulating epidemiological evidence indicates that cannabis use is a risk factor for the development of schizophrenia. However, human neurochemical imaging studies that examined the impact of 9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis, on striatal dopamine release have provided inconsistent results.

**Objectives**—To assess the effect of a THC challenge on human striatal dopamine release in a large sample of healthy participants.

**Methods**—We combined human neurochemical imaging data from two previous studies that used [<sup>11</sup>C]raclopride positron emission tomography (PET) (n=7 and n=13, respectively) to examine the effect of THC on striatal dopamine neurotransmission in humans. PET images were re-analysed to overcome differences in PET data analysis.

**Results**—THC administration induced a significant reduction in [<sup>11</sup>C]raclopride binding in the limbic striatum (−3.65%, from 2.39±0.26 to 2.30±0.23, p=0.023). This is consistent with increased dopamine levels in this region. No significant differences between THC and placebo were found in other striatal subdivisions.

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Statement of interest

The authors declare no financial conflict of interest. The authors have full control of all primary data, and they agree to allow the journal to review their data if requested.

**Conclusions**—In the largest data set of healthy participants so far, we provide evidence for a modest increase in human striatal dopamine transmission after administration of THC compared to other drugs of abuse. This finding suggests limited involvement of the endocannabinoid system in regulating human striatal dopamine release, and thereby challenges the hypothesis that an increase in striatal dopamine levels after cannabis use is the primary biological mechanism underlying the associated higher risk of schizophrenia.

### Keywords

Dopamine; positron emission tomography (PET); 9-tetrahydrocannabinol (THC); [<sup>11</sup>C]raclopride; striatum; cannabis

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### Introduction

Many abused drugs that can lead to addiction increase synaptic dopamine levels in the human limbic striatum. Most likely, this rapid increase in dopamine release is associated with drug-induced reward, which together with subsequent conditioned responses may lead to changes in incentive motivation and ultimately in drug-seeking behaviour (Volkow et al. 2011; Wise 2009). Indeed, with the use of neuroimaging techniques such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) in combination with radioactive tracers that bind to striatal dopamine receptors, increased dopamine concentrations have been demonstrated in the human limbic striatum after the administration of amphetamine (Martinez et al. 2003; Martinez et al. 2007; Oswald et al. 2005; Wand et al. 2007), alcohol (Boileau et al. 2003; Urban et al. 2010) and nicotine (Brody et al. 2009; Takahashi et al. 2008). This was indicated by significant reductions in radiotracer binding in the limbic striatum, which were in the range of 10 - 15% after administration of amphetamine (Martinez et al. 2003; Martinez et al. 2007; Oswald et al. 2005; Wand et al. 2007) and alcohol (Boileau et al. 2003; Urban et al. 2010), and around 10% after nicotine administration (Brody et al. 2009; Takahashi et al. 2008).

Increased striatal dopamine release associated with the use of abused drugs is relevant to psychotic disorders such as schizophrenia as elevated striatal dopamine function is one of the most robust pathophysiological features of the disorder (for review see Howes and Kapur 2014). Accumulating epidemiological evidence indicates that cannabis use during adolescence is a risk factor for the development of schizophrenia (Arseneault et al. 2004; Moore et al. 2007). Therefore, elevated striatal dopamine release after the use of cannabis may explain how cannabis use contributes to the development and pathophysiology of schizophrenia. Indeed, in animals, it has been demonstrated that cannabinoid substances such as 9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis and partial agonist of the cannabinoid CB1 receptor, stimulate striatal dopamine signalling (see for reviews El Khoury et al. 2012; Gardner 2005). For example, in vivo single-neuron electrophysiological recordings have shown that cannabinoid agonists are able to enhance neuronal firing of mesolimbic dopamine neurons (French 1997; French et al. 1997; Gessa et al. 1998) and in vivo microdialysis techniques revealed an elevation of striatal dopamine levels following cannabinoid administration (Chen et al. 1990; Fadda et al. 2006; Malone and Taylor 1999; Ng Cheong Ton et al. 1988; Tanda et al. 1997). These effects appear to

depend on activation of CB1 receptors as they were blocked by the selective CB1 receptor antagonist SR-141716A (French 1997; French et al. 1997; Gessa et al. 1998; Malone and Taylor 1999; Tanda et al. 1997).

Results of human neuroimaging studies on the effects of THC on striatal dopamine release have been inconclusive. Using PET and the dopamine D<sub>2</sub>/D<sub>3</sub> receptor tracer [<sup>11</sup>C]raclopride in seven healthy participants, Bossong et al. (2009) found that inhaled THC (8 mg) induced a relatively modest but significant reduction in [<sup>11</sup>C]raclopride binding in the limbic striatum and precommissural dorsal putamen (3.4% and 3.9%, respectively), consistent with an increase in dopamine levels in these regions (Bossong et al. 2009). Stokes and colleagues (2009) imaged thirteen healthy participants using the same PET methodology, but did not find significant effects of oral THC administration (10 mg) on [<sup>11</sup>C]raclopride binding, despite an increase in psychotic-like symptoms (Stokes et al. 2009). Finally, using SPECT and [<sup>123</sup>I]IBZM, Barkus et al. (2011) found that intravenously administered THC (2.5 mg) had no effect on striatal dopamine release in nine healthy participants, despite inducing transient psychotic symptoms (Barkus et al. 2011).

In the current study, we re-analysed the [<sup>11</sup>C]raclopride PET images of Bossong et al. (2009) according to the methods described in Stokes et al. (2009) in order to overcome differences in PET data analysis between the two studies. This re-analysis included the assessment of [<sup>11</sup>C]raclopride binding in regions of interest (ROIs) that were automatically defined using an atlas comprised of three functional subdivisions of the striatum and the cerebellum as a reference region. Subsequently, both data sets were combined to test the hypothesis that THC induces dopamine release in the human striatum in a large sample of healthy participants with previous experience of cannabis use. This approach allows new and better powered analyses to be conducted, such as an interaction test between striatal subdivision and THC effect.

## Methods

Both the studies of Bossong et al. (2009) and Stokes et al. (2009) were approved by an independent ethics committee and were conducted in accordance with the Declaration of Helsinki 2008. All participants gave written informed consent before entry into the study. Participant recruitment, study design, drug administration, PET methodology and assessment of THC plasma concentrations are fully described for each study in Bossong et al. (2009) and Stokes et al. (2009), respectively.

## Participants

Twenty healthy volunteers (thirteen from the study by Stokes and colleagues and seven from that by Bossong and colleagues) with previous experience of cannabis use without significant adverse effects were recruited to the study through public advertisements. All participants underwent an extensive screening performed by a clinician before they were included in either study. Subjects were in good physical health, and subjects with a current or previous psychiatric disorder including alcohol or drug dependence were excluded from participation. Use of medication at the time of the study and past use of psychiatric medication was not allowed. On study days, volunteers underwent urine drug screen analysis

for use of recreational drugs including cannabis, amphetamine, cocaine and opiates. Any volunteer with a positive drug screen was excluded from the study. In addition, participants needed to abstain from alcohol for 24 hours before each study day.

### Study design and drug administration

Using a randomised, placebo-controlled, crossover design, volunteers underwent two [<sup>11</sup>C]raclopride PET scans: one with placebo and one with THC administration. Study days were scheduled at least 2 weeks apart to allow for complete clearance of drugs. Stokes et al. (2009) administered a capsule containing either 10 mg dronabinol (a synthetic form of THC) or placebo 90 minutes before each scan. In the study of Bossong and colleagues (2009), either 8 mg of THC or placebo was inhaled 45 minutes before each scan using a Volcano vaporizer (Storz-Bickel GmbH, Tuttlingen).

### Positron Emission Tomography

All PET scans were performed on an ECAT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) with an axial field of 15.5 cm. For each scan, [<sup>11</sup>C]raclopride was given as a bolus plus constant infusion, providing a state of constant equilibrium (Carson et al. 1997). A 10 minute transmission scan was performed to correct for photon attenuation.

### Plasma THC measurements

Venous blood samples were collected 10 minutes into the PET scan, which was 100 minutes (Stokes et al. 2009) and 55 minutes (Bossong et al. 2009) after administration of medication, respectively.

### Regions of Interest

Individual PET frames obtained during steady state (from 40 and 38 minutes post-injection onwards for the study of Bossong et al. and Stokes et al., respectively) were realigned to the first frame obtained at equilibrium to correct for motion, and summed over all frames. Striatal and cerebellar ROIs were automatically defined on each PET scan using an atlas comprised of the three functional subdivisions of the striatum (limbic, associative and sensorimotor striatum) as well as the cerebellum as a reference region. Striatal subdivisions are anatomically analogous to the ventral striatum (limbic striatum), precommissural dorsal putamen, precommissural dorsal caudate and postcommissural dorsal caudate (associative striatum) and postcommissural putamen (sensorimotor striatum) (Martinez et al. 2003). The atlas was coregistered to individual summed PET images in SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK) using an [<sup>11</sup>C]raclopride template. Activity was assessed for each ROI as the volume weighted average of left and right regions using Analyze software ([www.analyzedirect.com](http://www.analyzedirect.com)). Activity in the overall striatum was calculated as the volume weighted average of all three striatal ROIs.

### Outcome Measures

Nondisplaceable binding potential ( $BP_{ND}$ ; Innis et al. 2007) was used as measure of dopamine  $D_2/D_3$  receptor availability.  $BP_{ND}$  was defined as the distribution volume ratio (DVR) minus 1 (Lammertsma et al. 1996). As scans were performed during steady state,

DVR could be obtained using the average activity concentration in a striatal ROI divided by that of the cerebellum ROI, which was used as reference. Using this method,  $BP_{ND}$  was calculated for all striatal subdivisions as well as overall striatum for both placebo and THC sessions in twenty participants.

### Statistical Analysis

Group differences in  $BP_{ND}$  between placebo and THC were analysed using repeated measures ANOVA with factors drug (placebo and THC) and striatal subdivision (limbic, associative and sensorimotor striatum). Both post hoc analyses for individual subdivisions and statistical analyses for PET scan parameters were performed using paired t-tests. Correlation between [ $^{11}C$ ]raclopride binding in the overall striatum and THC plasma concentration was assessed with Pearson's  $r$ . A  $p$  value less than 0.05 was considered statistically significant, which was tested two-sided for all outcomes except the correlation analysis. Cohen's  $d$  effect sizes were calculated using pooled standard deviations. All statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, Illinois) and all data are presented as mean $\pm$ SD.

### Results

Results are reported on nineteen subjects as one participant was identified as being a significant outlier according to Chauvenet's criterion (Taylor, 1997) (see Supplementary Results S1). Thirteen male and four female participants were included, with a mean age of  $27.9\pm 7.7$  years (range 20 - 44).

#### PET scan parameters

There were no significant differences between placebo and THC sessions for either mean injected dose of [ $^{11}C$ ]raclopride ( $539\pm 175$  and  $559\pm 197$  MBq, respectively;  $p=0.237$ ) or the mean total mass of administered raclopride ( $3.72\pm 2.38$  and  $3.46\pm 1.46$   $\mu$ g, respectively;  $p=0.577$ ).

#### Dopamine $D_2/D_3$ receptor availability

Repeated measures ANOVA revealed a significant interaction effect between drug and striatal subdivision ( $F(2,36)=6.01$ ,  $p=0.015$ ), indicating that the effect of THC differs between subdivisions. Post hoc analysis showed that the  $BP_{ND}$  of [ $^{11}C$ ]raclopride, reflecting dopamine  $D_2/D_3$  availability, was significantly reduced in the limbic striatum after THC administration compared to placebo by 3.65% (from  $2.39\pm 0.26$  to  $2.30\pm 0.23$ ;  $p=0.023$ ). No significant differences between THC and placebo were found in other striatal subdivisions (Fig. 1a and 1b).

#### Plasma THC levels

Mean THC plasma concentration during the PET scan was  $4.41\pm 4.04$  ng/ml. THC plasma concentration showed a significant negative correlation with the percentage change in [ $^{11}C$ ]raclopride binding in the overall striatum ( $r=-0.50$ ,  $p=0.015$ ) (Fig. 1c).

## Discussion

In the largest study to date, we have found a significant reduction in [<sup>11</sup>C]raclopride binding after THC administration in the limbic striatum of healthy participants with previous experience of cannabis use. This result is consistent with a THC-induced increase in limbic striatal dopamine levels, and concurs with animal studies which found increased striatal dopamine neurotransmission after administration of cannabinoid agonists (Gardner 2005; El Khoury et al. 2012). Furthermore, although the original Stokes et al. study (2009) found no significant association between THC administration and limbic striatal dopamine release, the addition of further participants from the Bossong et al. (2009) study (analysed using the same protocol as Stokes et al. (2009)) resulted in a significant association of THC administration with limbic striatal dopamine release. One possible explanation for the discrepant findings of the current analysis and the original study of Stokes et al. (2009) is that the original study with thirteen participants may not have been statistically powered to detect small changes in [<sup>11</sup>C]raclopride binding after oral administration of 10 mg of THC. This idea is further supported by the fact that in the study by Stokes et al. (2009) THC administration was associated with a radiotracer displacement of 1.6% and 3.2% in the right and left limbic striatum, respectively, which is non-significant but in the same direction as that reported in the current analysis.

These findings should be interpreted in the context of results from studies of human striatal dopamine release produced by other recreational drugs. Amphetamine, which pharmacologically directly targets the dopamine system, as well as alcohol have been shown to cause reductions in limbic striatal dopamine D<sub>2</sub>/D<sub>3</sub> receptor availability in the range of 10 - 15% (Boileau et al. 2003; Martinez et al. 2003; Martinez et al. 2007; Oswald et al. 2005; Urban et al. 2010; Wand et al. 2007). Nicotine produces reductions in limbic striatal availability of around 10% (Brody et al. 2009; Takahashi et al. 2008), whereas we found a relatively modest decrease of 3.7% in the limbic striatum after THC administration.

Interestingly, this decrease in [<sup>11</sup>C]raclopride binding is consistent with animal findings. Assuming a ratio between the increase in dopamine levels and reduction in [<sup>11</sup>C]raclopride binding of approximately 40 : 1 (Breier et al. 1997; Laruelle et al. 1997), the 25 - 100% increase in striatal dopamine levels measured with microdialysis techniques after THC administration to animals (Chen et al. 1990; Malone and Taylor 1999; Tanda et al. 1997) indicates a reduction in [<sup>11</sup>C]raclopride binding of 0.6 - 2.5%, which is even lower than the 3.7% decrease demonstrated in this study. Since this modest effect of THC on striatal dopamine release is accompanied by robust behavioural effects (Bossong et al. 2009; Stokes et al. 2009), it seems unlikely that this impact of THC is exclusively mediated by the striatal dopamine system. This view is supported by two studies which found that pre-treatment with the dopamine D<sub>2</sub> receptor antagonist haloperidol did not completely reduce the acute psychotic effects of THC (D'Souza et al. 2008; Liem-Molenaar et al. 2010). This implies that the acute behavioural effects of THC may be partially mediated via direct activation of the endocannabinoid system, and thus suggests a principal role for the endocannabinoid system in the association between cannabis use and the increased risk of schizophrenia.

The relatively modest reduction in [<sup>11</sup>C]raclopride binding after THC administration in the limbic striatum of healthy participants is consistent with findings of PET studies that examined striatal dopamine function in the context of cannabis abuse. Contrary to other substance abusers (e.g. cocaine, methamphetamine, alcohol; see Volkow et al. 2004 for review), no significant differences in dopamine D<sub>2</sub>/D<sub>3</sub> receptor availability nor striatal dopamine release have been demonstrated between chronic cannabis users and controls (Sevy et al. 2008; Stokes et al. 2012; Urban et al. 2012; Volkow et al. 2014). The only study that investigated presynaptic dopamine function found reduced dopamine synthesis capacity in cannabis users, which was not associated with psychotic-like experiences (Bloomfield et al., 2014).

This study has several limitations. First, the two data sets were obtained after THC administration with different delivery methods. Whereas Bossong et al. (2009) used pulmonary THC administration with a Volcano vaporizer, Stokes and colleagues administered THC orally. Generally, oral consumption leads to slower absorption and lower bioavailability of THC, and a delay in the onset of acute behavioural effects compared to inhalation (Aguell et al. 1986). It is unlikely, however, that this has affected our [<sup>11</sup>C]raclopride PET results, as the THC plasma concentration during the PET scan was significantly correlated with the percentage change in overall striatal [<sup>11</sup>C]raclopride binding (Figure 1C). Second, as in the study of Bossong et al. (2009) the PET scan was performed 45-85 min after inhalation of THC, it could be argued that most of the effect of THC on dopamine release had dissipated at the time of the scan. However, this is highly unlikely, as application of advanced pharmacokinetic/pharmacodynamic (PK/PD) models to these data showed that 84.5-95.9% of the maximum CNS effects were still present during acquisition of the PET scan (Strougo et al. 2008). Moreover, it has been shown that drug-induced effects on striatal dopamine release can be detected for a long time after administration (Breier et al. 1997; Cardenas et al. 2004; Laruelle et al. 1997). Third, although the correlation between THC plasma concentration during the PET scan and the percentage change in overall striatal [<sup>11</sup>C]raclopride binding is presented as a linear relationship, there is a possibility that in fact THC produces a biphasic dopaminergic response, with lower levels of THC concentrations associated with increased striatal [<sup>11</sup>C]raclopride binding (Figure 1C). Indeed, biphasic responses have been demonstrated in behavioural animal studies with acute cannabinoid administration (Sulcova et al. 1998). Fourth, information about the participants' history of recreational drug use is not presented in this paper as this data is lacking for the study of Bossong and colleagues. Although a within-subject design was used in this study, this could be important in the interpretation of our results as long-term changes in the dopamine system can be observed following prolonged abstinence from drug use (Nader et al. 2006). Finally, effects of THC on striatal dopamine release could not be related to acute behavioural effects as these were assessed differently in the studies of Bossong et al. (2009) and Stokes et al. (2009), and, unfortunately, could thus not be pooled.

## Conclusion

The present analysis provides further human evidence for a comparatively modest increase in striatal dopamine transmission after administration of THC. This finding suggests limited involvement of the endocannabinoid system in regulating striatal dopamine release, and

thereby challenges the hypothesis that an increase in striatal dopamine levels after cannabis use is the primary biological mechanism underlying the associated higher risk of schizophrenia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>BP<sub>ND</sub></b>	non-displaceable binding potential
<b>DVR</b>	distribution volume ratio
<b>PET</b>	positron emission tomography
<b>ROI</b>	region of interest
<b>SPECT</b>	single photon emission computed tomography
<b>THC</b>	9-tetrahydrocannabinol

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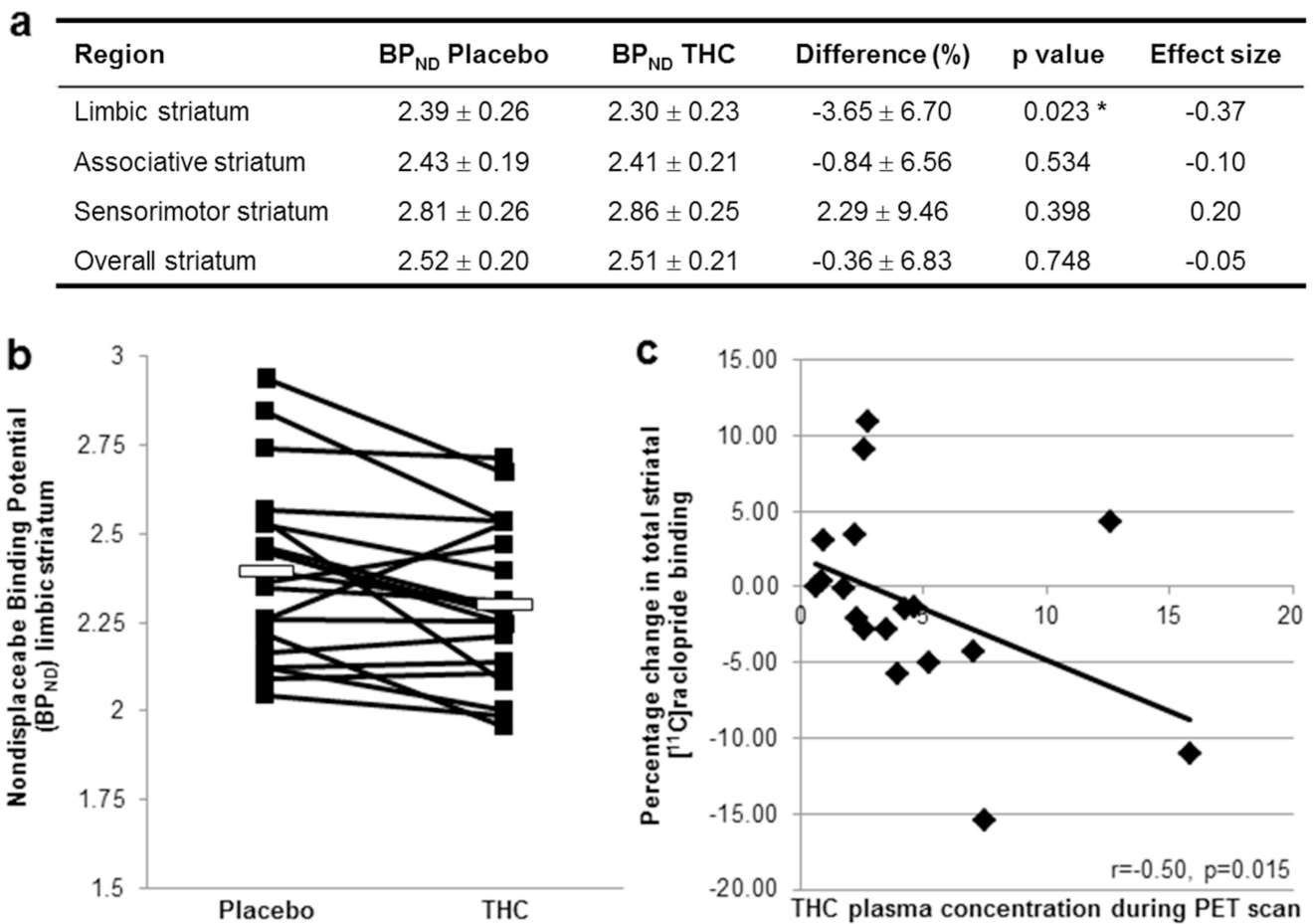
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**Fig 1.** Effects of  $\Delta^9$ -tetrahydrocannabinol (THC) on [ $^{11}\text{C}$ ]raclopride Nondisplaceable Binding Potential (BP<sub>ND</sub>), reflecting dopamine D<sub>2</sub>/D<sub>3</sub> receptor availability, in (1a) striatal functional subdivisions and overall striatum (mean $\pm$ SD), and (1b) limbic striatum of healthy subjects (n=19). (1c) Correlation between percentage change in [ $^{11}\text{C}$ ]raclopride binding in the overall striatum and THC plasma concentration during PET scan (Pearson's r, one-sided).  
\* Significant difference between placebo and THC.