The effects of acute Δ9-tetrahydrocannabinol on striatal glutamatergic function: a magnetic resonance spectroscopy (1H-MRS) study

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Abstract

Background: Cannabis and its main psychoactive component, Δ^9-tetrahydrocannabinol (THC), can elicit transient psychotic symptoms. A key candidate biological mechanism of how THC induces psychotic symptoms is the modulation of glutamate in the brain. We sought to investigate the effects of acute THC administration on striatal glutamate levels and its relationship to the induction of psychotic symptoms.

Methods: We used proton magnetic resonance spectroscopy to measure glutamate levels in the striatum in 20 healthy participants after THC (15mg, oral) and matched placebo administration in a randomised double-blind placebo-controlled design. Psychotic symptoms were measured using the psychotomimetic states inventory.

Results: We found that THC administration did not significantly change glutamate (Glx/Cre) concentration in the striatum (p = .58; scaled JZS Bayes Factor = 4.29). THC increased psychotic symptoms but the severity of these symptoms was not correlated with striatal glutamate levels.

Conclusions: These findings suggest that 15mg oral THC does not result in altered striatal glutamate levels. Further work is needed to clarify the effects of THC on striatal glutamate.

Introduction

Cannabis is one of the most widely-used recreational drugs in the world and use may increase further as cannabis policies become more permissive internationally (1). In the USA, the past year prevalence of cannabis use disorders among users is estimated at 30.6% (2). The primary psychoactive constituent of cannabis is Δ^9-tetrahydrocannabinol (THC) (3, 4). The THC content of cannabis has increased significantly over the past decade in Europe and the United states (5, 6). THC causes the rewarding aspects of cannabis use as well as inducing psychotic symptoms (7, 8). Long-term exposure to high THC cannabis is associated with increased risk of addiction and psychosis, and increased risk of relapse to psychosis (9-12). Therefore, there is concern that increases in THC exposure could have adverse effects on public health and rates of treatment for cannabis-related problems (13). Psychosis is associated with a range of alterations in the brain (14). THC and cannabis produce several effects on the brain which may account for the increased risk of psychopathology and psychotic symptoms (15-17). These include effects on the striatum which integrates sensorimotor, cognitive, motivational and emotional information to mediate reward and decision-making processes (7, 18-20). However, the precise mechanisms through which THC exposure causes psychotic symptoms have yet to be fully elucidated.

THC has been shown to affect striatal glutamate neurotransmission due to the abundance of type 1 endocannabinoid receptors (CB_1Rs) in the striatum (21). Research in Sprague-Dawley rats indicates that CB_1R activation is associated with reduced glutamatergic synaptic transmission in the striatum (22) and that THC dose-dependently inhibits potassium-evoked glutamate release and uptake (23). However,

it is possible that the observed inhibition in glutamate release could be caused by an increase in synaptic cleft glutamate (22). As the dopamine system is modulated by endocannabinoid-glutamate interactions (7, 24, 25), it is likely that THC disrupts the homeostatic role of the endocannabinoid system. However, evidence for the effects of THC on brain glutamate levels has not been conclusive (21). The majority of CB_1Rs in the brain are expressed on cholecystokinin interneurons whereby agonism results in reduced GABA release (26). THC likewise inhibits the release of GABA in several brain regions which is likely to result in suppression of inhibition of glutamatergic neurons (27).

Recent research using magnetic resonance spectroscopy (^{1}H-MRS) has reported that intravenous THC caused an increase in glutamate in the caudate head (n=16, one-tailed test) (28) and vaporized THC-dominant cannabis increased striatal glutamate when administered in a single dose (n=10, two tailed test) but not when delivered in three divided doses in the same study (n=10, two-tailed test) (29). Therefore, further research is needed to elucidate effects of THC on the glutamate system. Oral THC products have risen considerably in popularity in new legal markets in the USA (30), but no studies have investigated the effects of oral THC on striatal glutamate. Oral THC results in a slower onset and longer duration of effect compared to intravenous or vaporized administration, and greater concentrations of 11-OH-THC and THC-COOH compared to THC (31). In this study we aimed to investigate the acute effects of oral THC administration on the associative striatum, informed by previous research showing that glutamate levels in this striatal subdivision are elevated in first-episode psychosis and decrease after clinically effective antipsychotic

treatment (32, 33). This is in keeping with findings from dopamine imaging research whereby the associative striatum is implicated over other functional striatal subdivisions in the pathophysiology of psychosis (34). We further aimed to investigate if changes in glutamate following THC exposure were associated with the severity of psychotic symptoms induced by THC.

Methods

This study was approved by the UCL Research Ethics Committee (Reference 3325/002) and the study was conducted in accordance with the Declaration of Helsinki. All participants provided informed, written consent to take part in the study. Participants received a small honorarium to compensate for their time (£10 per hour).

Design

We used a within-subjects, randomised, double-blinded, crossover design. Participants attended the laboratory on two occasions, at least one week apart. On each visit they received either 15mg of oral THC or placebo. The order of administration was balanced and participants were randomly allocated to treatment order. The dose of oral THC was selected based on previous research (35) indicating it is well tolerated by participants with minimal cannabis use and can elicit state psychotic symptoms with the peak drug effect expected two hours post-administration.

Participants

We recruited twenty participants (10 males and 10 females) by public advertisement through flyers at university sites, electronic advertisement in websites and word of mouth. All participants had a screening interview to ascertain inclusion and exclusion criteria including past and current medical history, including psychiatric history, as well as drug use. In order to be eligible for the study participants were required to be healthy volunteers of a minimum age of 18 years old and a maximum of 35 years old. They were required to have a good level of English and to be able to give written informed consent. BMI was required to be within healthy range (18.5-24.9 kgm^{-2}) in order to minimise variation in drug absorption and elimination. All participants

were required to have at least one previous exposure to cannabis due to ethical concerns related to exposure to this drug.

The exclusion criteria for all participants were: current or past history of mood, psychotic, anxiety or substance use disorder assessed using the Structured Clinical Interview for DSM-IV (SCID) (36); family history of mental illness in first degree relatives; current use of psychotropic drugs; current use of cannabis more than once a week or cannabis dependency as assessed using the Cannabis Use Disorder Identification Test – Revised (CUDIT-R) (cut-off score of 15) (37); use of any other illicit drugs more than twice a month; alcohol dependency as assessed by the Alcohol Use Disorders Identification Test (AUDIT) (cut-off value of 12) (38); nicotine dependency as assessed by the Fagerström Test for Nicotine Dependence (cut-off value of 3) (39); liver dysfunction; pregnancy; any contraindications to MRI scans such as presence of non-removable ferromagnetic metals inside their body or claustrophobia. All participants were instructed to refrain from using cannabis for at least one week and alcohol for twenty-four hours prior to scanning. In addition, a urinary drug screen test (Cup Multi Screen Drug Test, Alere Toxicology, Abingdon, United Kingdom) was used to assess and exclude any current use of recreational drugs (including cannabis), as well as a carbon monoxide breath measure to assess recent tobacco smoking (Micro Smokerlyzer, Bedfont Scientific, Kent, United Kingdom) on both scanning days. All female participants underwent urinary pregnancy tests prior to participation to exclude pregnancy.

Drug administration

THC (Dronabinol) was obtained from THC Pharm (Frankfurt, Germany) and was formulated in 5mg capsules alongside matched placebo capsules. On each session, participants were given three capsules (either 15mg THC or placebo) for oral administration with water. Ten participants received placebo first and ten participants received placebo first.

Data acquisition

All participants were required to attend to both sessions at Hammersmith Hospital, London, starting at 9 am after fasting overnight. Scanning took place at the same time across all sessions to avoid diurnal variation in the Magnetic Resonance Spectroscopy measures. Participants underwent a series of questionnaires and behavioural tasks with the scanning session being performed at 11 am (Fig. 1). Testing sessions lasted an average of five and a half hours, ending at 14:30.

Figure 1. Testing sessions procedure. VAS: visual analogue scale; PSI: psychotomimetic states inventory.

Baseline measures

We obtained a detailed drug history from all participants using the Cannabis Experiences Questionnaire (CEQ) (40), lifetime drug history at the first session. The Beck Depression Inventory (41) was used to screen for depression (cut-off score of 21), and the Beck Anxiety Inventory (42)was used to screen for anxiety (cut-off score of 18) on the day of testing. The Wechsler Test of Adult Reading (WTAR) was used to assess intellectual functioning (43).

Subjective effects

Subjective effect rating scale. This Visual Analogue Scale measured "feel drug effect" (35). The scale was scored by participants from zero to ten to provide a measure of the severity of the symptom. Zero was anchored with "not at all" and ten was anchored as "extremely".

Psychotomimetic effects. We used the Psychotomimetic States Inventory (PSI) (44) to assess drug-induced psychotic experiences. This questionnaire consists of 48 items specifically designed to measure changes in psychotic symptoms induced by drugs such as cannabis or ketamine. The PSI has previously been shown to be sensitive to cannabis-induced psychotic effects (44) and has better test-retest reliability than the Clinician Administered Dissociative States Scale (45).

Pharmacokinetics. Blood samples were taken to determine cannabinoid concentrations (THC and metabolites OH-THC and THC-COOH) 150 minutes post drug administration alongside VAS_2 and the PSI. Blood samples were centrifuged, and

plasma was frozen at -80 °C. Cannabinoid concentrations were determined using Gas chromatography coupled with mass spectroscopy (GC/MS).

Magnetic Resonance Spectroscopy. All participants underwent MRI brain scans performed on a 3T Siemens MRI scanner at the Robert Steiner MRI Unit, Hammersmith Hospital, London, UK. An initial localizer scan was followed by acquisition of a whole-brain 3D Magnetization Prepared Rapid Acquisition GRE (3D-MPRAGE) scan (TR: 2300 ms, TE: 2.28 ms, flip angle: 9°, slice thickness: 1.00 mm, 0.9 mm x 0.9 mm in-plane resolution, axial orientation, 64 channels receive- only head coil). The region of interest was carefully positioned using an axial and coronal slice for localisation as previously reported (33) (Figure 2). PRESS (Point RESolved Spectroscopy) data were then acquired for analysis from the left associative striatum. PRESS data were obtained (TE 30ms, TR 3000ms, 96 acquisitions), with chemically-selective automatic water-suppression CHESS (Chemical Shift Selective Suppression), with a water suppression bandwidth of 50Hz and shimming. Siemen's automatic 'Brain' was used which has been optimised for brain spectroscopy. This used automatic higher order shim for all subjects and if this did not produce adequate homogeneity (FWHM of <20Hz) then we performed a manual first-order linear shim. Additional spectra were acquired without water suppression (TE 30ms, TR 3000ms, 6 acquisitions) for subsequent eddy current correction. Using the 3D MPRAGE as a reference, the associative striatum voxel (sized 20 mm x 20 mm x 20 mm) was positioned 3 mm dorsal to the anterior commissure to include the maximum amount of gray matter, based on a previous study in first-episode psychosis (33).

We analysed PRESS spectra (Fig. 3) using LC Model version 6.3-1L. The standard basis set of 16 metabolites (L-alanine, aspartate, creatine, phosphocreatine, GABA, glucose, glutamine, glutamate, glycerophosphocholine, glycine, myoinositol, L-lactate, N-acetyl aspartate, N-acetylaspartyglutamate, phosphocholine, taurine), included with LC Model was used. The basis set was experimentally acquired with the same field strength (3T), localisation sequence (PRESS) and echo time (30 ms) as the *in vivo* spectra. The spectra were required to have a signal-to-noise ratio (SNR) > 10 and a Cramér–Rao lower bound (CRLB) values < 20% per metabolite (Provencher, 2014). The CRLB is a reliability indicator as it is an estimated standard deviation of the estimated concentration (46). CRLB %SD values were taken from the LC model output. As the PRESS acquisition sequence is insensitive to GABA, we did not statistically analyse GABA levels (47).

Figure 2. Voxel placement in the left associative striatum

There are inherent difficulties in obtaining absolute concentrations of metabolites, as signal intensity is affected by a number of additional variables [36] (48). In the present study, relative measurements of glutamate were achieved by measuring metabolite signal intensity ratios with respect to creatine.

Statistical Analysis

We used IBM Statistical Package for Social Sciences (SPSS) version 24 to analyse all behavioural and imaging data. All tests were two-tailed. Two-way repeated measures ANOVA models were used for all data collected on the two experimental sessions, including within-subject factors of Drug (THC, Placebo) and Time (e.g. T0, T1, T2, T3) for the drug effect measures. We included additional factors where appropriate. We identified outliers by examination of studentized residuals for values greater than ±3. We winsorized these when appropriate. We assessed normality using Shapiro-Wilk's test of normality on the studentized residuals. We used Mauchly's test of sphericity and the Greenhouse-Geisser correction was applied where assumptions of sphericity were violated, with degrees of freedom rounded to the nearest integer. Post-hoc pairwise tests were Bonferroni-corrected locally within each ANOVA model. Where appropriate, we used additional one-way repeated measures ANOVA models to allow further interpretation of the data. We used paired-sample *t*-tests for comparing group mean metabolite levels. For the primary outcome analysis comparing glutamate levels in the associative striatum following THC versus placebo, frequentist statistical analysis was supplemented by a Bayesian analysis to enable a test of evidence to support the null hypothesis. The scaled Jeffreys-Zellner-Siow (JZS) Bayes Factor was

calculated using a scaled information prior of r=1 (49). A Bayes Factor of 3 of greater provides evidence to support the null hypothesis (49). We excluded metabolites with CRLB values > 20% from the analysis. We used Pearson's product-moment correlations to study the relationship between metabolite concentrations relative to creatine in the striatum and psychotomimetic scores. We assessed the presence of a linear relationship between the variables by visually inspecting a scatterplot. We used a Spearman's correlation when the assumption of normality was violated.

Results

Descriptive Data

The age range was 19-35 years and there was an equal number of participants of each sex (10 female, 10 male). No participants had a history of mood, psychotic, anxiety nor psychotropic drug use. Sample descriptive data are reported in table 1.

Twelve of the participants (60%) reported being current users of cannabis, of these the most frequent pattern of use was once weekly (n=4 participants), meaning that current cannabis users were occasional (once a week or less) users. No participants reporting using cannabis more than once a week. No users met DSM criteria for any drug use disorders.

Subjective effects

For the VAS measure of "feel drug effects", there was a trend interaction between drug and time ($F_{2,36}$= 3.169, p=.055, η_p^2=.157). This interaction was driven by higher mean value at time 2 (150 min after drug administration, t_{18}= -2.83, p=.011), and time 3 (240 minutes after drug administration, t_{18}= -2.968, p=.008) in the THC condition compared to placebo. Scores at time 1 (45 minutes after drug administration) did not differ between the THC and placebo conditions (t_{17}=.740, p=.470). The drug by time interaction was driven by higher feel drug scores on time 2 (t_{17}= -3.02, p=.008) versus time 1 on THC. There was also a main effect of time ($F_{2,36}$=3.300, p=.048, η_p^2= .155), and a main effect of drug ($F_{1,18}$= 9.444, p=.007, η_p^2=.344).

Psychotomimetic State Inventory (PSI).

For PSI scores, there was an interaction between drug and time ($F_{2,37}$= 3.81, p=.045, η_p^2=.175). The interaction was driven by higher scores after drug administration in the THC condition compared to placebo. This was seen both for the PSI_1 150 minutes after drug administration (t_{18}= 2.537, p= .021) and PSI_2 240 minutes after drug administration (t_{18}= 3.027, p= .007); while the scores for PSI_0 (before drug administration) did not differ between the THC and placebo conditions (t_{18}= 1.163, p= .260). The interaction between drug and time reflected an increase in PSI values from PSI_0 to PSI_1 (t_{18}= -2.793, p= .012) in the THC condition. Increased values were still maintained at PSI_2 in comparison to PSI_0 in the THC condition (t_{18}= -2.396, p= .028). In contrast, PSI values did not increase from PSI_0 to PSI_1 during the placebo condition (t_{18}= -1.003, p= .329). There was also a main effect of drug ($F_{1,18}$=9.557 p=.006, η_p^2= .347) and a main effect of time ($F_{1,25}$= 6.666, p=.009, η_p^2= .270).

Pharmacokinetics measures

The mean concentration of THC in plasma (ng/ml) 150 minutes after THC administration was 2.27 (SD = 2.06). The mean concentration of metabolites in plasma (ng/ml) 150 minutes after administration was 7.02 for THC-OH (SD = 6.20), and 64.09 for THC-COOH (SD = 48.35).

Proton Magnetic Resonance Spectroscopy

Data quality. Example spectra are provided in figure 3. Striatal spectra from four participants were excluded due to CRLB values > 20% and/or SNR values < 10 in relation to the concentration of glutamate. In addition, striatal spectra from two participants were excluded due to poor voxel location.

Figure 3 - Example PRESS 1H-MRS spectra from the left dorsal striatum (LC Model output). Raw data is shown in black and fitted data is shown in red. The metabolite signals assignments displayed are based on Prescot *et al.* 2011 (50). NAA= N-acetylaspartate; Glu= glutamate; Gln= glutamine; Cre= creatine, mI= myo-inositol

Metabolite concentration differences in the associative striatum between THC and placebo conditions.

There was no significant effect of drug order. Analysis of the primary ^{1}H-MRS measure of Glx/Cre in the associative striatum did not provide evidence for a difference following THC administration compared to placebo (t_{df}= .565$_{13}$, p=.582, Cohen's d=0.39). This was corroborated by a Bayesian analysis producing a scaled JZS Bayes Factor of 4.29, providing evidence to support a lack of effect of THC versus placebo on this measure. Data from further metabolites are available in the supplementary materials for which there was also no evidence for a difference between THC and placebo. There was no relationship between striatal Glx/Cre under either drug condition and previous cannabis exposure (*p=.433).*

Figure 4: Mean concentrations of glutamate plus glutamine relative to creatine (Glx/Cre) in the left associative striatum after THC or placebo administration. Error bars indicate mean and standard errors.

Striatal glutamate levels and psychotomimetic effects after THC administration.

There was no correlation between Glx/Cre measures in the striatum and PSI_0 values (r_s = -.024, p = .93), PSI_1 values (r_s = .206, p = .48) or PSI_2 values (r_s = -.069, p = .81) (figure 5).

Figure 5: The relationship between glutamate plus glutamine relative to creatine (Glx/Cre) in the left associative striatum and PSI scores 240 minutes after drug administration (PSI_2).

Discussion

To our knowledge, this is the first study investigating associative striatal glutamatergic function and its relationship to the psychotic effects of an acute oral THC challenge in human participants. We found that a single 15mg oral dose of THC increased psychotic symptoms. However, THC did not alter striatal glutamate levels, which was corroborated by a Bayesian analysis providing evidence to support a lack of THC effect compared to placebo. Additionally, there was no relationship between glutamate levels and the severity of THC-induced psychotic symptoms. These findings do not support our hypothesis that changes in striatal glutamate underlie THC-induced psychotic symptoms.

Our findings contrast with recent studies reporting that intravenous THC and vaporised THC-dominant cannabis caused increases in glutamate in the caudate head (28) and striatum (29), respectively. However, they are consistent with findings that vaporised THC-dominant cannabis did not increase glutamate in the striatum when delivered in three divided doses (29). In our study, Bayesian analysis provided evidence to support a lack of effect of oral THC on associative striatum glutamate levels. This analysis showed that the null hypothesis was over four times more likely than the experimental hypothesis given the data, indicating that the lack of effect was not attributable to low statistical power. Overall, the evidence suggests that the acute effects of THC on striatal glutamate are dependent on pharmacokinetic factors associated with the dose and route of administration. For example, the results of our study using oral THC are similar to those in a previous study administering vaporized

THC in three divided doses (29) which may better resemble the slower onset and longer duration of oral THC effects than a single dose administered by intravenous or vaporized administration. Our findings are also consistent with the other study which showed that when Glx levels were corrected by creatine instead of water, the difference in left striatum was no longer significant (28).

Importantly, we found evidence that THC can induce psychotic symptoms in the absence of detectable changes in associative striatum glutamate levels. This suggests that alternative mechanisms were responsible for the psychotogenic effects of THC in our study. People experiencing psychosis have dorsal striatal hyperglutamatergia (51) suggest that the mechanisms through which THC induces acute psychotic effects may differ from those seen in schizophrenia without cannabis use. Further work is therefore needed to understand the functional significance of these findings and investigate the complex relationships between THC-induced effects on glutamate, GABA and dopamine signalling.

Strengths and limitations

Major strengths of our study include the use of *in vivo* neurochemical imaging in humans alongside measures of psychotic symptoms and plasma THC levels using a within-subject design. The careful design of timed testing sessions reduces the potential for diurnal variations in ^{1}H-MRS data confounding our data. However, this study has several limitations. The plasma levels of THC in the present study are lower than those obtained in other studies using an inhalation route (52) and oral route (35). It is therefore possible that our findings are due to lower plasma levels secondary to first pass metabolism associated with oral THC. Furthermore, ^{1}H-MRS is not able to

measure compartmental shifts in glutamate, which poses challenges when translating findings from animal research. Due to data quality considerations, ^{1}H MRS data were excluded from six participants in this study. In addition, previous exposure to cannabis in the sample could have resulted in tolerance, affecting the changes of striatal glutamate measured. Finally, THC offers an experimental model of psychotic symptoms, but it may tap into different mechanisms from idiopathic schizophrenia.

Conclusion

In this study investigating the effects of oral THC on striatal glutamate levels in humans in vivo we have found that acute THC did not alter glutamate levels in the associative striatum compared to placebo. We also found no relationship between associative striatal glutamate levels and THC-induced psychotomimetic symptoms. Further work is needed to clarify the mechanisms underpinning THC-induced increases in psychotic symptoms.

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Disclosures

The authors declare no conflict of interest.

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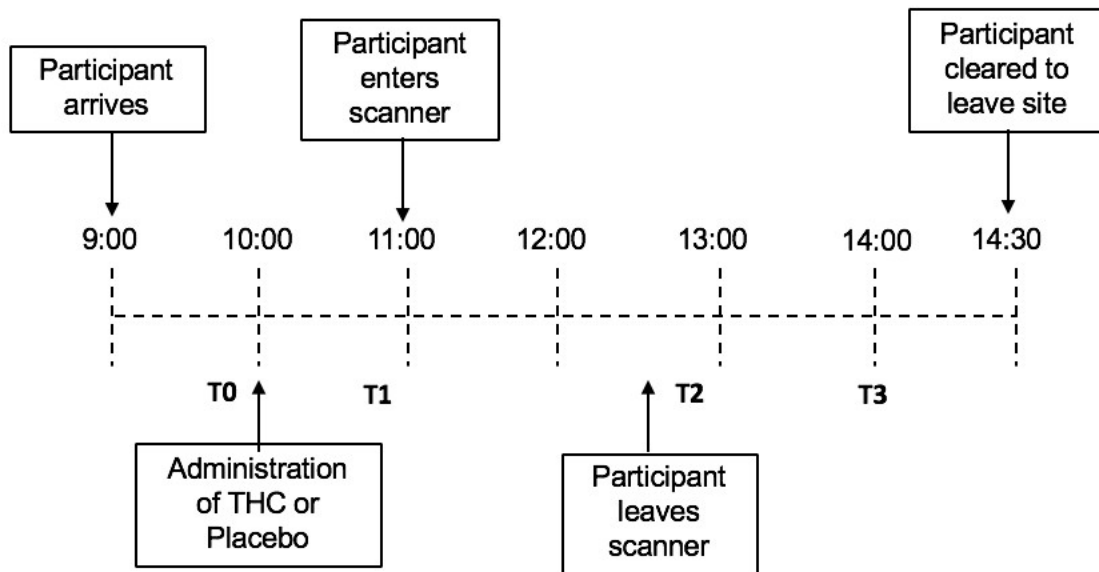
Table 1: Participant Details

Variable (*n*=20)	Statistic	
	Mean	SD
Age	23.5	3.94
WTAR	117	6.18
BDI	2.89	5.63
BAI	2.42	4.76
CUDIT-R	1.75	1.74
AUDIT	6.84	4.63
FTND	.10	.31

AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CUDIT-R = Cannabis Use Disorder Identification Test; FTND = Fagerström Test for Nicotine Dependence; WTAR = Wechsler Test of Adult Reading
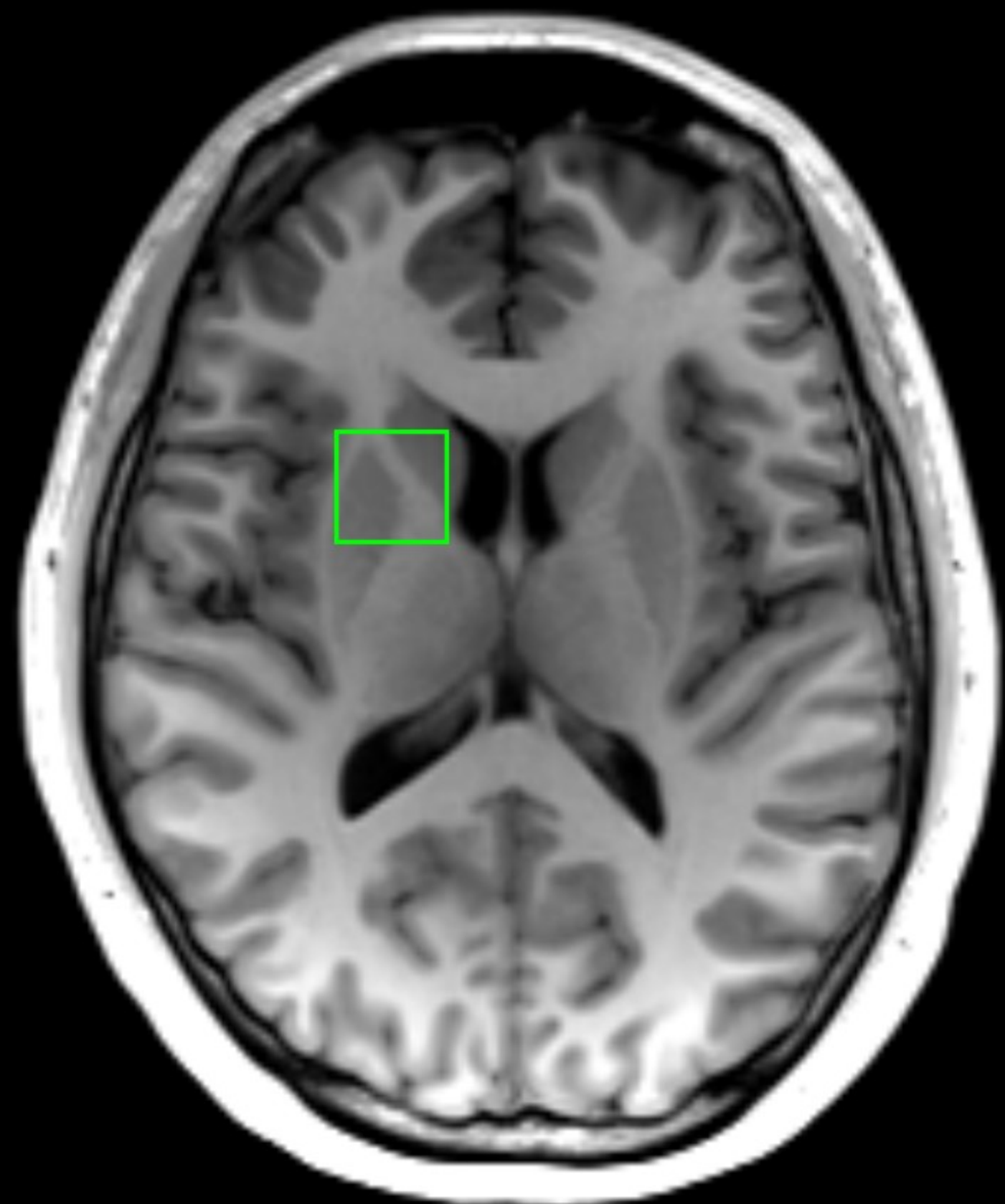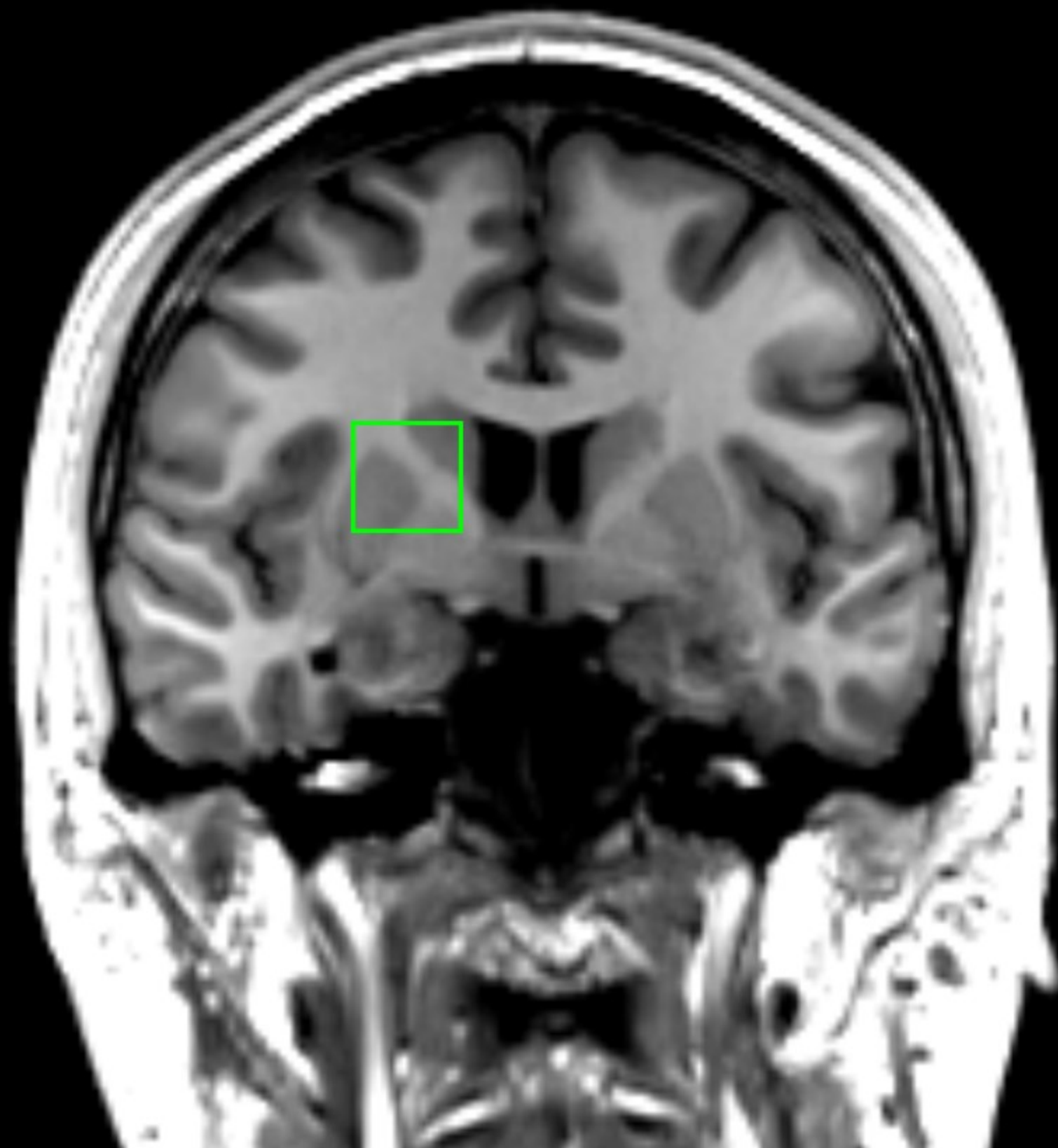
Brain Region	THC	Placebo	Statistics	
Parameter	*M* (SD)	*M* (SD)	*t*	*p*
Associative striatum				
Cramér-Rao lower bound				
Glu	5.93 (0.90)	6.39 (1.01)	1.49	0.16
Glu/Cre	1.02 (0.16)	1.01 (0.15)	1.60	0.13
GluCorr	6.59 (1.04)	7.12 (1.22)	1.36	0.20
Glx	7.50 (1.35)	7.88 (1.60)	0.63	0.53
Glx/Cre	1.30 (0.28)	1.35 (0.24)	0.57	0.58
GlxCorr	8.34 (1.60)	8.79 (1.87)	0.61	0.55
Full width at half maximum	0.07(0.04)	0.06 (0.01)	1.01	0.33
Signal to noise ratio	19.79 (6.40)	21.14 (5.56)	0.72	0.48
Grey Matter (%)	46.86 (15.17)	52.48 (13.88)	1.18	0.26
White Matter (%)	52.41 (13.52)	47.34 (13.90)	-1.00	0.34
Cerebrospinal Fluid (%)	0.73 (1.70)	0.17 (0.13)	-1.21	0.25

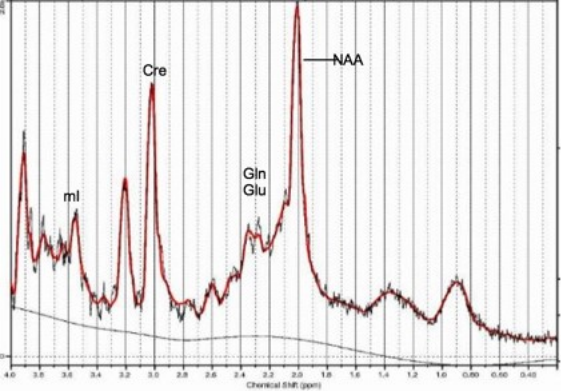**Table 2. Voxel segmentation and spectral quality**

Glu glutamate, Glu/Cre glutamete/creatine, GluCorr glutamate corrected, Glx

glutamate + glutamine, Glx/Cre glutamate + glutamine / creatine, GlxCorr
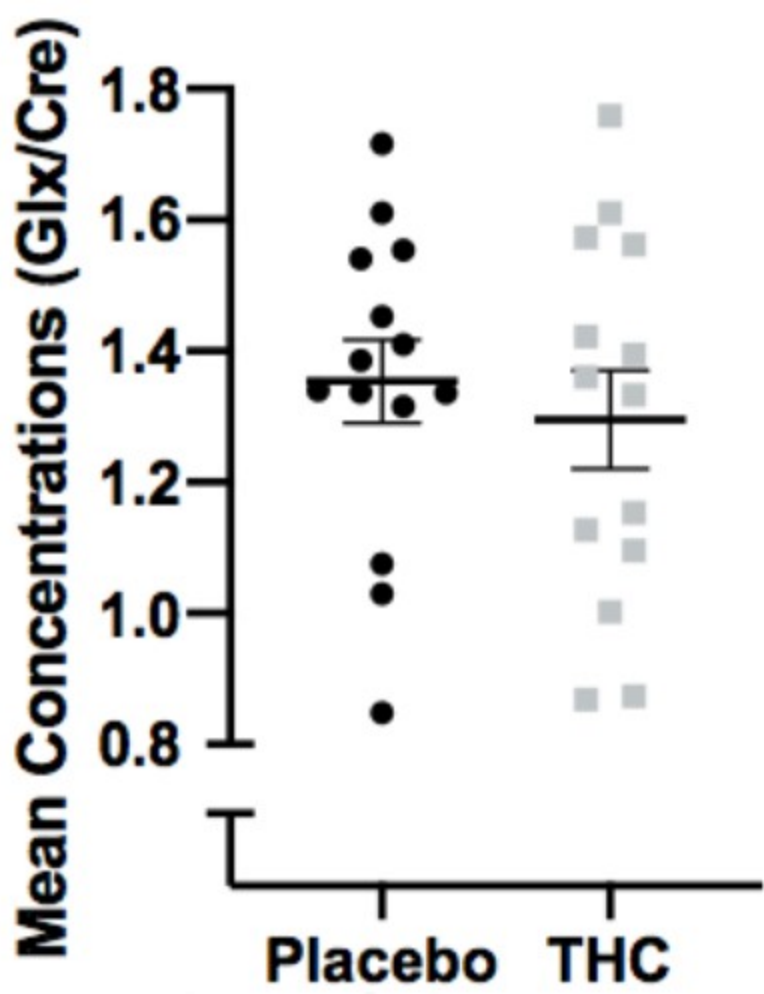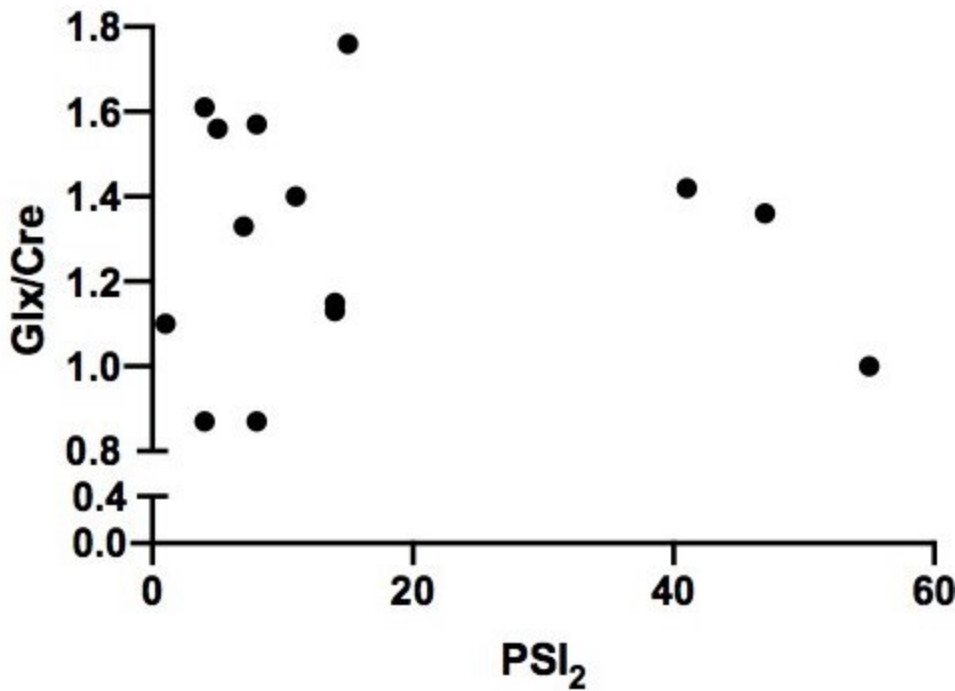
glutamate + glutamine corrected.

| Participant arrives | | Participant enters scanner | | | | Participant cleared to leave site |
| 9:00 | 10:00 | 11:00 | 12:00 | 13:00 | 14:00 | 14:30 |

T0   T1   T2   T3

Administration of THC or Placebo

Participant leaves scanner

Time	Minutes since drug administration	Measurements taken
T0	-30	PSI_0
T1	+45	VAS_1: Feel drug effect
T2	+150	VAS_2: Feel drug effect PSI_1
T3	+240	VAS_3: Feel drug effect PSI_2

Chemical Shift (ppm)

Supplementary material

Brain metabolite	THC M (SD)	Placebo M (SD)	Statistics t	P
NAA+NAAG	6.89 (1.05)	6.93 (0.79)	0.14	0.89
NAA+NAAG / Cre	1.18 (.018)	1.21 (0.17)	0.42	0.68
Cre	5.87 (0.93)	5.79 (0.71)	- 0.39	0.70
mI	3.31 (0.84)	3.45 (0.80)	0.55	0.59
mI / Cre	0.57 (0.12)	0.60 (0.15)	1.00	0.33
GPC+PCh	1.41 (0.20)	1.34 (0.26)	- 1.07	0.30
GPC+PCh / Cre	0.24 (0.02)	0.23 (0.03)	- 1.55	0.14

Supplementary Table 1. Metabolites level in the associative striatum

NAA+NAAG N-acetylaspartate + N-Acetylaspartylglutamic acid, Cre Creatine, mI Myo-inositol, GPC+PCh Choline