Task-independent acute effects of delta-9-tetrahydrocannabinol on human brain function and its relationship with cannabinoid receptor gene expression: a neuroimaging meta-regression analysis

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Abstract:

Background

The neurobiological mechanisms underlying the effects of delta-9-tetrahydrocannabinol (THC) remain unclear. Here, we examined the spatial acute effect of THC on human on regional brain activation or blood flow (hereafter called 'activation signal') in a 'core' network of brain regions that subserve a multitude of processes. We also investigated whether the neuromodulatory effects of THC are related to the local expression of its key molecular target, cannabinoid-type-1 (CB1R) but not type-2 (CB2R) receptor.

Methods

A systematic search was conducted of acute THC-challenge studies using fMRI, PET, and arterial spin labelling in accordance with established guidelines. Using pooled summary data from 372 participants, tested using a within-subject repeated measures design under experimental conditions, we investigated the effects of a single dose (6-42mg) of THC, compared to placebo, on brain signal.

Findings

As predicted, THC augmented the activation signal, relative to placebo, in the anterior cingulate, superior frontal cortices, middle temporal and middle and inferior occipital gyri, striatum, amygdala, thalamus, and cerebellum crus II and attenuated it in the middle temporal gyrus (spatially distinct from the cluster with THC-induced increase in activation signal), superior temporal gyrus, angular gyrus, precuneus, cuneus, inferior parietal lobule, and the cerebellum lobule IV/V. Using post-mortem gene expression data from an independent cohort from the Allen Human Brain atlas, we found a direct relationship between the magnitude of THC-induced brain signal change, indexed using pooled effect-size estimates, and CB1R gene expression, a proxy measure of CB1R protein distribution, but not CB2R expression. A dose-response relationship was observed with THC dose in certain brain regions.

Interpretation

These meta-analytic findings shed new light on the localisation of the effects of THC in the human brain, suggesting that THC has neuromodulatory effects in regions central to many cognitive tasks and processes, with greater effects in regions with higher levels of CB1R expression.

1.0 Introduction

The extract of *Cannabis sativa* contains more than 140 different phytocannabinoids(1). Delta-9-tetrahydrocannabinol (THC) is the most abundant and extensively investigated cannabinoid in human and preclinical studies. While there is growing interest in the therapeutic potential of THC(2–11), there is also considerable evidence of its psychotomimetic effects in healthy(12–17) and vulnerable people(18), as well as those with schizophrenia(19), and an association between THC content of recreational cannabis with a greater risk of onset(20,21) and relapse(22) of psychotic disorders. Thus, there is a pressing need to better understand the effects of THC on the human brain.

A substantial number of studies have investigated the effects of THC-rich cannabis or THC isolate using single photon emission tomography (SPECT)/ positron emission tomography (PET) to measure cerebral blood flow (rCBF)(23–31) at rest, and functional MRI (fMRI) to measure the blood oxygen level dependent haemodynamic signal during cognitive activation(32,33) to index brain function. However, conflicting results from these studies have not resulted in a clearer understanding as evident from two recent systematic reviews(33,34).

Further, the molecular underpinnings of the effects of THC on human brain function remain unclear. As the cannabinoid-type-1 receptor (CB1R), the main molecular target for THC is present throughout the brain(35,36), systemic administration of THC cannot selectively target receptors only in those brain regions involved in discrete cognitive tasks. Therefore, consistent with recent neuroimaging evidence that a core network of brain regions subserve a wide range of cognitive processes(37,38), it is likely that the diverse behavioural and neuroimaging effects of THC are, at least in part, mediated by effects on such a core network of brain regions. However, whether THC has neuromodulatory effects, that is, effects on regional brain activation or blood flow (hereafter, referred collectively as 'activation signal') that occur across diverse (as opposed to specific/unique) cognitive tasks and at rest on a common ‘core’ network of brain regions that subserve a multitude of processes, has never been tested.

Therefore, to answer these questions, here we first meta-analysed original studies that had examined the acute effects of THC, relative to placebo, on brain function in humans using PET, SPECT, fMRI, and arterial spin labelling (ASL), with a view to investigate which brain regions are modulated acutely by a single dose of THC in humans. We hypothesised that a single dose of THC will modulate the function of a distributed set of brain regions that are engaged across a range of cognitive tasks in line with previous literature(37,38). Specifically, we predicted THC effects on dorsal attention (superior parietal lobule extending to the intraparietal sulcus, middle temporal complex and frontal eye fields), frontoparietal (lateral prefrontal cortex, temporoparietal junction, inferior parietal lobule and anterior cingulate cortex) and visual (striate and extrastriate cortex) networks as well as on the amygdala, striatum, thalamus and lateral cerebellum. Next, we used gene expression data from the Allen Human Brain atlas(39,40), to investigate whether the effect of THC on the activation signal across different brain regions, as quantified using a meta-analytic approach, was directly associated with regional CB1R(41) and CB2R(42) gene expression. Previous studies have linked gene expression levels in the human brain with anatomical(43) and functional(44,45) indices measured using neuroimaging techniques. In accordance with current understanding about the molecular targets of THC(46) we hypothesised that the pooled estimate of the effect of THC on the activation signal across different brain regions will be directly associated with CB1R but not CB2R gene expression in these brain regions.

2.0 Methods

The protocol for the meta-analytic synthesis was registered in PROSPERO (CRD42019145453) and we followed recommendations for neuroimaging meta-analyses(47). A detailed description of the methods are reported in Supplementary Methods.

2.1 Search Strategy

A systematic search of published human literature was conducted within Ovid MEDLINE, Embase, Global Health, and PsychINFO databases in accordance with the Cochrane Handbook(48) and MOOSE guidelines(49). Search terms are detailed in Supplementary Methods.

2.2 Eligibility Criteria

Studies were included if they (i) assessed the effect of THC on brain function using an acute drug challenge paradigm in humans, (ii) used fMRI, PET, SPECT or arterial spin labelling (ASL) to measure brain function, (iii) conducted whole-brain analysis (thus excluding small volume correction and region of interest analyses), (iv) applied consistent statistical thresholding across brain regions, and (v) published in a peer-reviewed journal. Additional details are reported in Supplementary Methods.

2.3 Data Extraction

For all articles that met the inclusion criteria, authors or corresponding authors were contacted by email with a request for providing whole brain statistical maps. Some studies used multiple task contrasts, therefore, combined maps with reduced variance were calculated to avoid dependent data in the analyses(50). Where maps were unavailable, whole-brain coordinates with their t-statistic were manually extracted from the published article for the conditions of interest (THC<PLB and THC>PLB). See Supplementary Methods for further details.

2.4 Data analysis

Voxel-wise meta-analyses of regional brain differences were conducted using the anisotropic effect-size version of the Seed-based Mapping (AES-SDM 5.15) software package (https://www.sdmproject.com/)(51,52). For studies for which we could not obtain the map, AES-SDM uses an anisotropic non-normalized Gaussian kernel to recreate an effect-size map and an effect-size variance map for the contrast between THC and placebo from peak coordinates and effect sizes for each individual fMRI study. Once contrasts were obtained for all studies, a mean map was created by performing a voxel-wise calculation of the random-effects mean of the study maps (measured as Hedge's g), weighted by sample size and variance of each study and between-study heterogeneity. Statistical significance was determined using standard randomisation tests(53). For details on Q_H statistics, Egger's test, and jack-knife leave-one-out sensitivity analysis see Supplementary Methods.

2.5 Meta regression analysis: Dose

A multiple meta-regression analysis was carried out using approaches described previously(54) using a significance threshold of $P< .0005$(51,54). We set out to investigate the association between THC dose and pooled effect-size (Hedge's g). To control for the confounding effect of the route of THC administration, we also entered the route of THC delivery (inhalation via respiratory tract versus oral capsule) as categorical predictor. Cook's distance(55) was calculated to identify any studies that were a potential outlier.

2.6 Whole brain correlation with CNR1 and CNR2 gene expression

Detailed description of the analytic pipeline including processing of genetic data from the Allen Human Brain Atlas is reported in Supplementary Methods. In summary, from the neuroimaging data synthesis, using SDM, we extracted the effect-size estimates of the voxel of the centroid for each of the 78 regions of the Desikan-Killiany(56) atlas from our main analysis. Then, we carried out linear regression analysis with the SDM effect-size estimates for brain regions in the Desikan-Killiany(56) atlas as the dependent variable and the corresponding average CNR1 and CNR2 gene expression values derived from the Allen Human Brain Atlas as the predictor variables using Python 3.7.9(57). We followed the recommendations put forward by Arnatkevičiūtė and colleagues with regard to processing mRNA microarray expression data from the Allen Human Brain Atlas(39) and used the package *abagen*(58) to conduct a reproducible workflow in processing and preparing the data.

2.7 Subgroup analysis

To better understand sources of heterogeneity, we conducted subgroup analysis. When three or more contrasts were available, we looked at more homogeneous groups based on type of imaging activation paradigm, as well as methodological variables that may have influenced the results focusing on fMRI based studies, those that administered THC isolate, and scanner magnetic field strength.

3.0 Results

3.1 Included Studies

A final set of 22 manuscripts met the study inclusion criteria (Table 1)(12,15,67–76,59,77,78,60–66). Of these manuscripts, 17 used fMRI(12,15,72–76,59–62,67–70), 4 PET(63–66), and 1 used arterial spin labelling(71). Figure 1 shows the PRISMA flowchart(79). Twenty-three separate contrasts, derived from 22 manuscripts, were included in the analysis due to some studies reporting multiple contrasts (see Supplementary Methods). Therefore, the final sample size of participants, including those with multiple contrasts, was 372 (372 under THC condition vs 370 under placebo condition). Our key analysis included 16 studies that administered THC isolate(12,15,72,73,75–78,59–62,67,69–71) and 6 that administered THC-rich cannabis(63–66,68,74).

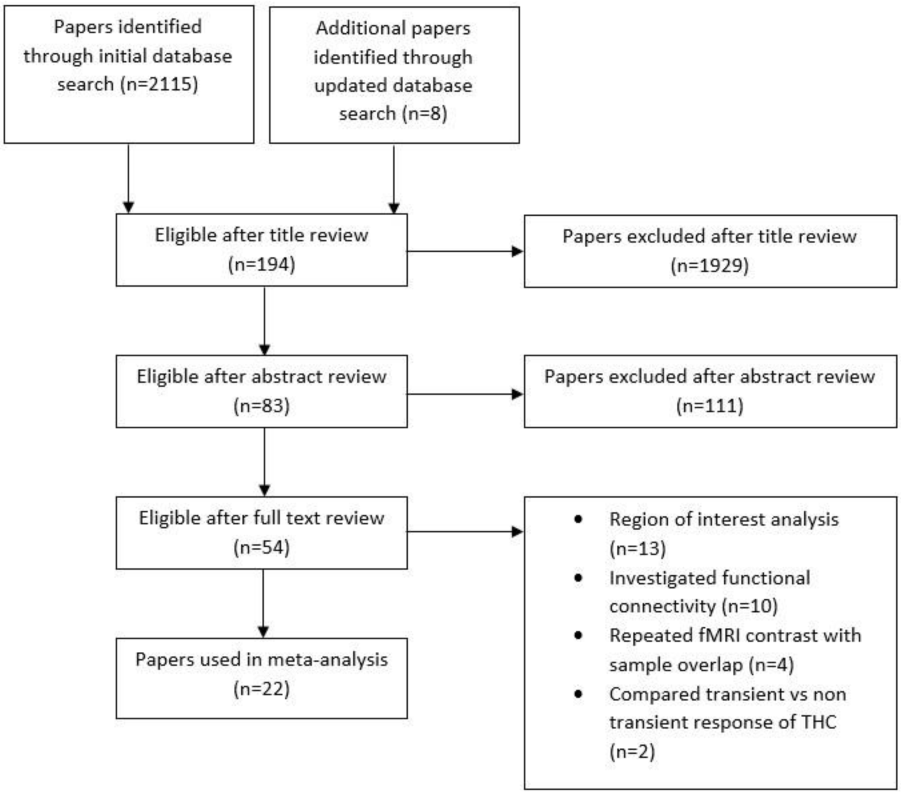

Figure 1. PRISMA flowchart of search strategy for meta-analysis

Studies included cognitive paradigms that engaged reward(61,67,68), memory(15,69,77), emotion(62,70,72), attentional salience(12,63,64,66,74,78) and sensory processing(59,60,75,76). One arterial spin labelling study did not use a cognitive task(71).

Table 1. Studies included in meta-analysis. T=Tesla, INH=inhalation, OC= oral capsule, VPA= verbal paired associates task, MIDT= monetary incentive delay task, NA= not available, DB= double blind, PC= placebo controlled, R= randomised, WS= within subject, ‘= minute, A= alcohol, C= cannabis, D= illicit drug, T= tobacco, NAD= nicotine addiction disorder

Author	***Route***	***Mode***	***Paradigm***	***Baseline condition***	***Scanner strength (T)***	***Design***	***Sample size***	***Mean age (SD)***	***Time to scanning***	***Pre-scan screens***	***Dose***	***THC plasma level (SD) ng/ml***
Battistella(74)	INH	fMRI	Visuo-motor tacking	Visually track a target	1.5	DB, PC, R, WS	31	24.1 (3)	45'	A,C,D,T	42mg	9.3
Bhattacharyya(12)	OC	fMRI	Attentional processing	Oddball vs standard	1.5	DB, PC, R, WS	15	26.7 (5.7)	1-2h	A,C,D	10 mg	1h= 3.9 (7.3) 2h=5.1 (5.6)
Bhattacharyya(15)	OC	fMRI	VPA	Presented with pairs of words- state if font is the same	1.5	DB, PC, R, WS	15	26.7 (5.7)	1-2h	A,C,D	10 mg	1h= 3.9 (7.3) 2h=5.1 (5.6)
Bhattacharyya(72)	OC	[11C]MePPEP PET & fMRI	Fear processing	Neutral expression	1.5	DB, PC, R, WS	14	23.8 (4.5)	1-2h	A,C,D,T	10mg	NA
Bhattacharyya(73)	OC	fMRI	Go/No-Go	Oddball vs standard	1.5	DB, PC, R, WS	36	26.0 (5.5)	1-2h	A,C,D,T	10mg	1h= 3.9 (7.3) 2h=5.1 (5.6)
Bossong(69)	INH	fMRI	Sternberg Item Recognition	Load 1 of memory paradigm	3	DB, PC, R, WS	13	21.6 (2.1)	5'	A,C,D,T	6mg	70 (40.6)

Bossong(70)	INH	fMRI	Happy/Fearful Face Matching	Sensorimotor control condition (geometric shape matching)	3	DB, PC, R, WS	14	21.5 (2.5)	5'	A,C,D,T	6mg	82.3 (45.9)
Bossong(71)	INH	ASL	Resting	NA	3	DB, PC, R, WS	33	22.6 (4.3)	5'	A,C,D,T	6mg	84.9 (43.5)
Bossong(77)	INH	fMRI	Associative memory	Pictural cue	3	DB, PC, R, WS	13	21.6 (2.1)	5’	A,C,T	6mg	58.1 (31.3)
Bossong(78)	INH	fMRI	Continuous performance task	Watch stimuli	3	DB, PC, R, WS	20	22.9 (4.9)	5’	A,C,T	6mg	78.4627.0 ng/ml
Freeman(68)	INH	fMRI	Musical Reward	Scrambled sound	1.5	DB, PC, R, WS	16	26.2 (7.3)	5'	C,D	8mg	NA
Jansma(67)	INH	fMRI	MIDT	No monetary reward	3	DB, PC, R, WS	10	25.6 (2.1)	5'	A,C,T	6mg	82.8 HC 82.8 NAD
Lee(75)	OC	fMRI	Capsaicin induced pain	No pain	3	DB, PC, R, WS	12	24- 34	3h	A, C.D,T	15mg	3.5h= 1-1.2 (estimated)

O'Leary(65)	INH	H2150 PET	Self-paced counting task	NA	1.5	DB, PC, NR, WS	12	21.7 (1.4)	10-15'	C	20mg	Occasional=17.6 (8.7) Chronic=35.8 (19.7)
O'Leary(64)	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, NR, WS	12	30.5 (8.6)	10-15'	C,D	20mg	2.6 (3.6)-37.1 (27.1)
O'Leary(66)	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, NR, WS	12	23.5 (4.3)	10-15'	C,D	20mg	10.3 (2.5)-107.2 (59.7)
O'Leary(63)	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, R, WS	5	26.2 (8)	10-15'	C	20mg	NA
Rabinak(62)	OC	fMRI	Emotional processing task	Neutral expression	3	DB, PC, R, WS	14	20.8 (2.6)	2h	A,C,D	7.5mg	NA
van Hell(61)	INH	fMRI	MIDT	No monetary reward	3	DB, PC, R, WS	11	21.7 (2.3)	5'	A,C,T	6mg	60.1 (33.7)
Walter(76)	OC	fMRI	Visual DSDT	Control visual cue	3	DB, PC, R, WS	13	25.5 (2.3)	2h	A, C.D,T	20mg	NA

Walter(76)	OC	fMRI	Nociceptive pain DSDT	Different pain intensity	3	DB, PC, R, WS	22	26.1 (2.9)	2h	A, C.D,T	20mg	NA
Walter(60)	OC	fMRI	Olfactory and pain response	Different gaseous stimuli	3	DB, PC, R, WS	15	26.6 (2.9)	2h	A,C,D,T	20mg	NA
Winton-Brown(59)	OC	fMRI	Auditory and visual stimulation	Independent of sensory load	1.5	DB, PC, R, WS	14	26.7 (5.7)	1-2h	A,C,D	10 mg	1h= 3.9 (7.3) 2h=5.1 (5.6)

3.2 Main meta-analysis results: Effects of THC vs placebo

There were 9 regions of significantly increased activation signal (Table 2, Figure 2) under THC compared with placebo. Seven regions showed a significant attenuation of activation signal under THC compared with placebo (Table 2, Figure 2).

Table 2. Main meta-analytic findings showing areas of increased and attenuated activation signal following THC, compared with placebo, obtained from the main multimodal meta-analysis

	MNI coordinate			***SDM-Z***	***P***	***Voxels***	***Region***	***Egger's Test P value***
	x	**y**	**z**					
THC>PLB	6	62	-4	3.172	<0.001	434	R medial orbital superior frontal gyrus (extending to R medial & orbital superior frontal gyrus, R anterior cingulate/ paracingulate gyri, R striatum, L medial orbital superior frontal gyrus)	0.044
	6	34	-12	2.631	0.001	196	R medial orbital superior frontal gyrus (extending to the L+R gyrus rectus, L+R anterior cingulate/ paracingulate gyri, L medial orbital superior frontal gyrus)	0.067
	48	-76	20	2.883	<0.001	166	R middle temporal gyrus (extending to R middle occipital gyrus, R middle temporal gyrus)	0.961
	38	-76	-48	2.411	0.001	152	R cerebellum crus II (extending to R lobule VIII/VIIB)	0.303
	32	-88	-8	2.451	<0.001	76	R inferior occipital gyrus (extending to R middle occipital gyrus)	0.720
	24	0	-16	2.042	0.002	47	R amygdala (extending to R temporal pole, superior temporal gyrus, R hippocampus)	0.069
	-12	-74	44	3.367	<0.001	37	L cerebellum lobule VIIB (extending to L lobule VIIB/ VIII)	0.654
	-24	-24	54	2.177	0.001	19	L precentral gyrus (adjacent to deep white matter)	0.688
	0	-20	-12	2.134	0.001	16	L thalamus	0.817
THC<PLB	-44	-12	8	-3.117	0.001	1118	L insula (extending to L Rolandic operculum, L temporal pole, L superior temporal gyrus, L Heschl gyrus, L postcentral gyrus, L supramarginal gyrus, L inferior frontal gyrus opercular part)	0.037
	48	-8	10	-2.429	<0.001	474	R Rolandic operculum (extending to R insula, R Heschl gyrus, R postcentral gyrus, R temporal pole, R superior temporal gyrus, R supramarginal gyrus)	0.044
	4	-72	28	-2.48	0.001	204	R cuneus cortex (extending to R precuneus, L precuneus, L cuneus cortex)	0.238
	-56	0	20	-2.349	0.001	86	L precentral gyrus (extending to L inferior frontal gyrus, opercular part, L postcentral gyrus, L Rolandic operculum)	0.971
	64	-16	-4	-2.323	0.001	65	R superior temporal gyrus (extending to R middle temporal gyrus)	0.135
	-56	60	40	-2.273	0.002	38	L angular gyrus (extending to L inferior parietal gyri, excluding supamarginal gyri)	0.902
	4	-60	-8	-2.333	0.001	26	Cerebellum lobule IV/V	0.318

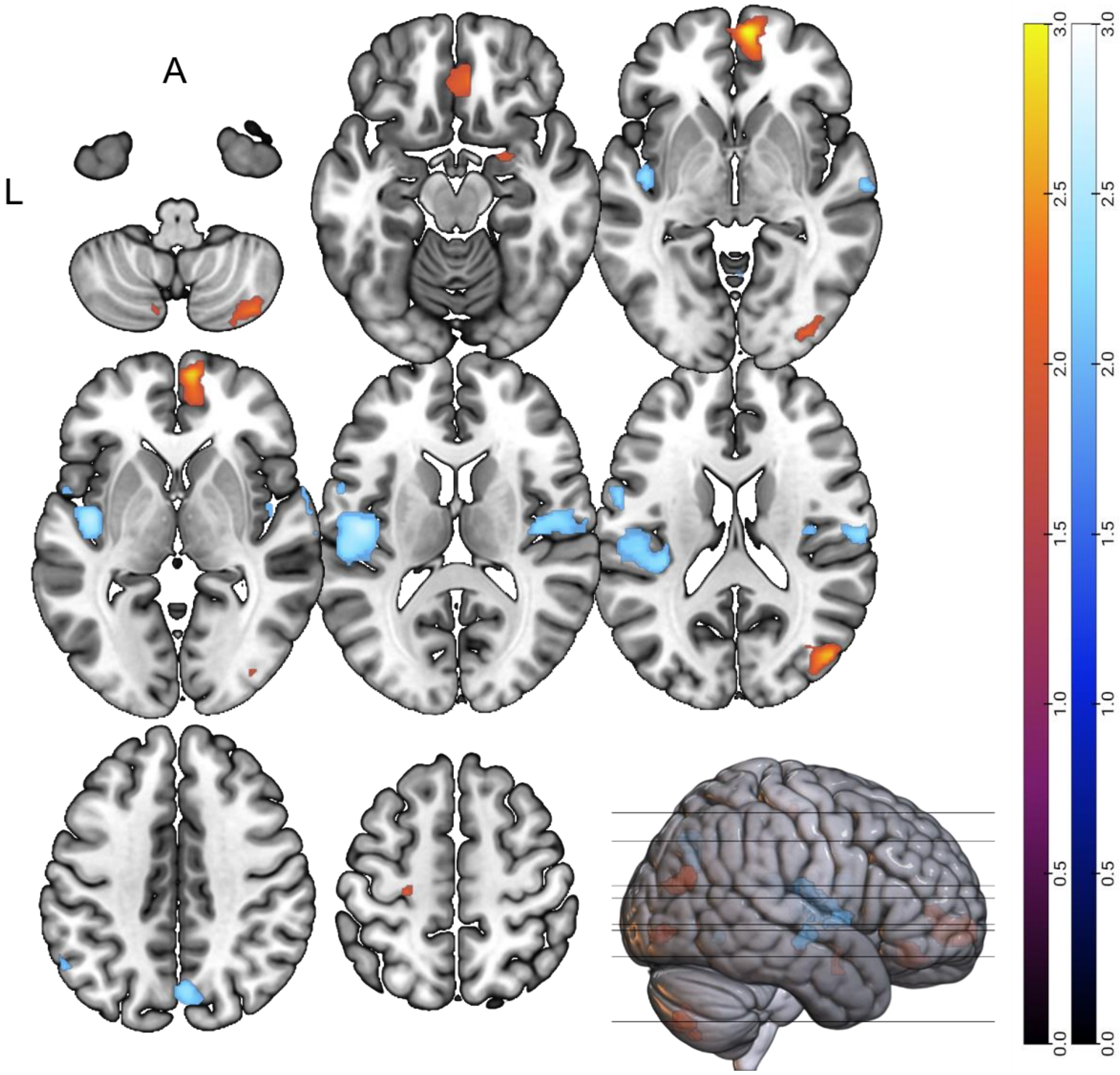

Figure 2. Differences in brain signal following THC compared with placebo obtained from main multimodal meta-analysis. Orange= areas of increased activation signal (THC>placebo). Blue= areas of attenuated activation signal (THC<placebo). Left side of the brain sections indicates the left side of the brain; A= anterior.

3.3 Sensitivity, Heterogeneity, and Publication Bias

Jack-knife sensitivity analysis showed that out of a total of 368 clusters, 87% survived following repeat analyses leaving one study out at a time (Supplementary Table 1). Funnel plots were created and examined for each cluster. Egger's tests were performed to look for publication bias (see Table 2 and Supplementary Results). Visual inspection of overlap of meta-analytic activation maps and heterogeneity maps indicated no areas within our main analysis were significantly influenced by heterogeneity.

Different imaging modalities may be a source of heterogeneity. To ensure these factors minimally influenced our core findings, we conducted subgroup analysis of fMRI studies (Supplementary Table 7). There was significant overlap between the findings of our main results and those from the fMRI subgroup alone (Supplementary Figure 25).

Results of subgroup analyses based on cognitive paradigm and methodological variables are reported in Supplementary Tables 2-9.

3.4 Meta-regression analysis: Dose

Meta-regression analysis identified brain regions where there was a significant correlation between the pooled effect-size estimates of THC effect on activation signal and THC dose (6mg to 42mg) (Table 3, Figure 3).

Table 3. Meta-regression results showing regions where THC dose was associated with modulation of brain signal under THC compared with the placebo condition

	MNI coordinate			***SDM-Z***	***P***	***Voxels***	***Region***
	x	y	z				
Positive correlation	4	38	-4	5.044	<0.001	1592	R anterior cingulate/ paracingulate gyri (extending to L+R medial orbital and medial superior frontal gyrus, L anterior cingulate/ paracingulate gyri, L+R gyrus rectus, L+R olfactory cortex)
	4	-32	60	3.132	<0.001	214	R paracingulate lobule (extending to R+L paracentral lobule, R+L precuneus, R supplementary motor area, L median cingulate, R median cingulate)
	44	-10	60	3.042	0.001	36	R precentral gyrus
Negative correlation	-8	-18	12	-2.837	<0.001	125	L thalamus (extending to L caudate nucleus)
	12	2	70	-2.890	<0.001	93	R supplementary motor area (extending to R dorsolateral superior frontal gyrus)
	-48	-54	0	-2.930	<0.001	65	L middle temporal gyrus (extending to L inferior temporal gyrus)
	14	-8	14	-2.828	<0.001	52	R thalamus (extending to R caudate nucleus)
	-48	-66	0	-2.552	<0.001	29	L middle temporal gyrus (extending to L inferior and middle occipital gyrus)
	-54	22	8	-2.438	0.001	26	R inferior frontal gyrus, triangular part (extending to opercular part)

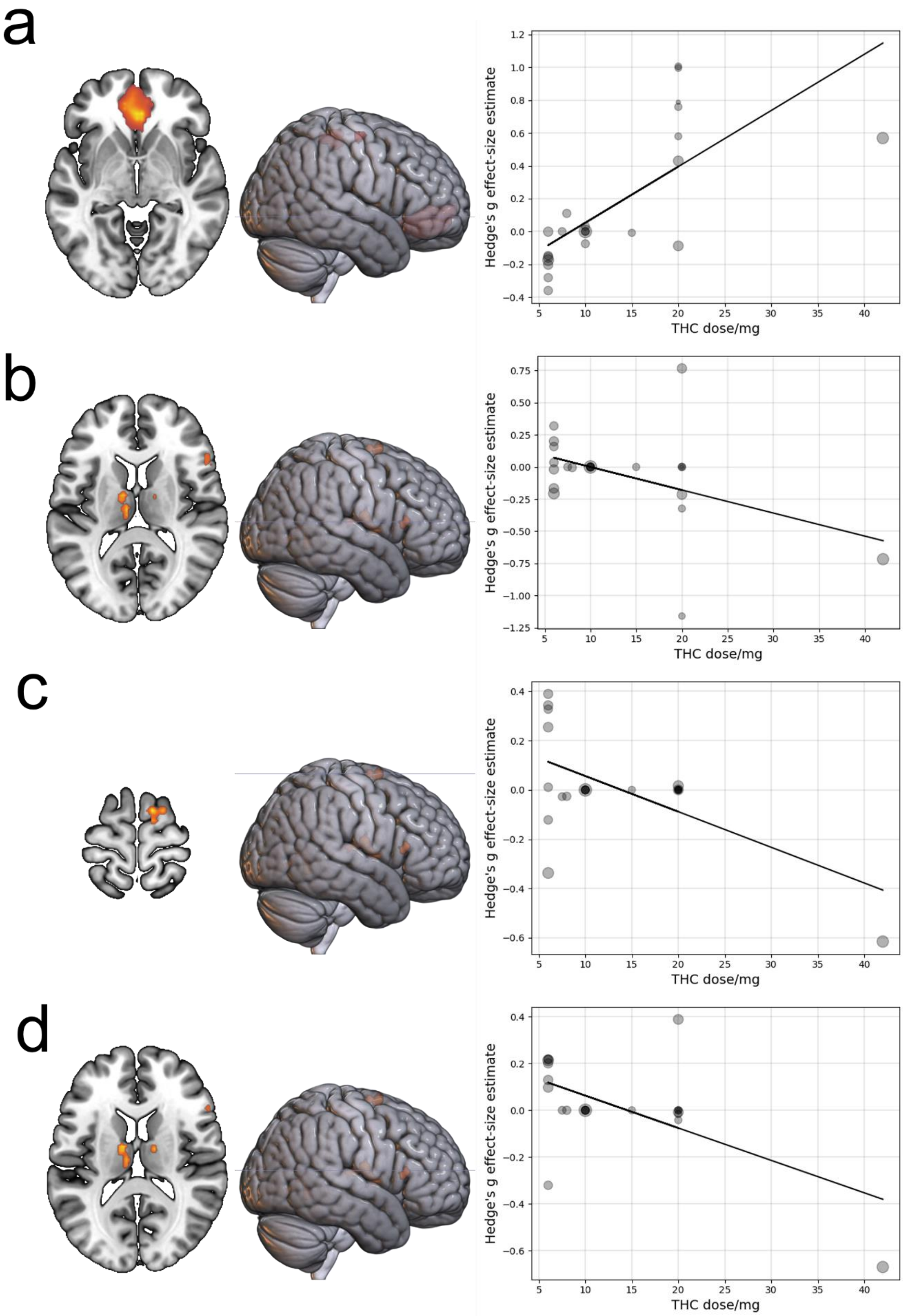

Figure 3. Meta-regression analysis showing relationship between THC dose (mg) and Hedge's g effect-size estimate of brain signal modulation by THC compared to placebo. Bubble size= inverse of effect-size variance. Bubble intensity= overlap of contrasts.

a) Effect-size estimates from right anterior cingulate/ paracingulate cluster
b) Effect-size estimates from left thalamus cluster
c) Effect-size estimates from right supplementary motor area cluster
d) Effect-size estimates from right thalamus cluster

Cook’s distance(55) estimate identified the study by Battistella et al.,(74) as being a potential outlier (further discussed in Supplementary Discussion 4).

3.5 Whole brain correlation with CNR1 and CNR2 gene expression

Cortical and sub-cortical spatial expression of CNR1, CNR2 expression, and Hedge’s g effect size estimate of brain regions parcellated across the Desikan-Killiany(56) atlas are displayed in Figure 4. Multiple regression analysis indicated that there was a significant direct relationship between Hedge’s g effect-size estimate and CNR1 (t=2.415, P=0.018, coefficient= 0.122, 95%CI= 0.021- 0.223, Figure 5) but not CNR2 gene expression (t=-0.036, P=0.971, coefficient= -0.002, 95%CI= -0.131- 0.126) across the 78 brain regions of the atlas.

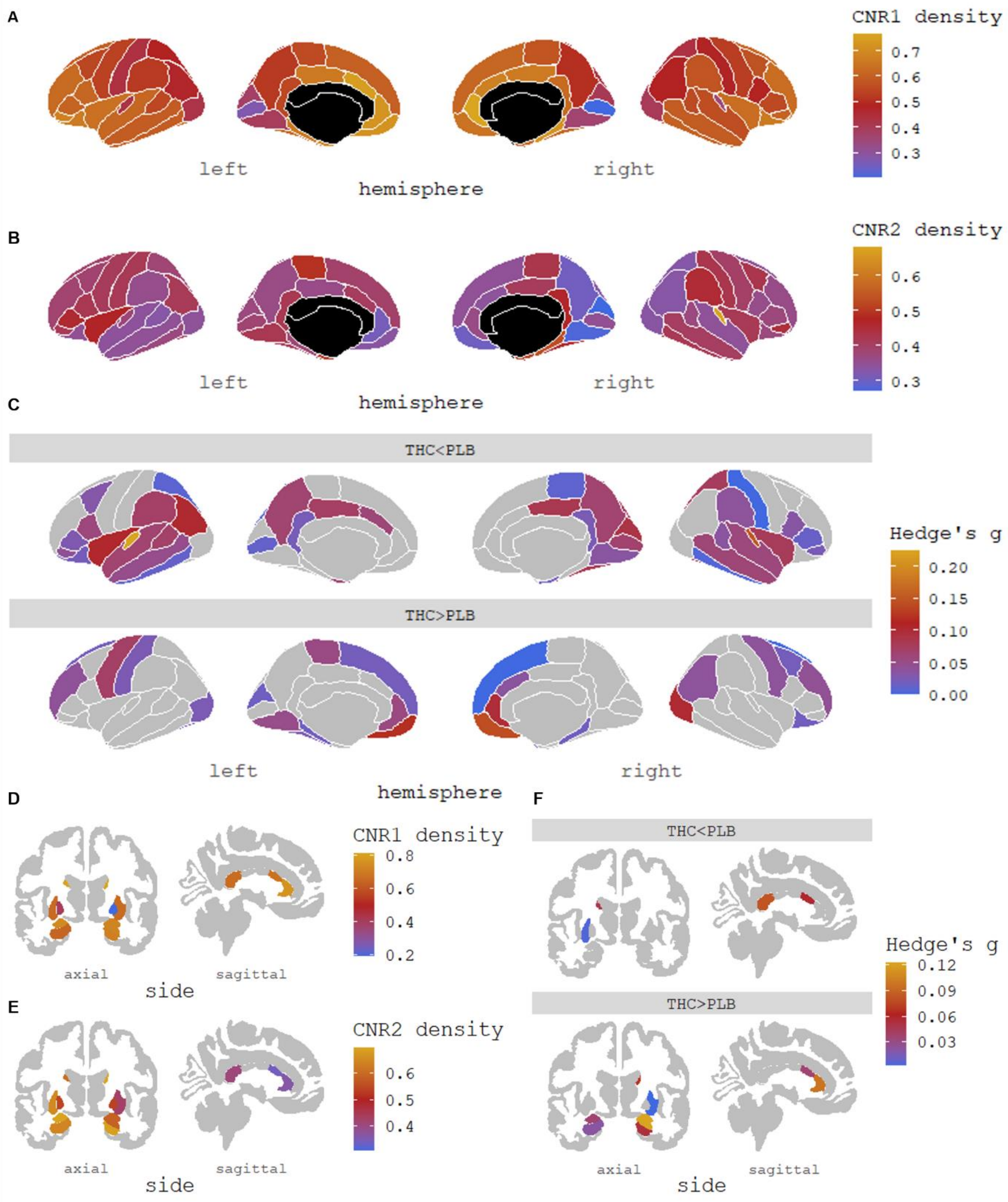

Figure 4. Cortical spatial gene expression of (A) CNR1 , (B) CNR2 , and (C) Hedge's g effect size estimate derived from the main meta-analytic findings displaying regions of increased activation (THC>PLB), and attenuated activation (THC<PLB). Sub-cortical spatial distribution of (D) CNR1, (E) CNR2, and (F) Hedge's g effect size estimate derived from the main meta-analytic findings displaying regions of increased activation (THC>PLB), and attenuated activation (THC<PLB). Figures produced using ggseg(80) *in R studio*(81) *parcellated across 78 regions of the Desikan–Killiany brain atlas*(56)*. Hedge's g was extracted from the centroid of each brain parcel. Gene expression data was obtained from the Allen Human Brain Atlas*(82)*.*

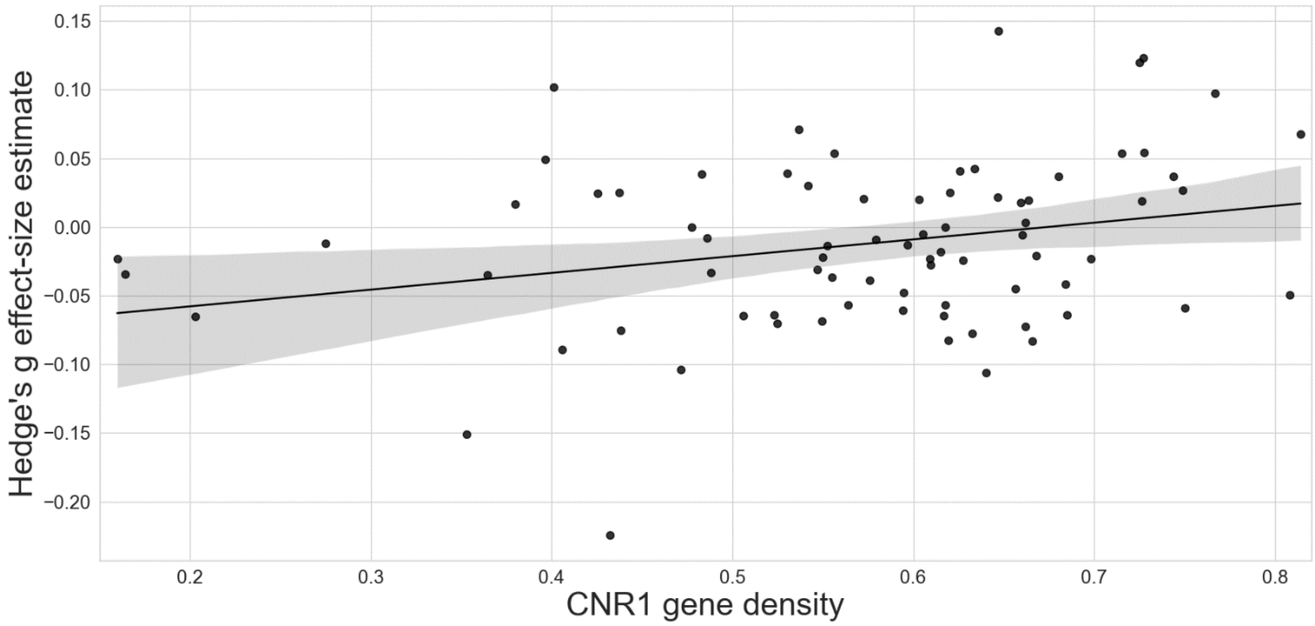

Figure 5. Scatterplot showing the relationship between CNR1 expression values and Hedge's g effect size estimate of THC effect compared with placebo across the brain (based on parcellation implemented in the Desikan Killiany atlas). P=0.018, t= 2.415, R^2= 0.073, coefficient= 0.122, 95%CI= 0.021- 0.223). Shaded band around the regression line indicates 95% confidence interval.

4.0 Discussion

In this meta-analytic synthesis, we examined the acute effect of THC isolate and THC-rich cannabis (hereafter referred to as THC) on human brain activation signal measured using different neuroimaging modalities including fMRI(12,15,72–76,59–62,67–70), PET(63–66), and ASL(71). Using pooled summary data from 372 participants who were tested using a within-subject repeated measures design under experimental conditions acutely (5 minutes to 3 hours after administration) following a single dose of THC (ranging from 6 – 42 mg) or placebo administered orally or through inhalation, we tested whether a single dose of THC modulates the brain activation signal in a ‘core’ network of brain regions that subserve a multitude of processes. When combining data from all studies, we found that THC modulated the function of 16 brain regions. Within our predicted network of regions, THC augmented the activation signal relative to placebo in the anterior cingulate, superior frontal cortices, temporal pole, middle temporal and middle and inferior occipital gyri, striatum, amygdala, thalamus, and cerebellum crus II. There was also an attenuation of activation signal under the influence of THC in the temporal pole, middle temporal gyrus (spatially distinct from the cluster with THC-induced increase in activation signal), superior temporal gyrus, angular gyrus, precuneus, cuneus, inferior parietal lobule, and the cerebellum lobule IV/V. Further, we also found that THC augmented activation signal in regions that we had not predicted, including the paracingulate and precentral gyri (adjacent to deep white matter), gyrus rectus and the hippocampus. An attenuating effect of THC was also observed in other brain regions that we had not predicted in the insula, Rolandic operculum, Heschl’s gyrus, precentral (spatially distinct from increase in activation signal) and postcentral gyri (see Table 2 for coordinates).

Our second prediction was that the acute effect of THC on activation signal across different brain regions will be directly associated with pooled CNR1 but not CNR2 gene expression data from a set of 6 unrelated healthy volunteers (who did not take part in the neuroimaging studies reported here) in the same brain regions, as obtained from the Allen Human Brain atlas. As predicted, we found that there was a direct relationship between the effect of THC on brain activation signal with CNR1 gene expression, a proxy measure of CB1R distribution.

One of the main motivations for the present study and the analytic approach adopted here was to answer questions that previous individual studies in isolation could not address. Consistent with this objective, we identified that at the meta-analytic level, THC has effects on components of a common core network of brain regions, that has been described as a 'domain-general' core network that facilitates cross-task cognitive function(37). In their study, Shine et al. performed principal component analysis (PCA)(83) to identify an 'integrative core' network of brain regions engaged across seven diverse cognitive tasks(37) which spatially mapped onto dorsal attention, frontoparietal and visual networks as well as the striatum, thalamus, cerebellum and amygdala(37). The spatial overlap between the modulatory effects of THC that we report here and the regions within the domain-general core described by Shine and colleagues, which subserve a multitude of cognitive processes, might explain the diverse cognitive, behavioural, and neural effects of THC. Previous experimental work in cannabis users has shown that cannabis has wide-ranging effects on regional brain activation across numerous tasks(84), as well as effects on behavioural performance during those tasks(34). Please see Supplementary Discussion 1 for additional discussion regarding the effects of THC on activation signal in brain regions that were not part of the hypothesised core network, and results of analyses of cognitively homogenous subgroups of studies.

From a neurobiological perspective, effects on a common core network of brain regions makes sense: THC acts primarily via partial agonism of CB1R(36,46) which are ubiquitously distributed throughout the brain, with particularly high densities in cortex, amygdala, basal ganglia outflow tracts and cerebellum(35). THC does not selectively target CB1R only in those brain regions involved in a specific cognitive task, and instead has effects on receptors throughout the brain. In turn, THC affects the neurophysiology of these brain regions which subserve a multitude of cognitive and emotional processes. This was further demonstrated by our fMRI subgroup analysis (see Supplementary Results). We combined cognitive-specific effects from fMRI paradigms and intoxication-related effects from THC. Overlap in the brain substrates modulated by THC was observed across our main findings and the fMRI subgroup analyses. Shine and colleagues also demonstrated that the dynamic function of this integrative core is strongly influenced by the modulatory effect of neurotransmitters, and propose that any dysregulation in neurotransmitter systems, for example, in the context of neuropsychiatric disorders or as induced through pharmacological manipulation, could conceivably facilitate or impede neurotransmission through actions on this integrative core(37). In this regard, the endocannabinoid system itself may be an exemplary candidate, poised at the synapse as a critical mediator of neural homeostasis and signalling: endocannabinoids are released postsynaptically and via retrograde signalling, bind to presynaptic CB1 where they inhibit neurotransmitter release. The administration of exogenous cannabinoids such as THC may subvert this on-demand fine-tuning by indiscriminately binding CB1 receptors, and therefore may cause widespread alterations to synaptic signalling resulting in impairment of the function of the common core network which, in turn may explain the diverse acute and long-term behavioural and cognitive consequences of cannabis use(21,85,86).

Our second major finding was that the effect of THC on the pooled effect-size of regional brain signal was related to a proxy measure of regional CB1R density. The multiple linear regression model identified no significant relationship between CNR2 gene expression (a proxy measure of CB2R(36) with the effect size estimate). This is perhaps unsurprising as studies have shown that CB2 receptors are predominately distributed peripherally(87) with limited central distribution. Moreover, THC has less efficacy in its partial agonistic affinity to CB2 receptors compared with CB1 receptors in vitro(46). The brain regions found to be modulated by THC in our core analysis, including the anterior cingulate, amygdala, striatum, and cerebellum are known to be rich in CB1R(35). We show, for the first time, that a linear relationship exists between the effect of THC on increases in brain signal (as indexed by the pooled effect-size estimate) and CNR1 gene expression levels (as estimated on the basis of an average from 6 post-mortem brains of healthy individuals obtained from Allen Human Brain Atlas), a proxy measure of CB1R availability, across the whole brain(41). These findings are important as the CB1R is the main molecular target of THC in the human brain, where it has partial-agonist effects(46,88). Our findings thus provide novel —albeit indirect— evidence that the effects of THC on human brain function are in part related to local CB1 receptor availability, and complement independent experimental evidence that the acute effects of THC on human behaviour may be mediated by its effects on CB1R. See Supplementary Discussion 2 for additional discussion on CB1R mediating the effects of THC.

Our third key result was the identification of a relationship between THC dose and the effect-size estimates of activation signal across a range of brain substrates. We found a positive relationship between THC dose and its effects in the anterior cingulate cluster (comprising the dorsal and ventral regions), and a negative relationship in the supplementary motor area. These findings are significant as the anterior cingulate is believed have a role in social evaluation(89) and cognition(90), with functional alterations in individuals with high trait anxiety(91) and psychosis(92,93). Therefore, the dose-dependent effect of THC on the ventral cingulate may explain the findings of THC challenge studies(13,94) that investigated cognitive and psychological outcomes and have reported an association between higher doses of THC and increased psychotomimetic, anxiolytic, and cognitive impairments. Cannabis use has also been associated with motor impairments(95) with epidemiological reports suggesting a dose-related risk of motor vehicle accidents(96). However, one study has reported increased supplementary motor cortex activation with reduced psychomotor performance in chronic cannabis users during visual motor tasks(97). Interestingly, greater undirected functional connectivity between the dorsal anterior cingulate and supplementary motor area has been observed during proactive vs reactive motor control task conditions(98). Together, these findings suggest that the dose-response effects of THC on psychomotor dysfunction may, in part, be mediated by its effects on these brain regions, which could have implications for understanding how THC impairs the operation of heavy machinery in everyday life in cannabis users or patients prescribed THC-based medications. Emotional and cognition-agnostic effects of THC and its relationship with frontal cortical executive functioning as well as top-down control of subcortical structures are further discussed in Supplementary Discussion 3. Although, in our dose-response analyses, we identified the study by Battistella et al.,(74) as being a potential outlier, we refrained from excluding the study from dose-response association analyses in accordance with current thinking in this regard (please see further elaboration of this in Supplementary Discussion 4) and instead advise appropriate caution in the interpretation of the dose-response results.

Limitations

The results presented here are to be considered in light certain key limitations. Firstly, our results are based on summary data from individual studies rather than individual participant level imaging data from the same participants carrying out multiple different cognitive and emotional processing tasks as well as actual baseline CB1R data in the same participants measured using PET imaging. This would have allowed more direct testing of our hypotheses. While future endeavours should aim to carry out such studies, conducting them in over 300 participants as reported herein is likely to be challenging both in terms of resources as well as logistics. The present meta-analysis, in contrast, provides an early insight into these questions using existing data. Another key caveat to be considered while interpreting our meta-analytic results is related to the issue of heterogeneity across the included studies. While this is inherent to any meta-analytic endeavour, our steps to examine the extent to which they may have influenced our results indicate that they are unlikely to have substantially affected our key conclusions. Limitations are discussed in greater detail in Supplementary Discussion, Methodological considerations & heterogeneity.

Notwithstanding these limitations, the three major findings of the current study extend previous evidence on the effects of THC to specifically link (a) the molecular effects of THC at the CB1 receptor to (b) its physiological (haemodynamic) effects on regional brain signal activation, which together may underlie (c) the acute cognitive and behavioural consequences of cannabis use. Only through meta-analytic synthesis of 22 studies across 372 participants in computational unison were we able to demonstrate that the pleiotropic effects of THC at each of these levels of observation may be related to its molecular target—the CB1 receptor. Here we present a potential mechanistic explanation for the pleiotropic effects of THC by reporting its effects on a ‘integrative core’ of brain regions engaged across diverse cognitive and emotional processes(37), where its effects are in turn related to the availability of its main central molecular target across the brain.

References

1. Lumir Ondrej Hanus, Stefan Martin Meyer, Eduardo Munoz, Orazio Taglialatela-Scafati, Giovanni Appendino. Phytocannabinoids: a unified critical inventory. Nat Prod Rep [Internet]. 2016 [cited 2020 Jan 22];33:1347–448. Available from: www.rsc.org/npr
2. Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. N Engl J Med [Internet]. 2015 Sep 10 [cited 2020 Nov 24];373(11):1048–58. Available from: https://www.nejm.org/doi/10.1056/NEJMra1407304
3. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy [Internet]. Vol. 2015, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2015 [cited 2020 Nov 24]. Available from: http://doi.wiley.com/10.1002/14651858.CD009464.pub2
4. Davis MP. Cannabinoids for symptom management and cancer therapy: The evidence [Internet]. Vol. 14, JNCCN Journal of the National Comprehensive Cancer Network. Harborside Press; 2016 [cited 2020 Nov 24]. p. 915–22. Available from: https://jnccn.org/view/journals/jnccn/14/7/article-p915.xml
5. Marinelli L, Balestrino M, Mori L, Puce L, Rosa GM, Giorello L, et al. A randomised controlled cross-over double-blind pilot study protocol on THC:CBD oromucosal spray efficacy as an add-on therapy for post-stroke spasticity. BMJ Open [Internet]. 2017 Sep 1 [cited 2020 Nov 24];7(9):16843. Available from: http://bmjopen.bmj.com/
6. Collin C, Davies P, Mutiboko IK, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol [Internet]. 2007 Mar 1 [cited 2020 Nov 24];14(3):290–6. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1468-1331.2006.01639.x
7. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful

HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology [Internet]. 2007 Feb 13 [cited 2020 Nov 24];68(7):515–21. Available from: https://n.neurology.org/content/68/7/515

8. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults [Internet]. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018 [cited 2020 Nov 24]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012182.pub2/full

9. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy. J Pain. 2008 Mar 1;9(3):254–64.

10. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ [Internet]. 2004 Jul 31 [cited 2020 Nov 24];329(7460):253. Available from: http://www.bmj.com/

11. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain. J Pain. 2008 Jun 1;9(6):506–21.

12. Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, et al. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012;69(1):27–36.

13. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y Te, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. Neuropsychopharmacology. 2004 Aug;29(8):1558–72.

14. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, et al. The acute effects of synthetic intravenous 9- tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med. 2009 Oct;39(10):1607–16.

15. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, et al. Modulation of mediotemporal and ventrostriatal function in humans by A9-tetrahydrocannabinol a neural basis for the effects of cannabis sativa on learning and psychosis. Arch Gen Psychiatry. 2009 Apr;66(4):442–51.

16. Colizzi M, Weltens N, McGuire P, Lythgoe D, Williams S, Van Oudenhove L, et al. Delta-9-tetrahydrocannabinol increases striatal glutamate levels in healthy individuals: implications for psychosis. Mol Psychiatry [Internet]. 2019 Feb 15 [cited 2019 Jul 9];1. Available from: http://www.nature.com/articles/s41380-019-0374-8

17. Bhattacharyya S, Falkenberg I, Martin-Santos R, Atakan Z, Crippa JA, Giampietro V, et al. Cannabinoid Modulation of Functional Connectivity within Regions Processing Attentional Salience. Neuropsychopharmacology [Internet]. 2015;40(6):1343–52. Available from: http://dx.doi.org/10.1038/npp.2014.258

18. Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kambeitz J, Prata D, et al. Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of δ-9-tetrahydrocannabinol on midbrain and striatal function. Vol. 17, Molecular Psychiatry. 2012. p. 1152–5.

19. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. Biol Psychiatry. 2005 Mar 15;57(6):594–608.

20. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. The Lancet Psychiatry. 2015 Mar 1;2(3):233–

8.

21. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. The Lancet Psychiatry. 2019 May 1;6(5):427–36.

22. Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, et al. Continued versus discontinued cannabis use in patients with psychosis: A systematic review and meta-analysis. The Lancet Psychiatry. 2016 Mar 1;3(3):215–25.

23. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, et al. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res - Neuroimaging. 1996 May 31;67(1):29–38.

24. Mathew RJ, Wilson WH, Coleman RE, Turkington TG, Degrado TR. Marijuana intoxication and brain activation in marijuana smokers. Life Sci. 1997 May 2;60(23):2075–89.

25. Mathew RJ, Wilson WH, Chiu NY, Turkington TG, Degrado TR, Coleman RE. Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration. Acta Psychiatr Scand [Internet]. 1999 Jul [cited 2020 Jan 26];100(1):67–75. Available from: http://doi.wiley.com/10.1111/j.1600-0447.1999.tb10916.x

26. Mathew RJ, Wilson WH, Turkington TG, Hawk TC, Coleman RE, DeGrado TR, et al. Time course of tetrahydrocannabinol-induced changes in regional cerebral blood flow measured with positron emission tomography. Psychiatry Res - Neuroimaging. 2002 Dec 30;116(3):173–85.

27. Mathew RJ, Wilson WH, Tant SR. Acute changes in cerebral blood flow associated with marijuana smoking. Acta Psychiatr Scand. 1989 Feb;79(2):118–28.

28. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Ivanovic M, et al. Cerebellar metabolic activation by delta-9-tetrahydrocannabinol in human brain: A study with positron emission tomography and 18F-2-Fluoro-2-deoxyglucose. Psychiatry Res Neuroimaging. 1991;40(1):69–78.

29. Mathew RJ, Wilson WH, Humphreys DF, Lowe J V, Wiethe KE. Regional cerebral blood flow after marijuana smoking. J Cereb Blood Flow Metab. 1992;12(5):750–8.

30. Mathew RJ, Wilson WH. Acute changes in cerebral blood flow after smoking marijuana. Life Sci. 1993;52(8):757–67.

31. Mathew RJ, Wilson WH, G. Turkington T, Coleman RE. Cerebellar activity and disturbed time sense after THC. Brain Res. 1998 Jun 29;797(2):183–9.

32. Bhattacharyya S, Atakan Z, Martin-Santos R, A. Crippa J, K. McGuire P. Neural Mechanisms for the Cannabinoid Modulation of Cognition and Affect in Man: A Critical Review of Neuroimaging Studies. Curr Pharm Des. 2012 Sep 24;18(32):5045–54.

33. Gunasekera B, Davies C, Martin-Santos R, Bhatthacharyya S. The Yin and Yang of Cannabis - a systematic review of human neuroimaging evidence of the differential effects of delta-9-tetrahydrocannabinol and cannabidiol. Biol Psychiatry Cogn Neurosci Neuroimaging [Internet]. 2020 Oct [cited 2021 Jan 20]; Available from: https://pubmed.ncbi.nlm.nih.gov/33414100/

34. Bloomfield MAP, Hindocha C, Green SF, Wall MB, Lees R, Petrilli K, et al. The neuropsychopharmacology of cannabis: A review of human imaging studies. Vol. 195, Pharmacology and Therapeutics. Elsevier Inc.; 2019. p. 132–61.

35. Mackie K. Distribution of Cannabinoid Receptors in the Central and Peripheral Nervous System. In: Cannabinoids [Internet]. Berlin/Heidelberg: Springer-Verlag; 2005 [cited 2020 May 6]. p. 299–325. Available from: http://link.springer.com/10.1007/3-540-26573-2_10

36. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. Vol. 19, International Journal of Molecular Sciences. MDPI AG; 2018.

37. Shine JM, Breakspear M, Bell PT, Ehgoetz Martens K, Shine R, Koyejo O, et al. Human cognition involves the dynamic integration of neural activity and neuromodulatory systems. Nat Neurosci [Internet]. 2019 Feb 1 [cited 2021 Jan 20];22(2):289–96. Available from: https://www.nature.com/articles/s41593-018-0312-0

38. Krienen FM, Thomas Yeo BT, Buckner RL. Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Philos Trans R Soc B Biol Sci [Internet]. 2014 Oct 5 [cited 2021 Jan 20];369(1653). Available from: https://pubmed.ncbi.nlm.nih.gov/25180304/

39. Arnatkevičiūtė A, Fulcher BD, Fornito A. A practical guide to linking brain-wide gene expression and neuroimaging data. Neuroimage. 2019;189(July 2018):353–67.

40. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, et al. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature [Internet]. 2012 Sep 20 [cited 2021 Jan 26];489(7416):391–9. Available from: http://www.brain-map.

41. CNR1 cannabinoid receptor 1 [Homo sapiens (human)] - Gene - NCBI [Internet]. [cited 2021 Jan 26]. Available from: https://www.ncbi.nlm.nih.gov/gene/1268

42. CNR2 cannabinoid receptor 2 [Homo sapiens (human)] - Gene - NCBI [Internet]. [cited 2021 Apr 8]. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=1269

43. Manza P, Yuan K, Shokri-Kojori E, Tomasi D, Volkow ND. Brain structural changes in cannabis dependence: association with MAGL. Mol Psychiatry [Internet]. 2020 Dec 6 [cited 2021 Feb 8];25(12):3256–66. Available from:

http://www.nature.com/articles/s41380-019-0577-z

44. Hawrylycz M, Miller JA, Menon V, Feng D, Dolbeare T, Guillozet-Bongaarts AL, et al. Canonical genetic signatures of the adult human brain. Nat Neurosci [Internet]. 2015 Nov 25 [cited 2021 Feb 8];18(12):1832–44. Available from: https://pubmed.ncbi.nlm.nih.gov/26571460/

45. Richiardi J, Altmann A, Milazzo AC, Chang C, Chakravarty MM, Banaschewski T, et al. Correlated gene expression supports synchronous activity in brain networks. Science (80-) [Internet]. 2015 Jun 12 [cited 2021 Feb 2];348(6240):1241–4. Available from: www.sciencemag.org/content/348/6240/1238/suppl/DC1

46. Pertwee RG. The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin. Vol. 153, British Journal of Pharmacology. 2008. p. 199–215.

47. Müller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, et al. Ten simple rules for neuroimaging meta-analysis. Vol. 84, Neuroscience and Biobehavioral Reviews. Elsevier Ltd; 2018. p. 151–61.

48. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020) [Internet]. Cochrane. 2020 [cited 2020 Dec 11]. Available from: www.training.cochrane.org/handbook

49. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. J Am Med Assoc. 2000 Apr 19;283(15):2008–12.

50. Norman LJ, Carlisi C, Lukito S, Hart H, Mataix-Cols D, Radua J, et al. Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: A comparative meta-analysis. JAMA Psychiatry [Internet]. 2016

Aug 1 [cited 2020 Nov 16];73(8):815–25. Available from: https://jamanetwork.com/

51. Radua J, Rubia K, Canales-Rodríguez EJ, Pomarol-Clotet E, Fusar-Poli P, Mataix-Cols D. Anisotropic Kernels for Coordinate-Based Meta-Analyses of Neuroimaging Studies. Front Psychiatry [Internet]. 2014 [cited 2020 Jan 21];5. Available from: http://journal.frontiersin.org/article/10.3389/fpsyt.2014.00013/abstract

52. Radua J, Romeo M, Mataix-Cols D, Fusar-Poli P. A general approach for combining voxel-based meta-analyses conducted in different neuroimaging modalities. Curr Med Chem. 2013;20(3):462–6.

53. Radua J, Van Den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry [Internet]. 2010 Jul 1 [cited 2020 Nov 16];67(7):701–11. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1151078

54. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Vol. 195, British Journal of Psychiatry. 2009. p. 393–402.

55. Cook RD. Cook’s Distance. In: International Encyclopedia of Statistical Science [Internet]. Springer Berlin Heidelberg; 2011 [cited 2021 Apr 8]. p. 301–2. Available from: https://link.springer.com/referenceworkentry/10.1007/978-3-642-04898-2_189

56. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage [Internet]. 2006 Jul 1 [cited 2021 Feb 2];31(3):968–80. Available from: https://pubmed.ncbi.nlm.nih.gov/16530430/

57. Welcome to Python.org [Internet]. [cited 2021 Jan 26]. Available from: https://www.python.org/

58. Markello R, Shafiei G, Zheng Y-Q, Mišić B. A toolbox for the Allen Brain Atlas genetics data. Zenodo [Internet]. 2020 Oct 15 [cited 2021 Jan 26]; Available from: https://zenodo.org/record/4091537#.YBAFOOj7Q2w

59. Winton-Brown TT, Allen P, Bhattacharrya S, Borgwardt SJ, Fusar-Poli P, Crippa JA, et al. Modulation of auditory and visual processing by delta-9- tetrahydrocannabinol and cannabidiol: An fMRI study. Neuropsychopharmacology [Internet]. 2011;36(7):1340–8. Available from: http://dx.doi.org/10.1038/npp.2011.17

60. Walter C, Oertel BG, Felden L, Nöth U, Vermehren J, Deichmann R, et al. Effects of oral Δ9-tetrahydrocannabinol on the cerebral processing of olfactory input in healthy non-addicted subjects. Vol. 73, European Journal of Clinical Pharmacology. 2017. p. 1579–87.

61. Van Hell HH, Jager G, Bossong MG, Brouwer A, Jansma JM, Zuurman L, et al. Involvement of the endocannabinoid system in reward processing in the human brain. Psychopharmacology (Berl). 2012 Feb;219(4):981–90.

62. Rabinak CA, Sripada CS, Angstadt M, De Wit H, Phan KL. Cannabinoid modulation of subgenual anterior cingulate cortex activation during experience of negative affect. J Neural Transm. 2012 Jun;119(6):701–7.

63. O’Leary DS, Block RI, Flaum M, Schultz SK, Boles Ponto LL, Watkins GL, et al. Acute marijuana effects on rCBF and cognition: A PET study. Neuroreport. 2000 Nov 27;11(17):3835–41.

64. O’Leary DS, Block RI, Koeppel JA, Flaum M, Schultz SK, Andreasen NC, et al. Effects of smoking marijuana on brain perfusion and cognition. Neuropsychopharmacology. 2002;26(6):802–16.

65. O’Leary DS, Block RI, Turner BM, Koeppel J, Magnotta VA, Ponto LB, et al. Marijuana alters the human cerebellar clock. Neuroreport [Internet]. 2003 Jun 11

[cited 2020 Apr 28];14(8):1145–51. Available from: http://journals.lww.com/00001756-200306110-00009

66. O'Leary DS, Block RI, Koeppel JA, Schultz SK, Magnotta VA, Ponto LB, et al. Effects of smoking marijuana on focal attention and brain blood flow. Hum Psychopharmacol. 2007 Apr;22(3):135–48.

67. Jansma JM, Van Hell HH, Vanderschuren LJMJ, Bossong MG, Jager G, Kahn RS, et al. THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. Transl Psychiatry [Internet]. 2013 [cited 2020 Jan 25];3:3. Available from: www.nature.com/tp

68. Freeman TP, Pope RA, Wall MB, Bisby JA, Luijten M, Hindocha C, et al. Cannabis Dampens the Effects of Music in Brain Regions Sensitive to Reward and Emotion. Int J Neuropsychopharmacol. 2018;21(1):21–32.

69. Bossong MG, Jansma JM, Van Hell HH, Jager G, Oudman E, Saliasi E, et al. Effects of Δ9-tetrahydrocannabinol on human working memory function. Biol Psychiatry [Internet]. 2012;71(8):693–9. Available from: http://dx.doi.org/10.1016/j.biopsych.2012.01.008

70. Bossong MG, van Hell HH, Jager G, Kahn RS, Ramsey NF, Jansma JM. The endocannabinoid system and emotional processing: A pharmacological fMRI study with {increment}9-tetrahydrocannabinol. Eur Neuropsychopharmacol. 2013 Dec;23(12):1687–97.

71. Bossong MG, van Hell HH, Schubart CD, van Saane W, Iseger TA, Jager G, et al. Acute effects of ∆9-tetrahydrocannabinol (THC) on resting state brain function and their modulation by COMT genotype. Eur Neuropsychopharmacol [Internet]. 2019;29(6):766–76. Available from: https://doi.org/10.1016/j.euroneuro.2019.03.010

72. Bhattacharyya S, Egerton A, Kim E, Rosso L, Riano Barros D, Hammers A, et al.

Acute induction of anxiety in humans by delta-9-tetrahydrocannabinol related to amygdalar cannabinoid-1 (CB1) receptors. Sci Rep [Internet]. 2017;7(1):1–15. Available from: http://dx.doi.org/10.1038/s41598-017-14203-4

73. Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kambeitz J, Malhi S, et al. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. Eur Neuropsychopharmacol [Internet]. 2014;25(1):26–37. Available from: http://dx.doi.org/10.1016/j.euroneuro.2014.11.018

74. Battistella G, Fornari E, Thomas A, Mall JF, Chtioui H, Appenzeller M, et al. Weed or Wheel! fMRI, Behavioural, and Toxicological Investigations of How Cannabis Smoking Affects Skills Necessary for Driving. PLoS One. 2013;8(1).

75. Lee MC, Ploner M, Wiech K, Bingel U, Wanigasekera V, Brooks J, et al. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain [Internet]. 2013;154(1):124–34. Available from: http://dx.doi.org/10.1016/j.pain.2012.09.017

76. Walter C, Oertel BG, Felden L, Nöth U, Deichmann R, Lötsch J. Delta-9-tetrahydrocannabinol reduces the performance in sensory delayed discrimination tasks. A pharmacological-fMRI study in healthy volunteers. IBRO Reports [Internet]. 2019;7(November):117–28. Available from: https://doi.org/10.1016/j.ibror.2019.11.004

77. Bossong MG, Jager G, van Hell HH, Zuurman L, Jansma JM, Mehta MA, et al. Effects of Δ9-tetrahydrocannabinol administration on human encoding and recall memory function: A pharmacological fMRI study. J Cogn Neurosci. 2012;24(3):588–99.

78. Bossong MG, Jansma JM, van Hell HH, Jager G, Kahn RS, Ramsey NF. Default Mode Network in the Effects of Δ9-Tetrahydrocannabinol (THC) on Human Executive Function. PLoS One. 2013;8(7):1–10.

79. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic

reviews and meta-analyses: The PRISMA statement [Internet]. Vol. 339, BMJ (Online). British Medical Journal Publishing Group; 2009 [cited 2020 Nov 17]. p. 332–6. Available from: http://www.bmj.com/content/339/bmj.b2535?tab=related#datasupp

80. Plotting Tool for Brain Atlases • ggseg [Internet]. [cited 2021 Apr 7]. Available from: https://lcbc-uio.github.io/ggseg/index.html

81. RStudio [Internet]. [cited 2021 Mar 1]. Available from: https://rstudio.com/

82. Microarray Data :: Allen Brain Atlas: Human Brain [Internet]. [cited 2021 Mar 22]. Available from: http://human.brain-map.org/

83. Brendel W, Romo R, Machens CK. Demixed Principal Component Analysis. Adv Neural Inf Process Syst. 2011;22:2654–62.

84. Blest-Hopley G, Giampietro V, Bhattacharyya S. Residual effects of cannabis use in adolescent and adult brains — A meta-analysis of fMRI studies. Neurosci Biobehav Rev [Internet]. 2018;88(October 2017):26–41. Available from: https://doi.org/10.1016/j.neubiorev.2018.03.008

85. Schoeler T, Petros N, Di Forti M, Klamerus E, Foglia E, Ajnakina O, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. The Lancet Psychiatry. 2016 Oct 1;3(10):947–53.

86. Schoeler T, Theobald D, Pingault JB, Farrington DP, Jennings WG, Piquero AR, et al. Continuity of cannabis use and violent offending over the life course. Psychol Med [Internet]. 2016 Jun 1 [cited 2021 Mar 17];46(8):1663–77. Available from: https://www.cambridge.org/core/product/identifier/S0033291715003001/type/journal_article

87. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Vol. 54,

Pharmacological Reviews. Pharmacol Rev; 2002. p. 161–202.

88. Bossong MG, Jansma JM, Bhattacharyya S, Ramsey NF. Role of the endocannabinoid system in brain functions relevant for schizophrenia: An overview of human challenge studies with cannabis or {increment}9-tetrahydrocannabinol (THC). Vol. 52, Progress in Neuro-Psychopharmacology and Biological Psychiatry. Elsevier Inc.; 2014. p. 53–69.

89. Rigney AE, Koski JE, Beer JS. The functional role of ventral anterior cingulate cortex in social evaluation: Disentangling valence from subjectively rewarding opportunities. Soc Cogn Affect Neurosci [Internet]. 2018 Jan 1 [cited 2021 Feb 2];13(1):14–21. Available from: /pmc/articles/PMC5755235/?report=abstract

90. Apps MAJ, Rushworth MFS, Chang SWC. The Anterior Cingulate Gyrus and Social Cognition: Tracking the Motivation of Others [Internet]. Vol. 90, Neuron. Cell Press; 2016 [cited 2021 Mar 17]. p. 692–707. Available from: /pmc/articles/PMC4885021/

91. Paulus MP, Feinstein JS, Simmons A, Stein MB. Anterior cingulate activation in high trait anxious subjects is related to altered error processing during decision making. Biol Psychiatry [Internet]. 2004 Jun 15 [cited 2021 Mar 17];55(12):1179–87. Available from: http://www.biologicalpsychiatryjournal.com/article/S0006322304003464/fulltext

92. Smieskova R, Roiser JP, Chaddock CA, Schmidt A, Harrisberger F, Bendfeldt K, et al. Modulation of motivational salience processing during the early stages of psychosis. Schizophr Res. 2014 Sep 16;166(1–3):17–23.

93. Nielsen MO, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, et al. Alterations of the brain reward system in antipsychotic nave schizophrenia patients. Biol Psychiatry. 2012 May 15;71(10):898–905.

94. Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJA, Parsons LH. Keep off the grass? Cannabis, cognition and addiction [Internet]. Vol. 17, Nature Reviews

Neuroscience. Nature Publishing Group; 2016 [cited 2021 Jan 27]. p. 293–306. Available from: www.nature.com/nrn

95. Prashad S, Filbey FM. Cognitive motor deficits in cannabis users [Internet]. Vol. 13, Current Opinion in Behavioral Sciences. Elsevier Ltd; 2017 [cited 2021 Feb 11]. p. 1–7. Available from: /pmc/articles/PMC4966282/

96. Ramaekers JG, Berghaus G, Van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Vol. 73, Drug and Alcohol Dependence. Elsevier Ireland Ltd; 2004. p. 109–19.

97. King GR, Ernst T, Deng W, Stenger A, Gonzales RMK, Nakama H, et al. Altered brain activation during visuomotor integration in chronic active cannabis users: Relationship to cortisol levels. J Neurosci [Internet]. 2011 Dec 7 [cited 2021 Feb 11];31(49):17923–31. Available from: https://www.jneurosci.org/content/31/49/17923

98. Asemi A, Ramaseshan K, Burgess A, Diwadkar VA, Bressler SL. Dorsal anterior cingulate cortex modulates supplementary motor area in coordinated unimanual motor behavior. Front Hum Neurosci [Internet]. 2015 Jun 4 [cited 2021 Feb 11];9(JUNE):309. Available from: /pmc/articles/PMC4454840/