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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

The neurobiological mechanisms underlying the effects of delta-9-tetrahydrocannabinol (THC) remain unclear. Here, we examined the spatial acute effect of THC on human regional brain activation or blood flow (hereafter called 'activation signal') in a 'core' network of brain regions from 372 participants, tested using a within-subject repeated measures design under experimental conditions. We also investigated whether the neuromodulatory effects of THC are related to the local expression of the cannabinoid-type-1 (CB1R) and type-2 (CB2R) receptors. Finally, we investigated the dose-response relationship between THC and key brain substrates. 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, related to dose, with greater effects in regions with higher levels of CB1R expression.

1. Introduction

The extract of *Cannabis sativa* contains more than 140 different phytocannabinoids (Hanuš et al., 2016). 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 (Friedman and Devinsky, 2015; Smith et al., 2015; Davis, 2016; Marinelli et al., 2017; Collin et al., 2007; Abrams et al., 2007; Mücke et al., 2018; Narang et al., 2008; Svendsen et al., 2004; Wilsey et al., 2008), there is also considerable evidence of its psychotomimetic effects in healthy (Bhattacharyya et al., 2012a, 2009, 2015a; D'Souza et al., 2004; Morrison et al., 2009; Colizzi et al., 2020) and vulnerable people (Bhattacharyya et al., 2012b), as well as those with schizophrenia (D'Souza et al., 2005), and an association between THC content of recreational cannabis with a greater risk of onset (Di Forti et al., 2015, 2019) and relapse (Schoeler et al., 2016a) 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) (Volkow et al., 1996, 1991; Mathew et al., 1997, 1992, 1998, 1999, 2002, 1989; Mathew and Wilson, 1993) at rest, and functional MRI (fMRI) to measure the blood oxygen level dependent

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haemodynamic signal during cognitive activation (Bhattacharyya, Sep 24 et al., 2012; Gunasekera et al., 2021) to index brain function. However, conflicting results from these studies have not resulted in a clearer understanding as evident from two recent systematic reviews (Gunasekera et al., 2021; Bloomfield et al., 2019).

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 (Mackie, 2005; Zou and Kumar, 2018), 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 (Shine et al., 2019; Krienen et al., 2014), 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 (Shine et al., 2019; Krienen et al., 2014). 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 (Arnatkevičiūtė et al., 2019; Hawrylycz et al., 2012), 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 (National Center for Biotechnology Information, 2017) and CB2R (UniProt, 2015) gene expression. Previous studies have linked gene expression levels in the human brain with anatomical (Manza et al., 2020) and functional (Hawrylycz et al., 2015; Richiardi et al., 2015) indices measured using neuroimaging techniques. In accordance with current understanding about the molecular targets of THC (Pertwee, 2008) 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. Methods

The protocol for the meta-analytic synthesis was registered in PROSPERO (CRD42019145453) and we followed recommendations for neuroimaging meta-analyses (Müller et al., 2018). A detailed description of the methods is 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 (Higgins et al., 2019) and MOOSE guidelines (Stroup et al., 2000). 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. Studies that used multiple task contrasts related to the same cognitive paradigm were combined. This was to ensure reduced variance in the analyses (Norman et al., 2016).

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/) (Radua et al., 2014, 2013). 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 (Radua et al., 2010). Coordinates of cluster peaks and cluster extent are reported using MNI coordinates. Each cluster peak was examined using a human brain atlas in order to visually inspect the peak region (Adams, 1978).

Several steps were adopted to address the issue of heterogeneity. Firstly, to assess the level of heterogeneity between the studies included for analysis we used the classical measure of heterogeneity, Cochran's Q (Q_H). Q_H statistics were assessed in terms of a chi-square distribution and reported after conversion to standard z values to create a map. This map was overlaid on the final mean map for visual inspection of areas of overlapping significant heterogeneity with areas of thresholded activation or attenuation signal. The I^2 statistic was also estimated to determine the extent to which variability in estimates of effect-size in brain regions modulated by THC compared to placebo was a result of heterogeneity as opposed to sampling error. Between the studies included for meta-analysis, there were differences in THC dose, route of THC administration, type of imaging technique (e.g., fMRI, PET, ASL), and a presence or absence of activation tasks. Therefore, we employed a random-effects rather than a fixed-effects model to estimate the pooled effect-size. Further, to better understand the sources of heterogeneity, we conducted subgroup analysis to look at more homogeneous groups such as THC isolate, scanner magnetic field strength, and fMRI studies alone (when three or more contrasts were available, see Supplementary subgroup analyses). As heterogeneity in effect-sizes may also be a result of studies with extreme sizes, we also carried out jack-knife leave-one-out sensitivity analysis. In a jack-knife analysis, each analysis was repeated excluding 1 single study at a time to establish whether each cluster remained statistically significant. Finally, Egger's test was used to assess the asymmetry of funnel plots to examine potential publication

bias (Egger et al., 1997). This was conducted to assess whether small or imprecise studies reported larger effect sizes. 'Small' studies with negative results may be less likely to be published, and conversely, large studies are more likely to be published even with negative findings. Funnel plots also highlight heterogeneity in estimates between studies and was therefore used as a way to assess heterogeneity between the studies for each significantly cluster where brain signal was significantly modified following THC, compared with placebo.

2.5. Meta regression analysis: dose

A multiple meta-regression analysis was carried out using approaches described previously (Radua and Mataix-Cols, 2009) using a significance threshold of $P < 0.0005$ (Radua et al., 2014; Radua and Mataix-Cols, 2009). 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 (Cook, 2011) 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 (Desikan et al., 2006) 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 (Desikan et al., 2006) 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 (Python Software Foundation, 2016). We followed the recommendations put forward by Arnatkevičiūtė and colleagues with regard to processing mRNA microarray expression data from the Allen Human Brain Atlas (Arnatkevičiūtė et al., 2019) and used the package *abagen (*Markello et al., 2020*)* to conduct a reproducible workflow in processing and preparing the data.

2.7. Subgroup analysis

We performed subgroup analysis on studies that employed similar cognitive paradigms to investigate the differential effect of THC on brain activation when three or more contrasts were available.

3. Results

3.1. Included studies

A final set of 22 manuscripts met the study inclusion criteria (Table 1) (Bhattacharyya et al., 2012a, 2017, 2009; Jansma et al., 2013; Freeman et al., 2018; Bossong et al., 2012a, 2012b, 2013a, 2019, 2015b; Battistella et al., 2013; Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011, 2013b; Van Hell et al., 2012; Rabinak et al., 2012; O'Leary et al., 2000, 2002, 2003; O'Leary, Apr et al., 2007). Of these manuscripts, 17 used fMRI (Bhattacharyya et al., 2012a, 2017, 2009; Jansma et al., 2013; Freeman et al., 2018; Bossong et al., 2012a, 2013a, 2015b; Battistella et al., 2013; Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011; Van Hell et al., 2012; Rabinak et al., 2012), 4 PET (O'Leary et al., 2000, 2002, 2003; O'Leary, Apr et al., 2007), and 1 used arterial spin labelling (Bossong et al., 2019). Fig. 1 shows the PRISMA flowchart (Moher et al., 2009). 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 (Bhattacharyya et al., 2012a, 2017, 2009; Jansma et al., 2013; Bossong et al., 2012a, 2012b, 2013a, 2019, 2015b; Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011, 2013b; Van Hell et al., 2012; Rabinak et al., 2012) and 6 that administered THC-rich cannabis (Freeman et al., 2018; Battistella et al., 2013; O'Leary et al., 2000, 2002, 2003; O'Leary, Apr et al., 2007).

Studies included cognitive paradigms that engaged reward (Jansma et al., 2013; Freeman et al., 2018; Van Hell et al., 2012), memory (Bhattacharyya et al., 2009; Bossong et al., 2012a, 2012b), emotion (Bossong et al., 2013a; Bhattacharyya et al., 2017; Rabinak et al., 2012), attentional salience (Bhattacharyya et al., 2012a; Battistella et al., 2013; Bossong et al., 2013b; O'Leary et al., 2000, 2002; O'Leary, Apr et al., 2007) and sensory processing (Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011). One arterial spin labelling study did not use a cognitive task (Bossong et al., 2019).

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

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

3.3. Sensitivity, Heterogeneity, and Publication Bias

Jack-knife sensitivity analysis showed that out of a total of 16 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). All brain regions had an I^2 statistic of less than 30% (except for the Rolandic operculum cluster that was attenuated following THC compared with placebo, I^2 =31.80%) suggesting minimal influence of heterogeneity among the 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 2). There was significant overlap between the findings of our main results and those from the fMRI subgroup alone (Supplementary Figure 20). Further results of subgroup analyses examining methodological variables including THC isolate and fMRI scanner strength, and are reported in Supplementary Tables 3 and 4.

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 (6–42 mg) (Table 3, Fig. 3).

Cook's distance (Cook, 2011) estimate identified the study by Battistella et al. (2013) as being a potential outlier (further discussed in Supplementary Discussion 4). Following re-analysis without the Battistella et al. dataset, the correlation between THC dose and brain signal modulation, indexed by Hedge's g, persisted in the anterior cingulate / paracingulate (Z score= 4.41, $P < 0.001$) and caudate (Z score= $P = 0.03$).

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 (Desikan et al., 2006) atlas are displayed in Fig. 4. Multiple regression analysis indicated that there was a significant

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*	*Sex (% males)*	*Education*	*IQ*
*Battistella (*Walter et al., 2017*)*	INH	fMRI	Visuo-motor tacking	Visually track a target	1.5	DB, PC, R, WS	31	24.1 (Smith et al., 2015)	45'	A,C,D, T	42 mg	9.3	100	6 (2.3) (post-compulsory)	NA
Bhattacharyya (Bhattacharyya et al., 2012a*)*	OC	fMRI	Attentional processing	Oddball vs standard	1.5	DB, PC, R, WS	15	26.7 (5.7)	1–2 h	A,C,D	10 mg	1 h= 3.9 (7.3) 2 h= 5.1 (5.6)	100	16.5 (3.9)	98.7 (6)
Bhattacharyya (Bhattacharyya et al., 2009*)*	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)	1–2 h	A,C,D	10 mg	1 h= 3.9 (7.3) 2 h= 5.1 (5.6)	100	16.5 (3.9)	98.7 (6)
Bhattacharyya (Bossong et al., 2012b*)*	OC	[11 C] MePPEP PET & fMRI	Fear processing	Neutral expression	1.5	DB, PC, R, WS	14	23.8 (4.5)	1–2 h	A,C,D, T	10 mg	NA	100	NA	98.2 (5)
Bhattacharyya (Bossong et al., 2013b*)*	OC	fMRI	Go/No-Go	Oddball vs standard	1.5	DB, PC, R, WS	36	26.0 (5.5)	1–2 h	A,C,D, T	10 mg	1 h= 3.9 (7.3) 2 h= 5.1 (5.6)	100	NA	97.7 (6)
*Bossong (*Lee et al., 2013*)*	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	6 mg	70 (40.6)	100	NA	105.4 (5.4)
*Bossong (*Walter et al., 2019*)*	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	6 mg	82.3 (45.9)	100	NA	105.6 (5.6)
Bossong (Winton-Brown et al., 2011*)*	INH	ASL	Resting	NA	3	DB, PC, R, WS	33	22.6 (4.3)	5'	A,C,D, T	6 mg	84.9 (43.5)	100	NA	105.7 (5.2)
*Bossong (*O'Leary et al., 2000*)*	INH	fMRI	Associative memory	Pictural cue	3	DB, PC, R, WS	13	21.6 (2.1)	5'	A,C,T	6 mg	58.1 (31.3)	100	NA	104.6 (5.6)
*Bossong (*O'Leary et al., 2002*)*	INH	fMRI	Continuous performance task	Watch stimuli	3	DB, PC, R, WS	20	22.9 (4.9)	5'	A,C,T	6 mg	78.4627.0 ng/ml	100	NA	105.6 (5.6)
Freeman (Battistella et al., 2013*)*	INH	fMRI	Musical Reward	Scrambled sound	1.5	DB, PC, R, WS	16	26.2 (7.3)	5'	C,D	8 mg	NA	50	NA	NA
Jansma (Bhattacharyya et al., 2015b*)*	INH	fMRI	MIDT	No monetary reward	3	DB, PC, R, WS	10	25.6 (2.1)	5'	A,C,T	6 mg	82.8 HC 82.8 NAD	100	NA	105 (1.5)
*Lee (*Van Hell et al., 2012*)*	OC	fMRI	Capsaicin induced pain	No pain	3	DB, PC, R, WS	12	24–34	3 h	A, C.D, T	15 mg	3.5 h= 1–1.2 (estimated)	100	NA	NA
*O'Leary (*Bossong et al., 2019*)*	INH	H2150 PET	Self-paced counting task	NA	1.5	DB, PC, NR, WS	12	21.7 (1.4)	10–15'	C	20 mg	Occasional= 17.6 (8.7) Chronic= 35.8 (19.7)	50	Occasional: 14.7 (1.2) Chronic: 14.6 (1.4)	Occasional: 108.6 (12.1) Chronic: 113.2 (12.4)
*O'Leary (*Bossong et al., 2013a*)*	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, NR, WS	12	30.5 (8.6)	10–15'	C,D	20 mg	2.6 (3.6)– 37.1 (27.1)	50	NA	NA

(*continued on next page*)

Table 1 (*continued*)

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*	*Sex (% males)*	*Education*	*IQ*
O'Leary (Bhattacharyya et al., 2017)	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, NR, WS	12	23.5 (4.3)	10–15'	C,D	20 mg	10.3 (2.5)– 107.2 (59.7)	50	NA	NA
O'Leary (Bossong et al., 2012a)	INH	H2150 PET	Auditory Attention Task	NA	1.5	DB, PC, R, WS	5	26.2 (Mücke et al., 2018)	10–15'	C	20 mg	NA	60	NA	NA
Rabinak (Freeman et al., 2018)	OC	fMRI	Emotional processing task	Neutral expression	3	DB, PC, R, WS	14	20.8 (2.6)	2 h	A,C,D	7.5 mg	NA	50	NA	NA
van Hell (Jansma et al., 2013)	INH	fMRI	MIDT	No monetary reward	3	DB, PC, R, WS	11	21.7 (2.3)	5'	A,C,T	6 mg	60.1 (33.7)	100	NA	104.5 (6.0)
Walter (Rabinak et al., 2012)	OC	fMRI	Visual DSDT	Control visual cue	3	DB, PC, R, WS	13	25.5 (2.3)	2 h	A, C.D, T	20 mg	NA	46	NA	NA
Walter (Rabinak et al., 2012)	OC	fMRI	Nociceptive pain DSDT	Different pain intensity	3	DB, PC, R, WS	22	26.1 (2.9)	2 h	A, C.D, T	20 mg	NA	50	NA	NA
Walter (Markello et al., 2020)	OC	fMRI	Olfactory and pain response	Different gaseous stimuli	3	DB, PC, R, WS	15	26.6 (2.9)	2 h	A,C,D, T	20 mg	NA	47	NA	NA
Winton-Brown (Python Software Foundation, 2016)	OC	fMRI	Auditory and visual stimulation	Independent of sensory load	1.5	DB, PC, R, WS	14	26.7 (5.7)	1–2 h	A,C,D	10 mg	1 h= 3.9 (7.3) 2 h= 5.1 (5.6)	100	16.5 (3.9)	98.7 (7)

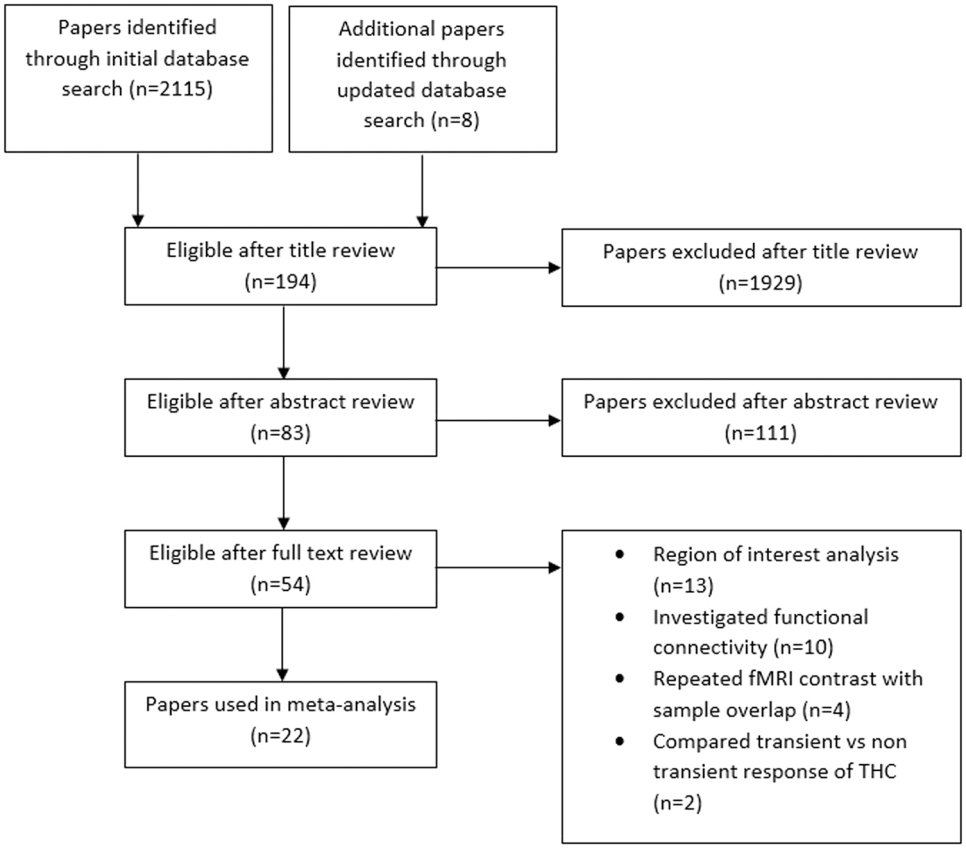

Fig. 1. PRISMA flowchart of search strategy for meta-analysis.

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	I^2 Statistic
	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	8.64
	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	19.61
	48	-76	20	2.883	< 0.001	166	R middle temporal gyrus (extending to R middle occipital gyrus, R middle temporal gyrus)	0.961	0.26
	38	-76	-48	2.411	0.001	152	R cerebellum crus II (extending to R lobule VIII/VIIB)	0.303	8.33
	32	-88	-8	2.451	< 0.001	76	R inferior occipital gyrus (extending to R middle occipital gyrus)	0.720	1.86
	24	0	-16	2.042	0.002	47	R amygdala (extending to R temporal pole, superior temporal gyrus, R hippocampus)	0.069	28.17
	-12	-74	44	3.367	< 0.001	37	L cerebellum lobule VIIB (extending to L lobule VIIB/ VIII)	0.654	6.08
	-24	-24	54	2.177	0.001	19	L precentral gyrus (adjacent to deep white matter)	0.688	1.53
	0	-20	-12	2.134	0.001	16	L thalamus	0.817	2.64
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	25.30
	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	31.80
	4	-72	28	-2.48	0.001	204	R cuneus cortex (extending to R precuneus, L precuneus, L cuneus cortex)	0.238	5.40
	-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	1.29
	64	-16	-4	-2.323	0.001	65	R superior temporal gyrus (extending to R middle temporal gyrus)	0.135	7.99
	-56	60	40	-2.273	0.002	38	L angular gyrus (extending to L inferior parietal gyri, excluding supamarginal gyri)	0.902	2.60
	4	-60	-8	-2.333	0.001	26	Cerebellum lobule IV/V	0.318	10.70

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, Fig. 5) but not CNR2 gene expression ($t = -0.036$, $P = 0.971$, coefficient= −0.002, 95%CI= −0.131 to 0.126) across the 78 brain regions of the atlas.

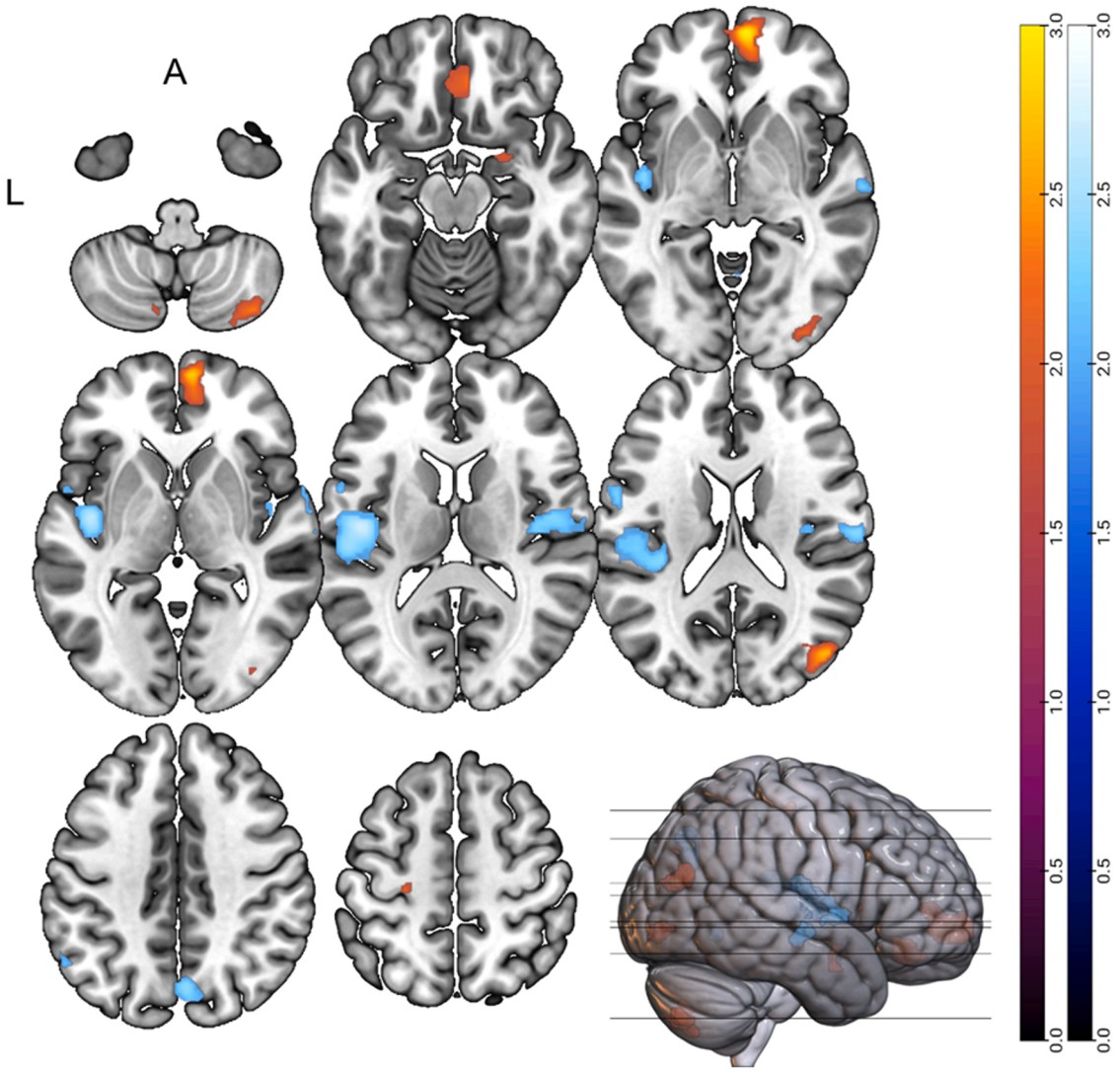

Fig. 2. Differences in brain signal following THC compared with placebo obtained from main multimodal meta-analysis. Orange= areas of increased activation signal (THC>placebo). Blue= areas of attenuated activation signal (THC<placebo). Left side of the brain sections indicates the left side of the brain;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

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)

3.6. Subgroup analyses

We performed subgroup analysis on studies that employed similar cognitive paradigms to investigate the differential effect of THC on brain activation.

3.6.1. Emotion processing

Within the emotional processing subgroup, 42 participants were compared in a crossover design following THC compared with placebo while processing emotional pictures (Bossong et al., 2013a; Bhattacharyya et al., 2017; Rabinak et al., 2012).

Table 4
Areas of increased and attenuated brain signal following THC, compared with placebo, during emotional processing stimuli.

Comparison	MNI coordinate			SDM-Z	P	Voxels	Region
	x	y	z				
THC>PLB	34	-18	-4	2.105	< 0.001	341	R putamen (extending to: R insula, R striatum, R heschl gyrus)
	12	-24	-2	2.124	< 0.001	187	R thalamus (extending to: R hippocampus, R thalamus)
	20	20	-16	1.891	< 0.001	85	R superior frontal gyrus, orbital part (extending to: R striatum, R gyrus rectus, R olfactory cortex)
	56	-26	16	1.628	0.003	21	R superior temporal gyrus (extending to: R supramarginal gyrus)
	28	-36	10	2.071	< 0.001	17	Caudate (extending to: R hippocampus)
	44	-34	4	1.527	0.003	14	Superior temporal gyrus
	48	8	-12	1.661	0.002	13	R temporal pole, superior temporal gyrus
THC<PLB	-44	-68	38	-2.169	< 0.001	330	L angular gyrus (extending to: L middle temporal gyrus)
	-40	-28	46	-2.129	< 0.001	241	L postcentral gyrus (extending to: inferior parietal [excluding supramarginal and angular] gyri)
	-4	24	58	-2.157	< 0.001	221	L supplementary motor area (extending to: L medial superior frontal gyrus)
	-60	8	12	-1.985	< 0.001	101	L inferior frontal gyrus, opercular part (extending to: pre and postcentral gyri)
	-8	-54	72	-1.933	0.001	16	L precuneus (extending to: L superior parietal gyrus)
	-14	-42	78	-2.046	< 0.001	16	L postcentral gyrus (extending to: L precuneus and L paracentral gyri)
	-8	-40	-8	-1.774	0.003	15	L cerebellum, hemispheric lobule IV / V

Table 5
Areas of increased and attenuated activation signal following THC, compared with placebo, during reward processing stimuli.

Comparison	MNI coordinate			SDM-Z	P	Voxels	Region
	x	y	z				
THC>PLB	-24	-4	44	1.829	< 0.001	155	L middle frontal gyrus (extending to: L precentral gyrus, L superior dorsolateral frontal gyrus)
	8	44	30	1.957	< 0.001	142	R median cingulate / paracingulate gyri (extending to: anterior cingulate gyrus and medial superior frontal gyrus)
	18	68	0	2.41	< 0.001	78	R superior frontal gyrus, dorsolateral
	12	58	-8	2.344	< 0.001	57	R superior frontal gyrus, medial orbital (extending to: R striatum)
	-40	-64	8	1.733	0.001	41	L middle temporal gyrus (extending to: L middle occipital gyrus)
	-16	12	70	1.692	0.002	42	L superior frontal gyrus, dorsolateral (extending to: L middle frontal gyrus)
	-8	-44	-60	1.811	0.001	24	Cerebellum
	-4	-56	-52	1.68	0.002	14	L cerebellum, hemispheric lobule IX
THC<PLB	40	-32	-16	-4.284	< 0.001	176	R parahippocampal gyrus/ fusiform gyrus
	-60	-44	12	-3.008	< 0.001	115	L superior temporal gyrus (extending to: L middle temporal gyrus)
	16	-26	40	-3.148	< 0.001	111	R median cingulate / paracingulate gyri
	-54	4	-4	-3.037	< 0.001	109	L superior temporal gyrus (extending to: L rolandic operculum, L temporal pole, L heschl gyrus)
	48	12	-28	-3.207	< 0.001	83	R temporal pole, middle temporal gyrus (extending to: R superior temporal gyrus)
	-8	-104	0	-3.096	< 0.001	64	L middle occipital gyrus (extending to: L superior occipital gyrus)
	32	8	54	-2.847	0.001	56	R middle frontal gyrus (extending to:R precentral gyrus)
	52	-28	48	-2.999	< 0.001	36	R postcentral gyrus (extending to: R inferior parietal [excluding supramarginal and angular] gyri)
	-48	16	44	-2.589	0.002	33	L middle frontal gyrus
	-12	44	-10	-2.527	0.002	16	L superior frontal gyrus, medial orbital
	64	-28	-8	-2.498	0.003	16	R middle temporal gyrus
	-56	-28	20	-2.419	0.004	10	L supramarginal gyrus

Table 6
Areas of increased and attenuated activation signal following THC, compared with placebo, during sensory processing stimuli.

Comparison	MNI coordinate			SDM-Z	P	Voxels	Region
	x	y	z				
THC>PLB	4	-24	28	1.67	0.004	73	R mid cingulum (extending to R median cingulate/ paracingulate gyri)
	52	-42	-6	2.05	0.001	37	R middle temporal gyrus (extending to R inferior frontal gyrus)
	14	-86	-10	1.69	0.004	25	R lingual gyrus
	26	-82	-4	1.70	0.003	14	R fusiform gyrus (extending to R lingual gyrus)
	52	-42	44	1.67	0.004	14	R supramarginal gyrus (extending to R inferior parietal gyri)
THC<PLB	-12	16	12	-1.72	< 0.001	77	L caudate nucleus

3.6.2. Reward paradigms

Within the reward processing subgroup, 37 participants were compared in a crossover design following THC compared with placebo while performing the MIDT (Jansma et al., 2013; Van Hell et al., 2012) and listening to musically rewarding stimuli (Freeman et al., 2018).

3.6.3. Sensory stimulation paradigms

Within the sensory stimulation subgroup, 64 participants were compared in a crossover design following THC compared with placebo (Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011).

3.6.4. Memory paradigms

Within the memory processing subgroup, 41 participants were compared in a crossover design following THC compared with placebo while performing the verbal paired associates task (Bhattacharyya et al., 2009), Sternberg item recognition (Bossong et al., 2012a), and the associative memory task (Bossong et al., 2012b).

3.6.5. Attentional salience paradigms

Within the attentional salience subgroup, 95 participants were compared in a crossover design following THC compared with placebo while performing a visuo-motor tracking (Battistella et al., 2013), visual

Table 7
Areas of increased and attenuated activation signal following THC, compared with placebo, during memory processing.

Comparison	MNI coordinate			SDM-Z	P	Voxels	Region
	x	y	z				
THC>PLB	-28	48	22	2.169	< 0.001	253	L middle frontal gyrus (extending to L superior frontal gyrus, dorsolateral & medial)
	-34	-56	-40	2.352	< 0.001	100	L cerebellum
	32	24	54	2.099	0.001	23	R middle frontal gyrus (extending to R superior frontal gyrus, dorsolateral)
	-14	40	16	1.996	0.002	20	L anterior cingulate cortex (extending to L medial superior frontal gyrus)
	-52	36	2	2.165	< 0.001	19	L inferior frontal gyrus, triangular part
	28	48	16	1.87	0.003	17	R middle frontal gyrus (extending to R superior frontal gyrus, dorsolateral)
	48	-72	28	1.959	0.002	16	R middle occipital gyrus (extending to R middle temporal gyrus)
	44	16	32	1.875	0.002	13	R inferior frontal gyrus, opercular part
	-12	44	40	1.897	0.002	13	L superior frontal gyrus, dorsolateral
	-24	-64	-56	2.241	< 0.001	10	L cerebellum, hemispheric lobule VIII
THC<PLB	-48	-6	-4	-2.397	0.002	350	L superior temporal gyrus (extending to L rolandic operculum, L heschl gyrus, L superior temporal gyrus, L insula, L supramarginal gyrus, L postcentral gyrus)
	12	-40	0	-3.11	< 0.001	223	R lingual gyrus (extending to R precuneus, L thalamus, R parahippocampal gyrus, R hippocampus, cerebellum vermic lobule IV/V)
	4	-48	56	-2.397	0.002	149	R precuneus (extending to L precuneus, R superior parietal gyrus, R paracentral lobule, R postcentral gyrus, L precuneus)
	4	-72	24	-2.397	0.002	140	R cuneus cortex (extending to R precuneus, R superior occipital gyrus, R superior parietal gyrus, L precuneus)
	-8	-32	-16	-2.772	< 0.001	98	L cerebellum (extending to L fusiform gyrus, L pons, L parahippocampal gyrus, L hippocampus, L cerebellum hemispheric lobule III)
	-30	-28	-6	-2.391	0.002	43	L hippocampus (extending to L parahippocampal gyrus)
	-14	-58	58	-2.388	0.002	42	L precuneus
	10	-58	-50	-2.388	0.002	34	R cerebellum, hemispheric lobule IX
	-52	6	16	-2.366	0.002	16	L precentral gyrus (extending to L inferior frontal gyrus, opercular part)
	-56	-22	44	-2.385	0.002	15	L inferior parietal (excluding supramarginal and angular) gyri
	22	-68	54	-2.388	0.002	14	R superior parietal gyrus

Table 8
Areas of increased and attenuated activation signal following THC, compared with placebo, during attentional processing.

Comparison	MNI coordinate			SDM-Z	P	Voxels	Region
	x	y	z				
THC>PLB	-4	56	-8	3.171	< 0.001	1422	L medial superior frontal gyrus (extending to R medial superior frontal gyrus, L+R gyrus rectus, L+R anterior cingulate/ paracingulate gyri, L+R olfactory cortex)
	-52	0	-40	2.126	0.002	34	L inferior temporal gyrus
	32	14	-14	2.001	0.004	13	R insula
THC<PLB	-34	-2	12	-2.842	< 0.001	1556	L insula (extending to L Rolandic operculum, L superior temporal gyrus, L Heschl gyrus, L lenticular nucleus putamen, L supramarginal gyrus, L postcentral gyrus)
	36	-4	8	-3.230	< 0.001	1266	R insula (extending to R Rolandic operculum, R lenticular nucleus putamen, R Heschl gyrus, R striatum, R postcentral gyrus, R precentral gyrus, R superior temporal gyrus, R inferior frontal gyrus)
	0	-60	-8	-2.490	< 0.001	481	Cerebellum vermic lobule IV/V
	-58	0	22	-2.283	0.001	51	L precentral gyrus (extending to L postcentral gyrus)
	10	-76	16	-1.912	0.005	42	R calcarine fissure
	-8	-4	4	-2.215	0.001	38	L thalamus (extending to L caudate nucleus)
	16	-26	12	-2.195	0.001	15	L thalamus

oddball (Bhattacharyya et al., 2012a), continuous performance (Bossong et al., 2013b), and auditory attention tasks (O'Leary et al., 2000, 2002; O'Leary, Apr et al., 2007).

4. 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 (Bhattacharyya et al., 2012a, 2017, 2009; Jansma et al., 2013; Freeman et al., 2018; Bossong et al., 2012a, 2013a, 2015b; Battistella et al., 2013; Lee et al., 2013; Walter et al., 2019, 2017; Winton-Brown et al., 2011; Van Hell et al., 2012; Rabinak et al., 2012), PET (O'Leary et al., 2000, 2002, 2003; O'Leary, Apr et al., 2007), and ASL (Bossong et al., 2019). Using pooled summary data from 372 participants who were tested using a within-subject repeated measures design under experimental conditions acutely (5 min to 3 h after administration) following a single dose of THC (ranging from 6 to 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

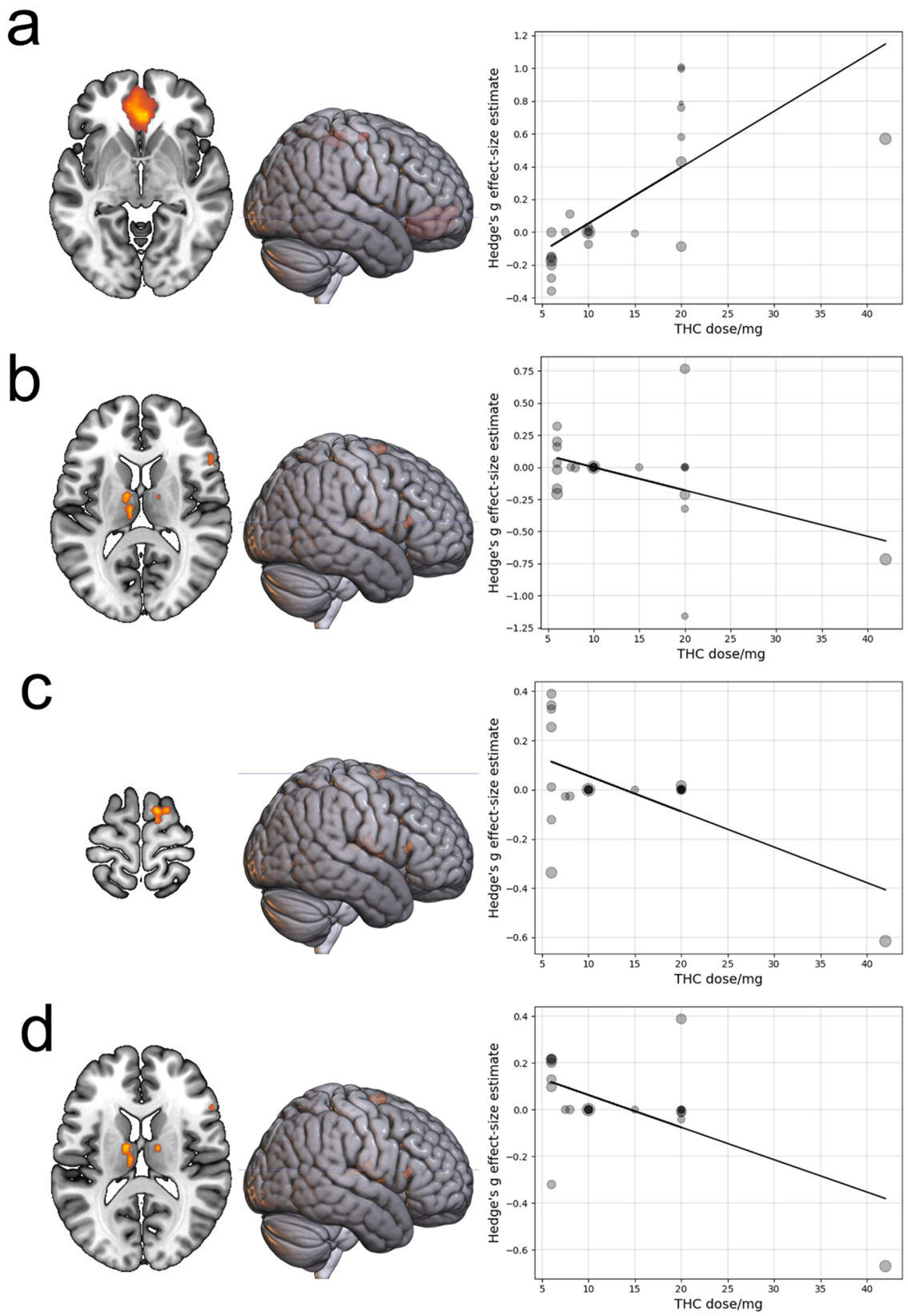

Fig. 3. Meta-regression analysis showing relationship between THC dose (mg) and Hedge's g effect-size estimate of brain signal modulation by THC compared to placebo. Bubble size= inverse of effect-size variance. Bubble intensity= overlap of contrasts. a) Effect-size estimates from right anterior cingulate/ 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.

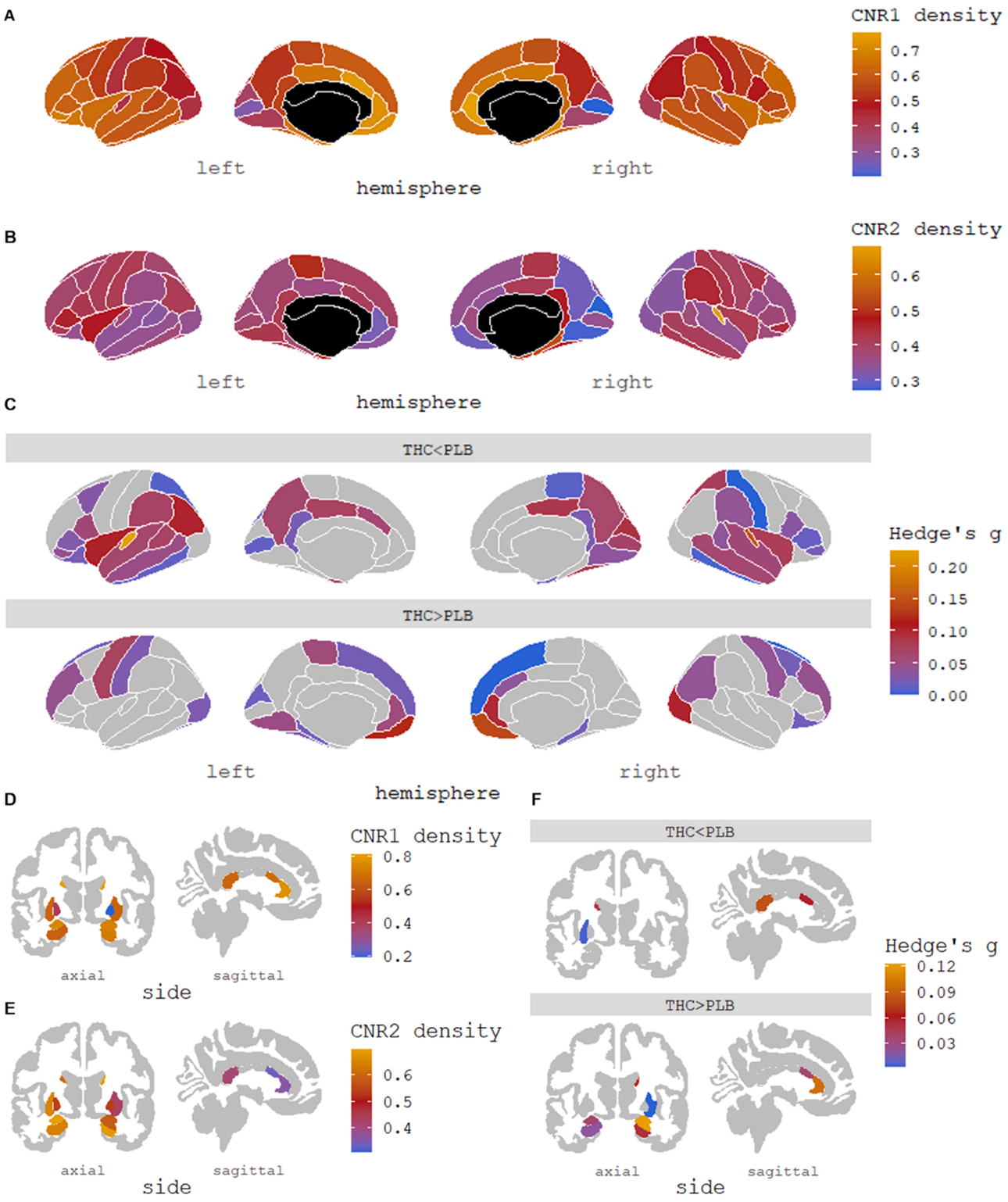

Fig. 4. Cortical spatial gene expression of (A) CNR1, (B) CNR2, and (C) Hedge's g effect size estimate derived from the main meta-analytic findings displaying regions of increased activation (THC>PLB), and attenuated activation (THC<PLB). Sub-cortical spatial distribution of (D) CNR1, (E) CNR2, and (F) 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 (Plotting Tool for Brain Atlases, 2021) in R studio (RStudio, 2021) parcellated across 78 regions of the Desikan–Killiany brain atlas (Desikan et al., 2006). Hedge's g was extracted from the centroid of each brain parcel. Gene expression data was obtained from the Allen Human Brain Atlas (Microarray Data, 2021).

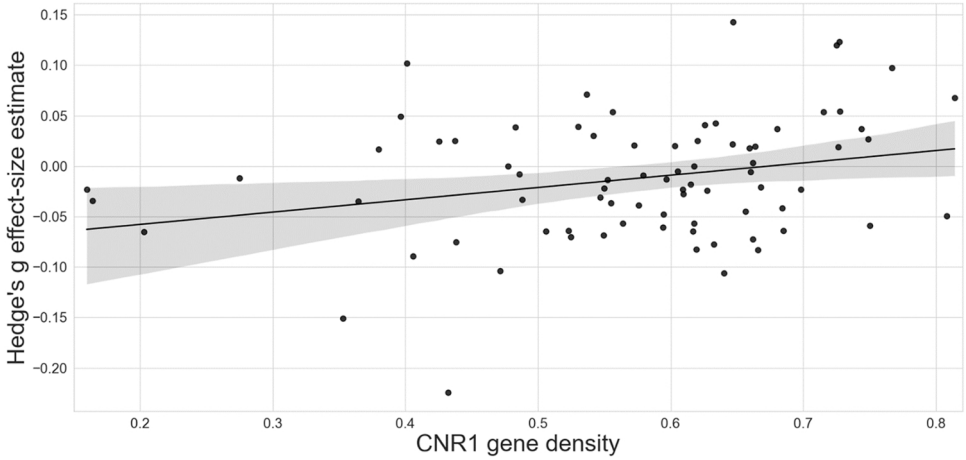

Fig. 5. Scatterplot showing the relationship between CNR1 expression values and Hedge's g effect size estimate of THC effect compared with placebo across the brain (based on parcellation implemented in the Desikan Killiany atlas). P = 0.018, t = 2.415, R^2 = 0.073, coefficient= 0.122, 95%CI= 0.021–0.223).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

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 (Shine et al., 2019). In their study, Shine et al. performed principal component analysis (PCA) (Brendel et al., 2011) to identify an 'integrative core' network of brain regions engaged across seven diverse cognitive tasks (Shine et al., 2019) which spatially mapped onto dorsal attention, frontoparietal and visual networks as well as the striatum, thalamus, cerebellum and amygdala (Shine et al., 2019). 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 (Blest-Hopley et al., 2018), as well as effects on behavioural performance during those tasks (Bloomfield et al., 2019). 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 (Zou and Kumar, 2018; Pertwee, 2008) which are ubiquitously distributed throughout the brain, with particularly high densities in cortex, amygdala, basal ganglia outflow tracts and cerebellum (Mackie, 2005). 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 (Shine et al., 2019). 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 (Di Forti et al., 2019; Schoeler et al., 2016b, 2016c).

As the CB1R has been shown to inhibit GABA and glutamate release from presynaptic terminals (Gerdeman and Lovinger, 2001; Katona et al., 1999), it may be argued that THC will increase activation in brain regions where CB1R tends to be expressed primarily on GABA terminals, while it will decrease activation in the brain regions where the CB1R are predominantly located on glutamatergic terminal. While we did not formally test this issue, upon exploring this possibility further in our sample no clear pattern seems to emerge. In non-human primates, the CB1R has been observed to be expressed by GABAergic neurons in the neocortex, hippocampus, and the amygdala (Eggan and Lewis, 2007; Katona et al., 2001; Hoffman et al., 2003). Therefore, regions with CB1R expression in GABAergic terminals seem to overlap with regions where we observed an increase in brain signal following THC, relative to placebo. However, in regions where the CB1R has been observed to be expressed by glutamatergic neurons, including the amygdala, hippocampus, striatum, midbrain, prefrontal cortex, and the somatosensory cortex (Robbe et al., 2001; Rodríguez et al., 2001; Köfalvi et al., 2005; Domenici et al., 2006; Fitzgerald et al., 2019), we did not observe an attenuative effect of THC, relative to placebo, on the pooled effect-size estimate of brain signal. Further, in the insula, parietal cortex, prefrontal cortex, postcentral and the superior temporal gyri, regions where the CB1R is also expressed in GABAergic neurons (Eggan and Lewis, 2007; Katona et al., 2001; Hoffman et al., 2003), we found an attenuative effect of THC, relative to placebo, on the activation signal instead of an increase in activation signal as would be expected if the direction

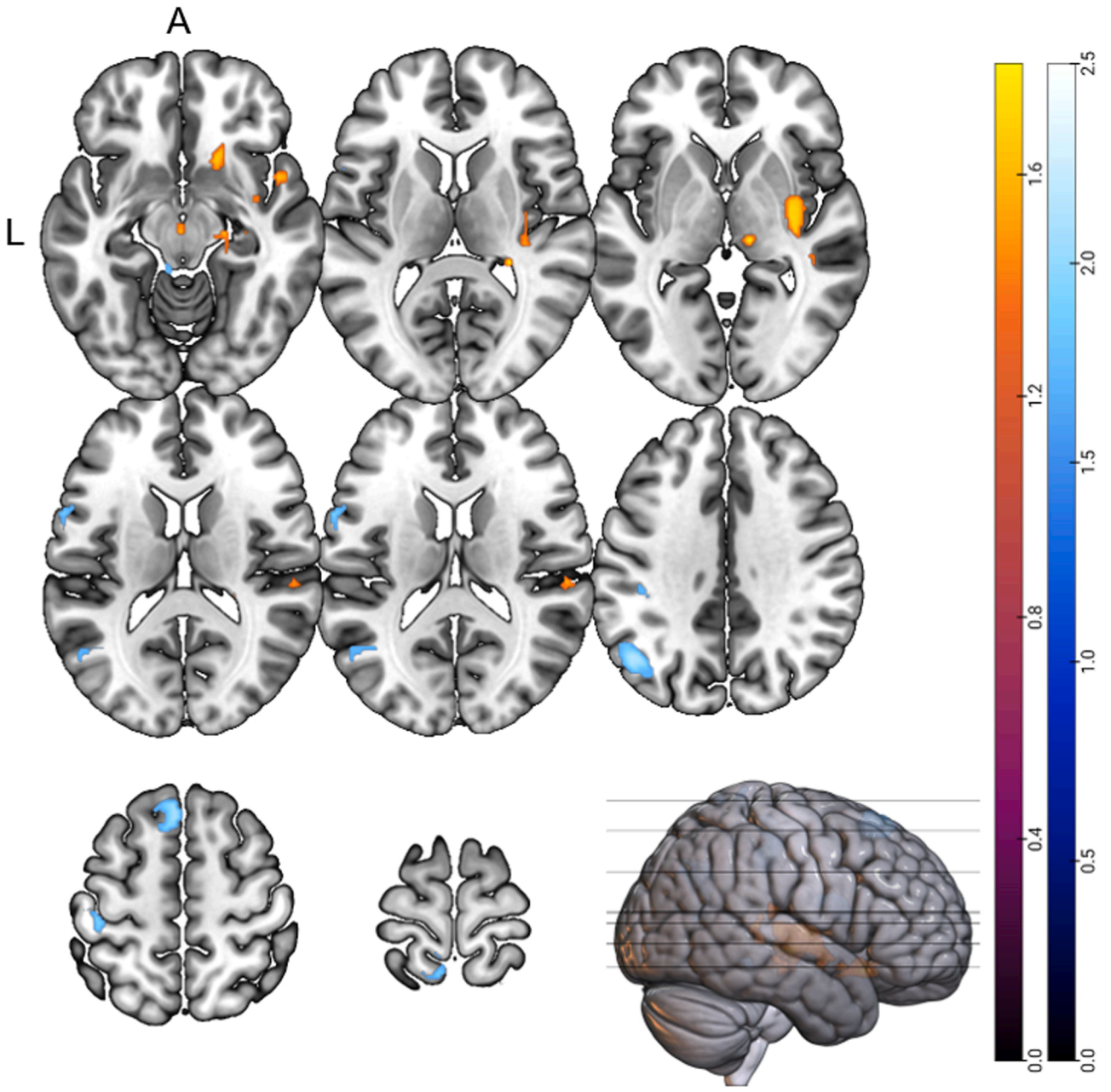

Fig. 6. Emotional processing: a) Areas of increased activation signal after THC compared with placebo, b) Areas of attenuated activation signal after THC compared with placebo.

of signal change was solely related to regional distribution of CB1R on GABAergic or glutamatergic neurons. Therefore, this suggests that the effect of THC on modulating the brain activation signal may not be solely related to the effect of THC on the CB1R in one region alone, but also related to THC effects on CB1 receptors in other regions that may be connected to that specific region.

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 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 (Mackie, 2005). 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 (National Center for Biotechnology Information, 2017). These findings are important as the CB1R is the main molecular target of THC in the human brain, where it has partial-agonist effects (Pertwee, 2008; Bossong et al., 2014). 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.

The multiple linear regression model identified no significant relationship between CNR2 gene expression (a proxy measure of CB2R (Zou and Kumar, 2018)) with the effect size estimate. This is perhaps unsurprising as there is lower CB2R expression in the brain relative to CB1R expression (Howlett et al., 2002). Therefore, it may be argued that inclusion of CB2R data in the regression model was not meaningful.

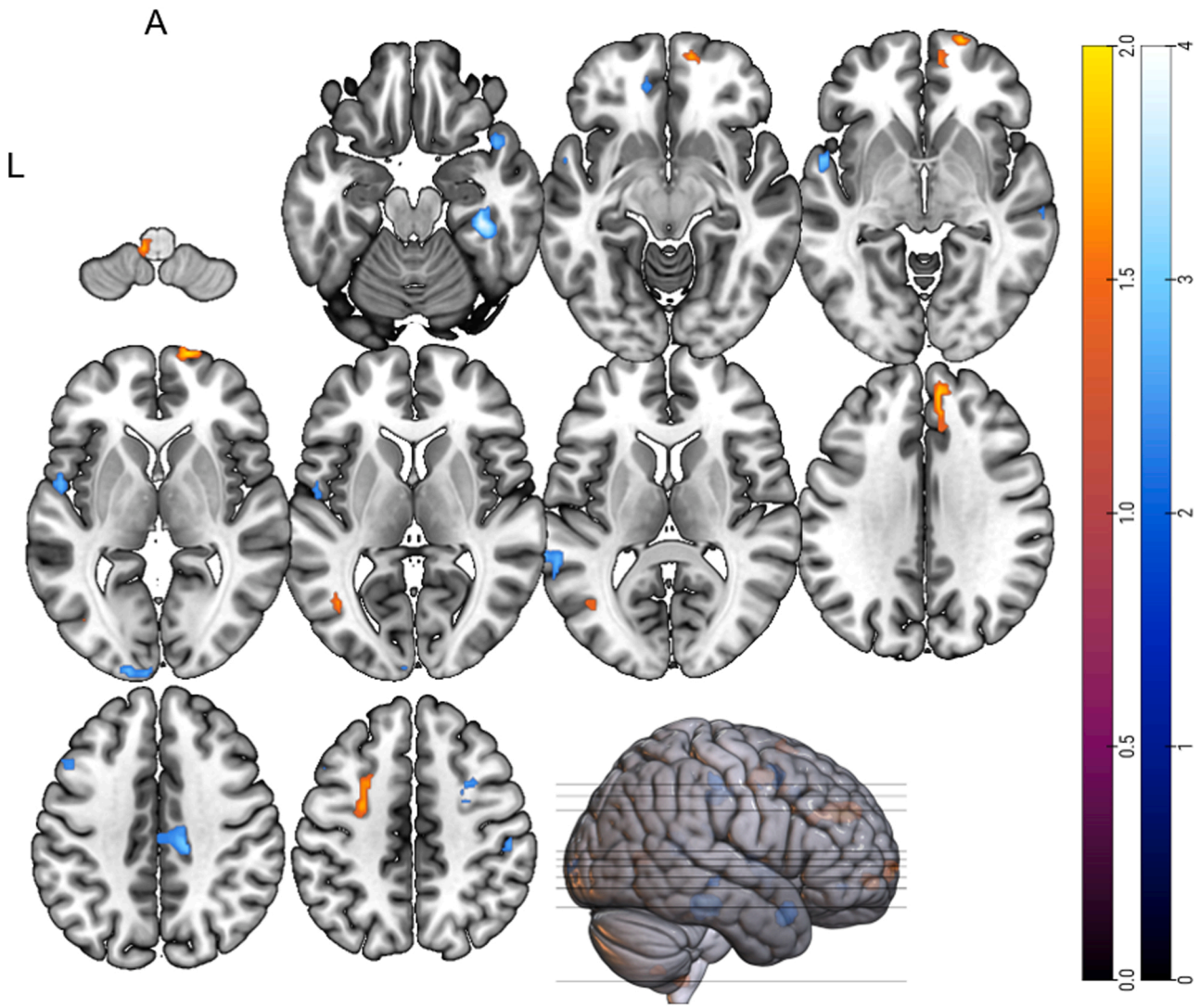

Fig. 7. Reward processing: a) Areas of increased activation signal after THC compared with placebo, b) Areas of attenuated activation signal after THC compared with placebo.

However, consistent evidence from non-human primates and rodents has shown that CB2Rs are moderately expressed in specific sub-populations of neurons as opposed to a ubiquitous low level throughout the brain (Chen et al., 2017; Lanciego et al., 2011; Zhang et al., 2014; Brusco et al., 2008; Gong et al., 2006; Ashton et al., 2006; Baek et al., 2009; Albayram et al., 2016; Liu et al., 2009; García-Gutiérrez et al., 2012; Navarrete et al., 2012; Li and Kim, 2015; Stempel et al., 2016; Galiègue et al., 1995; Van Sickle et al., 2005; Viscomi et al., 2009). THC also has high affinity to CB1R and CB2R, however, binds with less efficacy to CB2R, compared with CB1R, in vitro (Pertwee, 2008). Therefore, we reasoned that the effects of THC on brain function are likely a net result of its effect on regional CB1R but also CB2R and therefore partly determined by regional distribution of both receptors, albeit to a greater or lesser extent and entered both as potential predictors in the regression model.

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 (Rigney et al., 2018) and cognition (Apps et al., 2016), with functional alterations in individuals with high trait anxiety (Paulus et al., 2004) and psychosis (Smieskova et al., 2014; Nielsen et al., 2012). Therefore, the dose-dependent effect of THC on the ventral cingulate may explain the findings of THC challenge studies (D'Souza et al., 2004; Curran et al., 2016) 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 (Prashad and Filbey, 2017) with epidemiological reports suggesting a dose-related risk of motor vehicle accidents (Ramaekers et al., 2004). Two fMRI studies in adults and one in adolescents, employing a motor task, have reported attenuated anterior cingulate activation in cannabis users relative to healthy controls (Lopez-Larson et al., 2012; Pillay et al., 2004, 2008). However, one study has reported increased supplementary motor cortex activation with reduced psychomotor performance in chronic cannabis users during visual motor tasks (King et al., 2011). 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 (Asemi et al., 2015). In this context, it is also worth noting that the main meta-analysis identified a robust modulation of activation signal in the cerebellum following THC compared with placebo. The cerebellum is rich in CB1R (Herkenham et al., 1991; Marsicano and Kuner, 2008) and has a significant role in

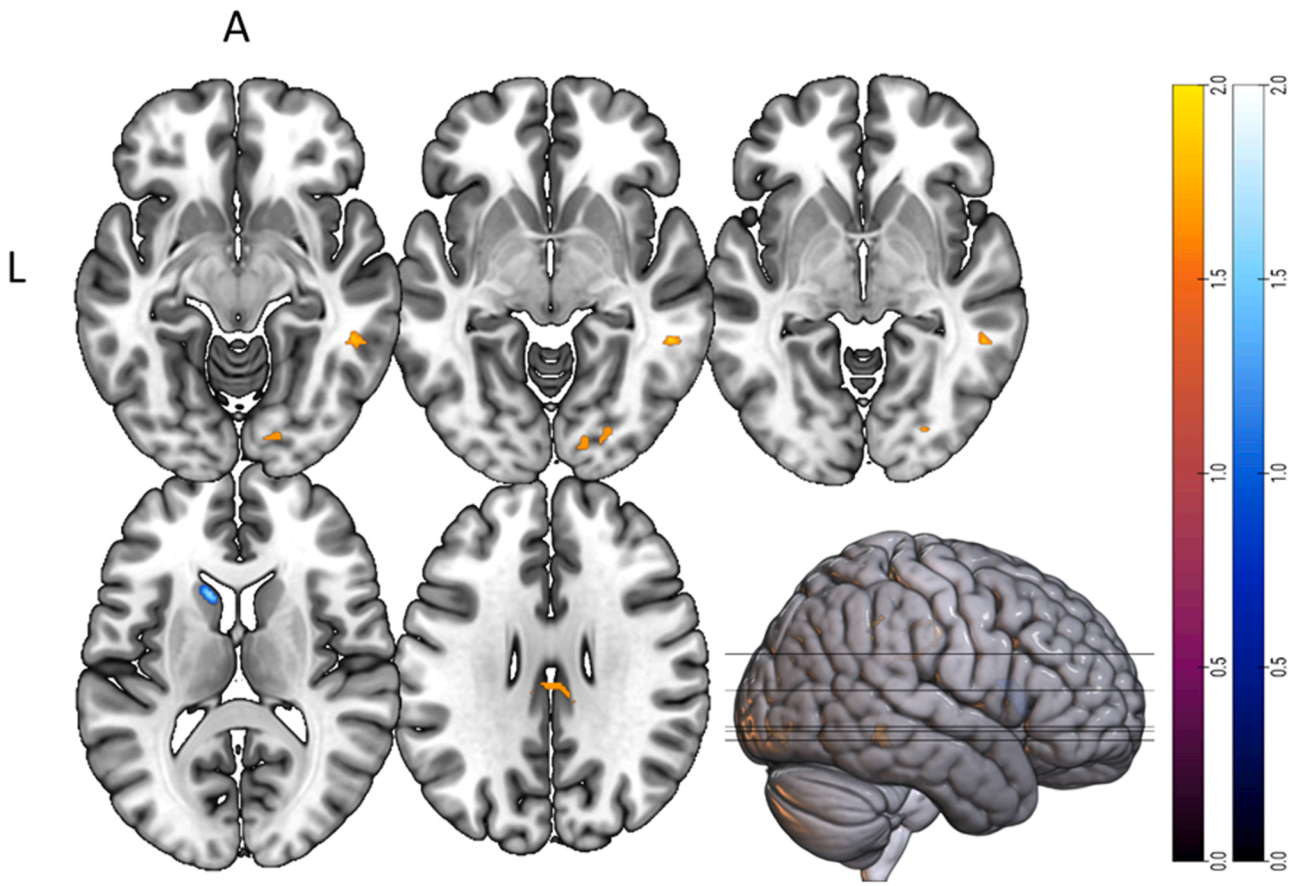

Fig. 8. Sensory processing: a) Areas of increased activation signal after THC compared with placebo, b) Areas of attenuated activation signal after THC compared with placebo.

postural (Ioffe et al., 2007, 2013) and motor control (Manto et al., 2012). Acute THC and THC-rich cannabis administration has been associated with increased postural sway in cannabis users (Liguori et al., 2002, 2003, 1998; Klumpers et al., 2012; Zuurman et al., 2010). Altered postural sway has also been observed in regular cannabis users, relative to non-drug using controls (Pearson-Dennett et al., 2017; Bolbecker et al., 2018). Moreover, fMRI studies have highlighted significantly attenuated activation of the cerebellum in adolescent cannabis users relative to healthy controls (Lopez-Larson et al., 2012). Therefore, our results highlight a modulatory effect of THC on the cerebellum, mediated through the CB1R, which may underlie the reported effects of THC and THC-rich cannabis on posture and motor control. 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. (2013) 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.

4.1. 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. General sources of heterogeneity consisted of comorbid exposure to alcohol, nicotine and other drugs between participants included in the various studies. Moreover, many studies did not control for the length of cannabis abstinence prior to scan acquisition, an issue when considering THC sensitisation. Broadly, participant cannabis history can be grouped into 1–25 uses in their lifetime (Bhattacharyya et al., 2012a, 2009, 2017, 2015b; Battistella et al., 2013; Winton-Brown et al., 2011; Rabinak et al., 2012) and 30–1415 uses in their lifetime (Jansma et al., 2013; Freeman et al., 2018; Bossong et al., 2012a, 2013a, 2019, 2012b, 2013b; Van Hell et al., 2012; O'Leary et al., 2000, 2002; O'Leary, Apr et al., 2007). One study was conducted within cannabis naïve participants (Lee et al., 2013), one was conducted within those with nicotine addiction (Jansma et al., 2013), and one used half a sample of those with chronic cannabis use (O'Leary et al., 2003). This heterogeneity is an accepted limitation, however, to assess the influence of individual studies on the main findings we conducted jack-knife leave-one-out sensitivity analysis, as detailed in Supplementary Table 1. The 22 studies included in this analysis were re-analysed, each

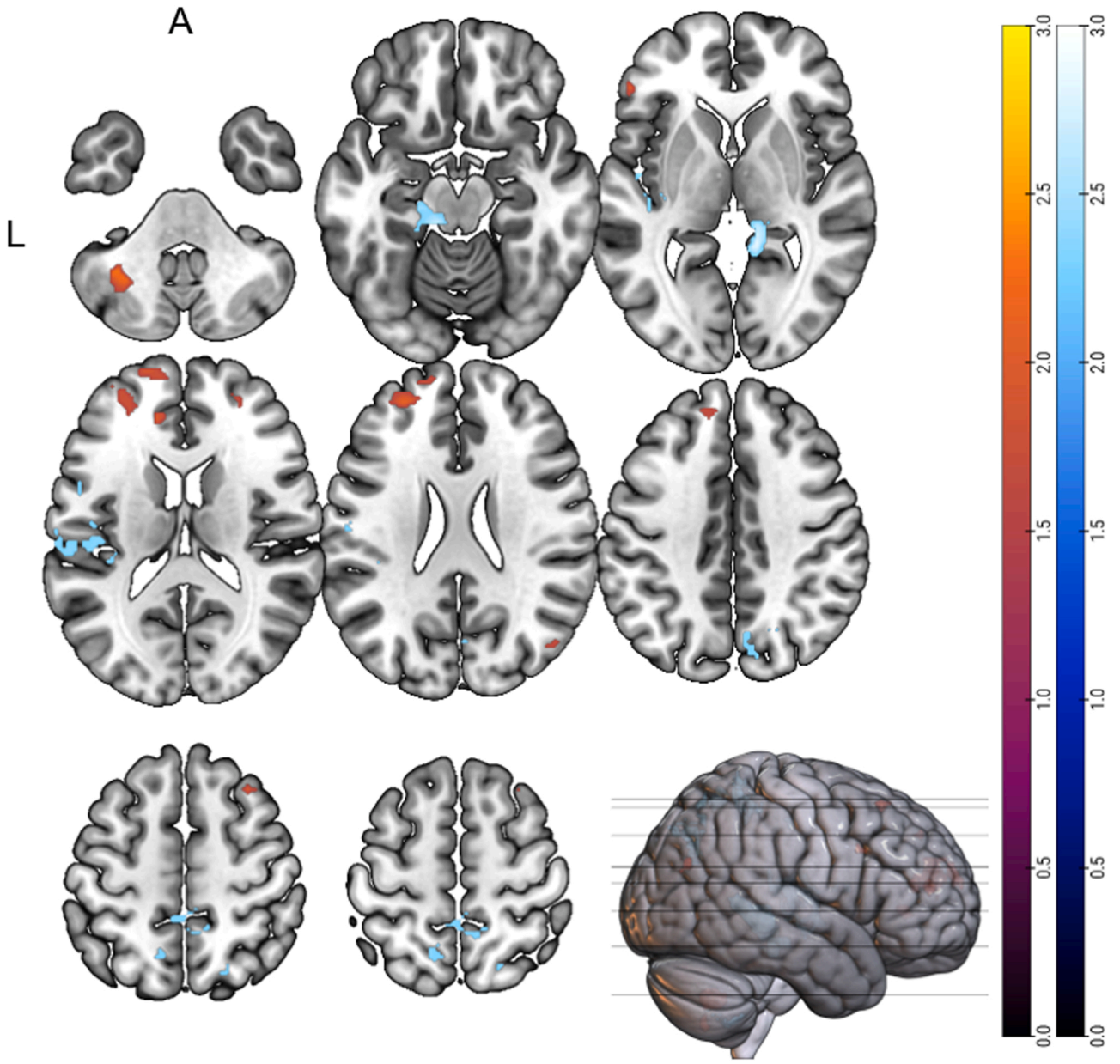

Fig. 9. Memory processing: a) Areas of increased activation signal after THC compared with placebo, b) Areas of attenuated activation signal after THC compared with placebo.

time excluding 1 single study at a time to establish whether each cluster remained statistically significant. Following this analysis there was an 87% cluster survival rate leaving one study out at a time. The high survival rate suggests that the results were unlikely to be driven by one largely influential study. Moreover, when leaving out the study with cannabis naïve participants, 14 out of the 16 clusters survived. Excluding the nicotine study and chronic cannabis study resulted in 12 out of the 16 clusters surviving. All brain regions had an I^2 statistic of less than 30% (except for the Rolandic operculum cluster that was attenuated following THC compared with placebo, I^2 =31.80%) suggesting perhaps a modest influence of heterogeneity on the results. Furthermore, visual inspection of overlap of meta-analytic activation maps and Q_H heterogeneity maps indicated that no areas in our main analysis were influenced by significant heterogeneity. When qualitatively comparing the clusters that were significantly modulated by THC, relative to placebo, following methodological subgroup analyses with the results of the main meta-analysis there was overlap in key cortical and sub-cortical regions. This suggests that the results in the main meta-analysis were unlikely to be driven by the sources of heterogeneity investigated in our sub-group analyses (further discussed in supplementary materials). 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.

A further limitation of this study is that we used mRNA expression to approximate cannabinoid gene expression. Therefore, we report an index of gene *transcriptional* activity as an indirect proxy of cannabinoid receptors, which is ultimately determined by gene *translation*. This distinction is important as previous reports highlight significant variance between mRNA and protein levels within a tissue (Futcher et al., 1999; Gygi et al., 1999; Greenbaum et al., 2003). This is particularly noteworthy in the present context as CB1R are located typically at axon terminals and mRNA is typically located in the cell bodies, indicating that their expression will not be identical in projection neurons (Stincic and Hyson, 2008). This may be reflected in the observation that gene expression (transcriptional activity) and protein abundance

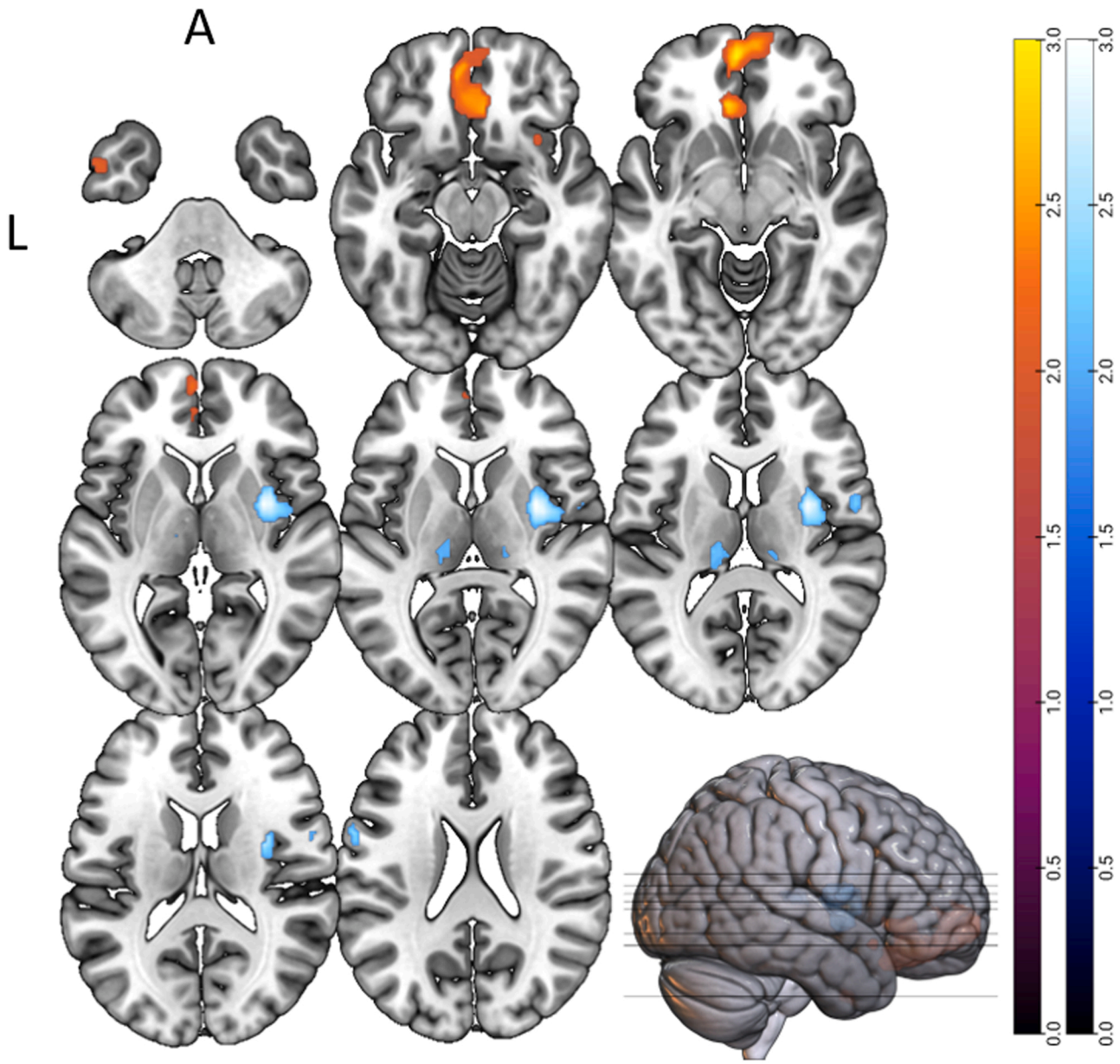

Fig. 10. Attention processing: a) Areas of increased activation signal after THC compared with placebo, b) Areas of attenuated activation signal after THC compared with placebo.

(translational activity) are not always positively correlated (Margineantu et al., 2007; Schwanhüusser et al., 2011). Therefore, although the mRNA measures are derived from tissue homogenates (including both axon terminals and cell bodies) where everything is averaged together, this represents a further caveat that needs to be considered while considering the present results. This limitation is also coupled with the caveat that the spatial of association between CB1R and the effect size estimate may not necessarily imply a causal association.

In addition, in present study, the gene expression data was obtained from 6 independent participants, downloaded from the Allen Human Brain Atlas database, who were not included in any of the neuroimaging studies of this meta-analysis. This prevented direct examination of the relationship between the acute effects of THC, compared to placebo, on brain function and CNR1 expression in the same participants. However, the core spatial architecture of receptor systems in the brain has been suggested to be consistent across individuals based on evidence from a number of previous studies (Rizzo et al., 2016; Veronese et al., 2016; Selvaggi et al., 2019). As the relative availability of CB1R and CB2R across brain regions are likely to be similar at the population level, the results presented here demonstrate an association between approximate population level estimates of CNR1 mRNA expression (as obtained from the Allen Human Brain Atlas database) and population level estimates of THC effects on brain signal (as obtained from meta-analytic effect-size estimates from included studies). Correlation between individualized mRNA expression data and neuroimaging data will allow a more precise delineation of the strength of the association between CNR1 expression and THC effect on brain signal and how inter-individual variation in receptor availability may underlie variability in brain functional response to THC (e.g as we have shown before (Bhattacharyya et al., 2017) and should be investigated in future studies. Similar approaches have been employed in independent studies to relate the spatial architecture of gene expression data (particularly using data from the Allen Human Brain Atlas database) to neuroimaging-based indices of brain function both in the absence of (Richiardi et al., 2015; Gryglewski et al., 2018; Vértes et al., 2016; Anderson et al., 2020; Martins et al., 2021) and under pharmacological manipulation conditions such as reported here

(Selvaggi et al., 2019). Further, in a separate study, neuroimaging-based brain functional indices have been shown to be correlated with brain expression data from unrelated samples across multiple datasets indicating the robustness of relationship between gene expression in the brain and brain function indices measured using fMRI at the population level, similar to the approach we have employed here (Wang et al., 2015). 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 (Shine et al., 2019), where its effects are in turn related to the availability of its main central molecular target across the brain.

CRediT authorship contribution statement

Conception and Design: Bhattacharyya; Data acquisition: Gunasekera, Davies, Bhattacharyya, Bossong, Ramsey, CBE Consortium collaborators; Statistical analysis: Gunasekera, Radua, Veronese, Blest-Hopley, (overseen by Bhattacharyya); Data interpretation: Gunasekera, Davies, Bhattacharyya; Drafting of the manuscript: Gunasekera, Davies, Bhattacharyya; Critical revision of the manuscript for important intellectual content: Gunasekera, Davies, Bhattacharyya, Blest-Hopley, Bossong, Ramsey, Radua, Veronese; Obtained funding: Not applicable; Technical support: Gunasekera, Blest-Hopley, Bhattacharyya, Radua, Veronese.

Conflict of interest statement

There are no known conflicts of interest associated with this publication and no significant financial support for this work that could have influenced its outcome other than those declared in the manuscript.

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AC and AWZ are coinventors of the patent "Cannabinoid-containing oral pharmaceutical composition, method for preparing and using same," INPI on September 16, 2016 (BR 112018005423–2). FSG, JECH, JAC and AWZ are coinventors of the patent "Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023," Def. US number Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR1120150164927; Mechoulam R, Zuardi AW, Kapczinski F, Hallak JEC, Guimarães FS, Crippa JAS, Breuer A). Universidade de São Paulo (USP) has licensed this patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1) and has an agreement with Prati-Donaduzzi to "develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders" (outside the submitted work). JAC is a consultant and/or has received speaker fees and/or sits on the advisory board and/or receives research funding from Janssen-Cilag, Torrent Pharm, Prati-Donaduzzi, PurMed Global, BSPG Pharm, and the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE) – National Health and Medical Research Council (NHMRC) over the past 3 years. AWZ, and JAC reported receiving grants from the São Paulo Research Foundation/FAPESP (2020/12110-9 and 2020/12066-0) and the National Institute of Translational Science and Technology in Medicine (INCT-TM, CNPq, Brasília, Brazil) and CNPq (Produtividade em Pesquisa - 1A).

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104801.

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