An insight into the acute effects of cannabidiol on human brain function and their relationship with the brain expression of its molecular targets: a neuroimaging meta-regression analysis

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Abstract

Background

Cannabidiol (CBD) is a non-intoxicating substance present in the extract of *Cannabis sativa* popularised by its therapeutic potential. A limited number of neuroimaging studies have investigated CBD effects on brain function primarily in healthy individuals, people with early/ clinical high risk of psychosis, and social anxiety disorder. As a result of heterogeneity in the population examined, imaging modality and neurocognitive paradigm, the acute brain effects of CBD and the molecular mechanisms that may underlie its effects remain unclear.

Methods

We meta-analysed neuroimaging studies that examined the acute effects of CBD, relative to placebo, on human brain function using SPECT and fMRI while performing diverse cognitive tasks. Subsequently, we examined the relationship between the spatially distributed pooled effects of CBD on brain signal and the distribution of candidate mechanistic targets for the effects of CBD including fatty acid amide hydrolase (*FAAH*), dopamine D_2, serotonin and cannabinoid-type-1 receptors as indexed by their gene expression data.

Results

CBD modulated the function of several brain regions, including the medial frontoparietal, midcingulo-insular, pericentral, lateral frontoparietal, and dorsal frontoparietal networks as well as the striatum and cerebellum. There was a significant inverse relationship between the magnitude of pooled CBD effect on brain activation and expression of *FAAH* but not the other targets.

Discussion

These preliminary findings suggest that the effect of CBD in the human brain may be linked to local FAAH availability and suggests that there is a strong case for directly examining whether the effects of CBD on FAAH underlie its effects on brain function and behaviour.

1.0 Introduction

Cannabidiol (CBD), a non-intoxicating substance present in the extract of *Cannabis sativa*(Hanuš *et al.*, 2016) has attracted particular attention in light of its therapeutic potential. It *can oppose some of the psychotomimetic and neurophysiological effects of* delta-9-tetrahydrocannabinol *(THC), the main psychoactive ingredient of cannabis, in healthy individuals* (Bhattacharyya *et al.*, 2010; Englund *et al.*, 2013; Gunasekera *et al.*, 2021) and may have antipsychotic efficacy in patients with psychosis (Leweke *et al.*, 2012; Boggs *et al.*, 2018; McGuire *et al.*, 2018), and excellent tolerability profile across different age groups (Chesney *et al.*, 2020; Velayudhan, McGoohan and Bhattacharyya, 2021).

A limited number of studies have investigated the effects of isolated CBD on the human brain using neuroimaging. These investigations have primarily taken place in healthy individuals, those with or at clinical high risk of psychosis and people with social anxiety disorder (Crippa *et al.*, 2004, 2011; Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012, 2015, 2018; Fusar-Poli *et al.*, 2009, 2010; Winton-Brown *et al.*, 2011; Grimm *et al.*, 2018; Pretzsch *et al.*, 2019; Wilson *et al.*, 2019; Lawn *et al.*, 2020; Davies *et al.*, 2020; O'Neill *et al.*, 2021). The neuroimaging techniques used include single photon emission tomography (SPECT) to measure cerebral blood flow (rCBF), or functional MRI (fMRI) to measure the blood-oxygen-level-dependent haemodynamic signal during cognitive tasks (Gunasekera *et al.*, 2021) as an index of brain function. Methodological heterogeneity across these studies, including from the specific population examined, imaging modality and choice of neurocognitive paradigm, has made interpretation of the acute neurophysiological effects of CBD challenging, as evident from recent systematic reviews (Bloomfield *et al.*, 2019; Gunasekera *et al.*, 2021). Further, the precise molecular mechanisms that may underlie the effects of CBD on human brain function remain unclear. A number of potential candidate mechanisms have been suggested, such as negative allosteric modulation of cannabinoid type 1 receptors (CB1R) (Laprairie *et al.*, 2015), weak antagonism of cannabinoid type 2 receptors (CB2R) (Thomas *et al.*, 2007), partial agonism of dopamine D_2 receptors (D2R) (a mechanism also shown by aripiprazole) (Tuplin and Holahan, 2017), inhibition of anandamide hydrolysis through fatty acid amide hydrolase (FAAH) inhibition (Bisogno *et al.*, 2001), and stimulation of vanilloid receptor type 1 (Bisogno *et al.*, 2001) and serotonin 1A receptor (5-HT1AR) (Sartim, Guimarães and Joca, 2016).

We take a meta-analytic synthesis approach to address these gaps in knowledge. First, we meta-analyse original neuroimaging studies that had examined the acute effects of CBD, relative to placebo, on brain function in humans using SPECT and fMRI, to quantify the acute effect of a single dose of CBD in humans. These pooled effects of CBD on regional brain activation or blood flow, and the spatial extent of these effects of CBD, have never been tested across a multitude of cognitive tasks, as opposed to specific paradigms (hereafter, referred collectively as 'activation signal'). Having quantified the effects of CBD, we then examine the relationship between the spatially distributed brain effects of CBD and local gene expression of molecular targets that are of interest as potential mechanistic targets for the central effects of CBD. Receptor gene expression levels may be a surrogate index of local receptor availability (Koussounadis *et al.*, 2015) and 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. Specifically, we focused on regional expression of genes coding for FAAH, D2R, 5-HT1AR and CB1R, the most likely candidate mechanistic targets for the effects of CBD in the brain, utilising gene expression data from the Allen Human Brain atlas (Hawrylycz *et al.*, 2012; Arnatkevičiūtė, Fulcher and Fornito, 2019).

Based on our previous qualitative synthesis of this literature (Gunasekera *et al.*, 2021), we hypothesised a meta-analytic effect of CBD on the medial frontoparietal, midcingular-insular, occipital, and pericentral networks as well as the cerebellar and striatal regions across a diverse range of cognitive paradigms. Here, we define these brain networks (and the anatomical regions encompassed by them) using the universal taxonomy of functional brain networks proposed by Uddin and colleagues (Uddin, Yeo and Spreng, 2019).

Given the accumulating evidence that CBD may function by indirectly enhancing endogenous anandamide levels via inhibition of its degrading enzyme (Bisogno *et al.*, 2001; Leweke *et al.*, 2012), FAAH (shown in rodents (Bisogno *et al.*, 2001; Ligresti *et al.*, 2006; Petrocellis *et al.*, 2011; Leweke *et al.*, 2012; Elmes *et al.*, 2015); we hypothesised that the pooled spatial effect of CBD on the activation signal across will be inversely associated with FAAH gene expression.

2.0 Methods

The protocol for this meta-analytic synthesis was registered in PROSPERO (CRD42019145442) in accordance with guidelines for neuroimaging meta-analyses (Müller *et al.*, 2018). Methods are reported in full in Supplementary Methods.

2.1 Search Strategy

A systematic search was conducted within Ovid MEDLINE, Embase, Global Health, and PsychINFO databases following recommendations by the Cochrane Handbook (Higgins *et al.*, 2019) and MOOSE guidelines (Stroup *et al.*, 2000). Search terms are outlined in Supplementary Methods.

2.2 Eligibility Criteria

Study inclusion criteria consisted of (i) an acute drug challenge that examined the effect of CBD, compared with placebo, on human brain function, (ii) indexed brain function with fMRI, PET, SPECT or arterial spin labelling (ASL), (iii) conducted whole-brain analysis (thereby excluding region of interest analyses), (iv) applied a uniform statistical threshold across all reported brain regions (thereby excluding those using small volume correction), and (v) published in a peer-reviewed journal. Exclusion criteria are reported in Supplementary Methods

Multiple imaging modalities (with and without activation/task paradigms) were included in the investigation to observe the global effects of CBD, as opposed to region-specific effects attributable to the type of cognitive paradigm employed.

2.3 Data Extraction

The authors or corresponding authors for articles that satisfied the inclusion criteria were contacted with a request for whole brain statistical maps. Whole-brain coordinates with their t-statistic for conditions CBD<PLB and CBD>PLB were extracted from published articles where it was not possible to obtain maps. A converter (Radua and Albajes-Eizagirre, 2019) was used to transform z or p-values into a t-value in cases where a t-statistic was not reported. Two researchers cross-checked the extracted data for errors.

2.4 Data analysis

The anisotropic effect-size version of the Seed-based Mapping (AES-SDM 5.15) software package (https://www.sdmproject.com/) (Radua *et al.*, 2013, 2014) was used to conduct a voxel-wise meta-analyses of differences in regional brain activation signal following CBD compared with placebo. From whole-brain coordinates and the t-statistic, AES-SDM utilises an anisotropic non-normalized Gaussian kernel to recreate an effect-size map and an effect-size variance map for the contrast between CBD and placebo for each study. A mean map was then established using a voxel-wise calculation of the random-effects mean of the study maps (using Hedge's g), factoring sample size and variance of each study and between-study heterogeneity. Standard randomisation tests were used to determine statistical significance (Radua *et al.*, 2010). Q_H statistics, Egger's test, and jack-knife leave-one-out sensitivity analysis are detailed in Supplementary Methods.

2.6 Subgroup analysis

The combination of populations (including healthy and psychosis groups) was one of the likely sources of heterogeneity in the main meta-analytic findings. Therefore, we also conducted subgroup analyses of healthy and psychosis subjects separately.

2.7 Whole brain correlation with *FAAH*, *DRD2*, *HTR1A* and *CNR1* gene expression

Details on genetic data processing from the Allen Human Brain Atlas are reported in full within the Supplementary Methods. In summary, effect-size estimates, obtained from the centroid voxel of each brain region parcellated across the Desikan-Killiany atlas (Desikan *et al.*, 2006), were extracted using SDM from our main imaging analysis with all participants. Multiple-linear regression analysis was then conducted where the SDM effect-size estimates for brain regions across the Desikan-Killiany atlas (Desikan *et al.*, 2006) were considered as the dependent variable and the corresponding average *FAAH*, *DRD2*, *HTR1A* and *CNR1* gene expression values, derived from the Allen Human Brain Atlas, were considered as the predictor variables using Python 3.7.9 (Python Software Foundation, 2016). The package *abagen* (Markello *et al.*, 2020) was used in conjunction with recommendations in processing mRNA microarray expression data from the Allen Human Brain Atlas (Arnatkevičiūtė, Fulcher and Fornito, 2019).

3.0 Results

3.1 Included Studies

A final set of 12 manuscripts met the study inclusion criteria (Table 1) (Crippa *et al.*, 2004, 2011; Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012, 2018; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011; Wilson *et al.*, 2019; Davies *et al.*, 2020; Lawn *et al.*, 2020; O'Neill *et al.*, 2021). Of these manuscripts, 10 used fMRI (Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012, 2018; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011; Wilson *et al.*, 2019; Davies *et al.*, 2020; Lawn *et al.*, 2020; O'Neill *et al.*, 2021) and 2 used SPECT (Crippa *et al.*, 2004, 2011). Figure 1 shows the PRISMA flowchart (Moher *et al.*, 2009). The final

combined sample size was 222 ([175 under CBD condition + 177 under placebo condition] – 130 cross-over). Our key analysis included 7 studies in healthy participants (Crippa *et al.*, 2004; Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011; Lawn *et al.*, 2020), 4 in participants at clinical high risk/ early psychosis (Bhattacharyya *et al.*, 2018; Wilson *et al.*, 2019; Davies *et al.*, 2020; O'Neill *et al.*, 2021), and 1 in social anxiety disorder (Crippa *et al.*, 2011).

In this analysis, we had partially-overlapping datasets within healthy (Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011) and psychosis (Bhattacharyya *et al.*, 2018; Wilson *et al.*, 2019; Davies *et al.*, 2020) participants. However, given that the subjects performed distinct fMRI paradigms that were unrelated in outcome measure we treated them as independent studies for the purposes of these analyses (Turkeltaub *et al.*, 2012) (detailed in Discussion).

Table 1. All studies that were included in the meta-analysis. T=Tesla, 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 controlled, C= cannabis controlled, D= illicit drug controlled, T= tobacco controlled, SAD= social anxiety disorder, CHR= clinical high risk for psychosis. FEP= first episode psychosis.

Author	*Route*	*Population*	*Mode*	*Paradigm*	*Baseline condition*	*Design*	*Sample size CBD*	*Sample size Placebo*	*Mean age (SD)*	*Time to scanning*	*Pre-scan screens*	*Dose (*
(Bhattacharyya *et al.*, 2009)	OC	Healthy	fMRI	VPA	Presented with pairs of words-state if font is the same	DB, PC, R, WS	15	15	26.7 (5.7)	1-2h	A,C,D	600
(Bhattacharyya *et al.*, 2012)	OC	Healthy	fMRI	Attentional salience	Oddball vs standard	DB, PC, R, WS	15	15	26.7 (5.7)	1-2h	A,C,D	600
(Bhattacharyya *et al.*, 2018)	OC	CHR	fMRI	VPA	Blank cue	DB, PC, R, BS	15	15	22.7 (5.1) CBD, 24.1 (4.5) plb	1-2h	A,C,D	600
(Borgwardt *et al.*, 2008)	OC	Healthy	fMRI	Go/No-Go	No-go and oddball contrasted against Go	DB, PC, R, WS	15	15	26.7 (5.7)	1-2h	A,C,D	600
(Crippa *et al.*, 2004)	OC	Healthy	99mTc-ECD SPECT	Rest	NA	DB, PC, R, WS	10	10	29.8 (5.1)	110'	A,C,D	400
(Crippa *et al.*, 2011)	OC	SAD	99mTc-ECD SPECT	Rest	NA	DB, PC, R, WS	10	10	24.2 (3.7)	110'	A,C,D	400
(Davies *et al.*, 2020)	OC	CHR	fMRI	Fear processing	Neutral expression	DB, PC, R, BS	15	15	22.7 (5.1) CBD, 24.1 (4.5) plb	1-2h	A,C,D	600
(Fusar-Poli *et al.*, 2009)	OC	Healthy	fMRI	Emotional face processing task	Neutral expression	DB, PC, R, WS	15	15	26.7 (5.7)	1-2h	A,C,D	600
(Lawn *et al.*, 2020)	OC	Healthy	fMRI	MIDT	No monetary reward	DB, PC, R, WS	23	23	23.74 (4.2)	2.5h	A,C,D	600
(O'Neill *et al.*, 2021)	OC	FEP	fMRI	VPA	Pair of rectangles	DB, PC, R, WS	13	13	27.73 (4.61) 66.7	3h	A,C,D	600
(Wilson *et al.*, 2019)	OC	CHR	fMRI	MIDT	No monetary reward	DB, PC, R, BS	15	17	22.7 (5.1) CBD, 24.1 (4.5) plb	1-2h	A,C,D	600
(Winton-Brown *et al.*, 2011)	OC	Healthy	fMRI	Auditory and visual stimuli	Independent of sensory load	DB, PC, R, WS	14	14	26.7 (5.7)	1-2h	A,C,D	600

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

Four regions of significantly increased augmented signal (Table 2, Figure 2) under CBD compared with placebo were observed. There were 6 regions of significantly attenuated activation signal under CBD compared with placebo (Table 2, Figure 2).

Table 2. Findings from the main meta-analysis containing both healthy and disease populations highlighting areas of augmented and attenuated activation signal following CBD compared with placebo.

	MNI coordinate			*SDM-Z*	*P*	*Voxels*	*Region*	*Egger's Test P value*
	x	y	z					
CBD>PLB	28	56	-10	1.55	<0.001	72	R middle orbital frontal gyrus (extending to R superior orbital frontal gyrus, R striatum)	0.31
	-22	-84	-42	1.16	0.003	38	L cerebellum crus II	0.26
	54	-10	-34	1.23	0.002	27	R inferior temporal gyrus (extending to R middle temporal gyrus)	0.54
	44	-36	-2	1.23	0.002	21	R middle temporal gyrus (extending to R superior temporal gyrus)	0.69
CBD<PLB	-18	-34	-20	-2.08	<0.001	253	L cerebellum lobule IV / V (extending to L parahippocampal gyrus, L hippocampus, L fusiform gyrus, L cerebellum lobule III, L pons)	0.026
	-10	8	46	-2.05	<0.001	78	L supplementary motor area (extending to L median cingulate / paracingulate gyri)	0.086
	52	-56	-6	-1.9	<0.001	50	R inferior temporal gyrus (extending to R middle temporal gyrus)	0.22
	64	2	24	-1.83	0.002	22	R precentral gyrus (extending to R postcentral gyrus)	0.002
	-34	2	-20	-1.76	0.003	22	L superior temporal pole (extending to L amygdala)	0.23
	8	14	42	-1.71	0.003	12	R median / paracingulate gyri	0.1

3.3 Sensitivity, Heterogeneity, and Publication Bias

Following jack-knife sensitivity analysis, 80% out of a total of 120 clusters survived after repeatedly excluding one study per iteration (Supplementary Table 1). To investigate potential publication bias, funnel plots were created and examined for each cluster in addition to performing Egger's tests (Table 2 and Supplementary Results). There was no indication that the brain regions identified within our main analysis were significantly influenced by heterogeneity after visual inspection of the overlap between the meta-analytic activation maps and heterogeneity maps.

3.4 Subgroup analyses

Within the healthy subgroup there were 3 regions which displayed a significant increase in activation signal (Table 3, Figure 3) under CBD relative to placebo. There was a significant attenuation of activation signal under CBD compared with placebo across 5 regions (Table 3, Figure 3).

Table 3. Meta-analytic findings highlighting regions of augmented and attenuated activation signal after CBD relative to placebo across healthy subjects.

	MNI coordinate			*SDM-Z*	*P*	*Voxels*	*Region*
	x	y	z				
CBD>PLB	34	-16	-34	1.43	<0.001	1921	R parahippocampal gyrus (extending to R inferior, middle, superior temporal gyrus, R Rolandic operculum, R parahippocampal gyrus, R hippocampus, R Heschl gyrus, R insula
	28	-6	4	1.22	<0.001	172	R striatum (extending to R lenticular nucleus, putamen)
	34	-42	0	1.47	<0.001	66	R fusiform gyrus (extending to R hippocampus)
CBD<PLB	-36	-4	-20	-1.48	0.001	251	L hippocampus (extending to L amygdala, L parahippocampal gyrus, L temporal pole superior temporal gyrus, L olfactory cortex)
	6	-46	28	-1.49	0.001	228	R posterior cingulate gyrus (extending to R median cingulate / paracingulate gyri, L posterior cingulate gyrus)
	4	-30	46	-1.44	0.002	53	R median cingulate / paracingulate gyri (extending to L median cingulate / paracingulate gyri)
	-48	-34	16	-1.52	<0.001	36	L superior temporal gyrus
	0	6	26	-1.38	0.003	11	L anterior cingulate (extending to paracingulate gyri)

Within the psychosis subgroup, 6 regions of significantly augmented activation signal were observed (Table 4, Figure 4), under CBD relative to placebo. There was a significant attenuation of activation signal across 5 regions following CBD relative to placebo (Table 4, Figure 4).

Table 4. Differences in increased and attenuated activation signal following meta-analytic comparisons between CBD with placebo across psychosis participants.

	MNI coordinate			*SDM-Z*	*P*	*Voxels*	*Region*
	x	**y**	**z**				
CBD>PLB	-6	-6	16	1.75	<0.001	334	L thalamus (extending to L caudate nucleus, L striatum)
	38	30	-12	1.75	<0.001	181	R inferior orbital frontal gyrus (extending to R insula)
	26	58	-8	1.75	<0.001	152	R superior orbital frontal gyrus (extending to R middle orbital frontal gyrus, R striatum)
	50	8	-20	1.51	0.002	141	R superior temporal pole (extending to R superior temporal gyrus, R middle temporal gyrus)
	20	-78	-14	1.59	0.001	96	R lingual gyrus (extending to R fusiform gyrus, R cerebellum lobule VI)
	54	-42	2	1.38	0.003	22	R middle temporal gyrus
CBD<PLB	-22	-36	-32	-2.69	<0.001	902	Middle cerebellar peduncles (extending to L cerebellum lobule III,VI,IV/V,VIIB,VIII, L fusiform gyrus, L parahippocampal gyrus, L pons)
	56	-20	38	-2.46	<0.001	440	R postcentral gyrus (extending to R precentral gyrus, R supramarginal gyrus, R middle frontal gyrus)
	0	-2	50	-1.78	0.002	217	R supplementary motor area (extending to L supplementary motor area, L median cingulate / paracingulate gyri)
	-46	-56	0	-2.09	<0.001	199	L middle orbital frontal gyrus (extending to L middle temporal gyrus, L middle and inferior occipital gyrus)
	38	-10	58	-1.83	0.002	17	R precentral gyrus (extending to R dorsolateral superior frontal gyrus)

3.5 Whole brain correlation with *FAAH*, *DRD2*, *HTR1A* and *CNR1* gene expression

Multiple regression analysis highlighted a significant negative relationship between FAAH expression and pooled Hedge's g effect-size estimate (t=-2.29, P=0.024, coefficient= -0.18, 95% CI= -0.34 to -0.024, Figure 5) across the 78 brain regions of the Desikan-Killiany atlas after controlling for the other genes entered into the model. There were no significant associations observed between Hedge's g effect size estimates and *DRD2*, *HTR1A* and *CNR1* expression levels. For regression diagnostics see Supplementary Results.

4.0 Discussion

In this meta-analytic synthesis, we examined the acute effect of CBD on human brain activation signal (Crippa *et al.*, 2004, 2011; Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012, 2018; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011; Wilson *et al.*, 2019; Davies *et al.*, 2020; Lawn *et al.*, 2020; O'Neill *et al.*, 2021). Our key analysis included 7 studies in healthy participants (Crippa *et al.*, 2004; Borgwardt *et al.*, 2008; Bhattacharyya *et al.*, 2009, 2012; Fusar-Poli *et al.*, 2009; Winton-Brown *et al.*, 2011; Lawn *et al.*, 2020), 4 in psychosis (Bhattacharyya *et al.*, 2018; Wilson *et al.*, 2019; Davies *et al.*, 2020; O'Neill *et al.*, 2021), and 1 in social anxiety disorder (Crippa *et al.*, 2011). Of these manuscripts, all but two (which used SPECT (Crippa *et al.*, 2004, 2011)) used fMRI. We investigated the effect of a single dose of oral CBD administration (ranging from 400 – 600 mg), compared with placebo, under experimental conditions (1 to 3 hours after administration) on brain activation during an array of cognitive processes using pooled summary data.

When combining data from all studies, we found that CBD modulated the function of 10 (peak) brain regions, with clusters extending to a number of other regions. Within our predicted network of regions (based on the taxonomic definitions proposed by Uddin et al. (2019)), CBD modulated the activation signal relative to placebo in the medial frontoparietal network (attenuation of the hippocampus/ parahippocampal gyrus, augmentation of the superior frontal gyrus, and both attenuation and augmentation of different parts of the middle temporal gyrus), midcingulo-insular network (attenuation of the amygdala) and the pericentral network (attenuation of the supplementary motor area and augmentation of the superior temporal gyrus). Increases in brain signal were also observed in the striatum and cerebellum. Furthermore, we found that CBD modulated activation signal in networks that we had not predicted, including the lateral frontoparietal network (augmentation of the middle frontal gyrus and the inferior temporal gyrus, as well as attenuation in a spatially distinct region of the inferior temporal gyrus) and the dorsal frontoparietal network (attenuation of the post central gyrus) (see Table 2 for coordinates). Contrary to our initial hypothesis, within our main results we found no significant effects in occipital network regions. Our second prediction was that the acute effect of CBD on activation signal across different brain regions will be directly associated with pooled *FAAH* gene expression data from a set of 6 unrelated healthy volunteers (who did not take part in the neuroimaging studies reported here), as obtained from the Allen Human Brain atlas. We observed an inverse relationship between the effect of CBD on brain activation signal from our main findings with *FAAH* gene expression –-a proxy measure of local *FAAH* availability–-but not the other genes of interest.

The findings of this meta-analytic synthesis highlight a general pharmacological effect of CBD in the human brain, which we localised primarily to the medial frontoparietal network. This macro-scale network is proposed to encompass the commonly termed "default mode network" and subsumes the "limbic

network", and while at a more granular level, a mediotemporal subsystem (involved in associative processing and recall) has been identified (Uddin, Yeo and Spreng, 2019). Although there is no current consensus on the broad central functions of the medial frontoparietal network, it has been associated with constructing, phasic binding, and continuous updating of associative representations obtained from goal-states (Uddin, Yeo and Spreng, 2019). It has also been proposed that this network is involved in the generation of predictions (predictive coding) and semantic associations via internal and external salience processing to provide value coding and goal-directed cognition (Bar *et al*., 2007; Roy, Shohamy and Wager, 2012; Nathan Spreng *et al*., 2014; Dohmatob, Dumas and Bzdok, 2017). Given that the tasks included in our meta-analysis broadly overlap with the aforenamed processes, such as processing salient stimuli in the MIDT (Wilson *et al*., 2019) and visual oddball detection (Bhattacharyya *et al*., 2012) tasks, it makes sense that brain regions within the medial frontoparietal network would be engaged. Therefore, this raises challenges when assessing whether the effects seen here are due to the pharmacological effects of CBD, or simply reflect a task-based neurophysiological response. It is also worth noting the possibility that the engagement of specific brain regions seen within this network, such as the hippocampus/ parahippocampal gyrus, may also reflect the limited cognitive paradigms employed. Although we attempted to observe the domain-general—rather than task-specific—effects of CBD on the brain activation signal, the most common task included in the meta-analysis was the verbal paired associates learning and memory task, which is well known to engage hubs of the medial frontoparietal network, such as the mediotemporal and frontal cortices (Bhattacharyya *et al*., 2009, 2018; O'Neill *et al*., 2021). This makes it difficult to distinguish whether the effects of CBD in the brain regions reported here are truly a result of its pharmacological effects, or rather a product of the types of cognitive paradigms employed (which each restrict findings to those spatial regions engaged by the task).

A further consideration for interpreting the main results of this meta-analysis is the heterogenous study group examined, including both healthy participants and those with psychiatric disorders such as psychosis (primarily) and social anxiety disorder. We opted for this analytical approach in an effort to boost power, given the limited number of studies that have so far examined the acute effects of CBD using neuroimaging. However, a key concern is that the effects of CBD may differ in patients relative to healthy control groups, which may be driven by differences in the neural pathology of patient cohorts. Contemporary preclinical models of psychosis suggest that alterations of brain regions within the medial temporal lobe (including the hippocampus, parahippocampus, and amygdala (Cutsuridis and Yoshida, 2017)) may drive subcortical dopamine dysfunction through projections to the striatum and midbrain (Modinos *et al*., 2015). Furthermore, neuroimaging studies in individuals at clinical high risk for psychosis suggests a relationship between the later onset of psychosis with greater alterations in parahippocampal structure (Mechelli *et al*., 2011) and function (Allen, Chaddock, *et al*., 2012; Allen *et al*., 2016, 2018) and to elevated striatal and midbrain dopamine activity (O. D. Howes *et al*., 2011; O. Howes *et al*., 2011; Allen, Luigjes, *et al*., 2012). This suggests large variation in the regional effects, and concurrent effect-size estimates, of studies included for analysis driven the different population samples (disease vs healthy). Given that the effects of CBD may differ in different population samples this increase in noise may have decreased our sensitivity to detect significant meta-analytic effects due to the thresholding set. To evaluate the extent to which our results may be influenced by psychiatric group differences, we visually compared the overlap between our main findings and those restricted to healthy participants following subgroup analysis. We found an overlap of brain regions including hippocampus and amygdala, suggesting that effects in these regions were not driven exclusively by the psychosis group. Overlap was also identified within the inferior and middle temporal lobes, further highlighting that these effects are likely associated with a pharmacological effect of CBD rather than group variances between healthy and neuropsychiatric subjects.

Our second major finding was the observation of a negative linear relationship between the effect of CBD on brain signal (as indexed by the pooled effect-size estimate) and *FAAH* gene expression levels (as estimated on the basis of an average from 6 post-mortem brains of healthy individuals obtained from the Allen Human Brain Atlas). This is of interest as previous studies have shown that CBD may enhance endogenous anandamide signalling indirectly, by inhibiting the intracellular degradation of anandamide (Bisogno *et al*., 2001; Leweke *et al*., 2012) catalysed by *FAAH* in rodents (Bisogno *et al*., 2001; Ligresti *et al*., 2006; Petrocellis *et al*., 2011; Leweke *et al*., 2012; Elmes *et al*., 2015). However, in contrast to robust findings of *FAAH* inhibition by CBD in rodents, one study has reported that CBD does not inhibit the enzymatic actions of human *FAAH* (Elmes *et al*., 2015). Elmes et al. transfected human *FAAH* into HeLa cells (Landry *et al*., 2013), with FABP5 knocked out (Berger *et al*., 2012; Kaczocha *et al*., 2012), and measured *FAAH* hydrolytic activity and [^{14}C]anandamide uptake inhibition using enzyme assays. CBD had no significant effect on anandamide levels and did not modulate the proportion of intracellular anandamide that is hydrolysed following uptake. Elmes and colleagues further identified that CBD did not inhibit anandamide hydrolysis by human *FAAH* in cell homogenates. These findings suggest that CBD may function by blocking the delivery of anandamide to *FAAH* but does not affect anandamide hydrolysis by *FAAH* (Elmes *et al*., 2015). The conflicting findings considering mode of action of CBD on *FAAH* may be attributed to rodent and human species specificity (Elmes *et al*., 2015). Nevertheless, the findings reported here, that the effects of CBD on human brain function are in part inversely related to local *FAAH* availability, complement independent experimental evidence that CBD has some effect on *FAAH* across both rodents and humans. Moreover, our findings are consistent with indirect human evidence that CBD significantly increases serum anandamide levels in people with psychosis, which was associated with its concomitant reduction of psychotic symptoms (Leweke *et al*., 2012). Taken together, while the results of this meta-analysis cannot provide direct evidence on the underlying molecular mechanisms by which CBD exerts its effects, they may suggest that there is a strong case for investigating *FAAH* as a potential mechanism of action of CBD. It is noteworthy that the absence of a significant relationship between the effect-size estimates and the other genes in the regression model (*DRD2*, *HTR1A* and *CNR1*) should be interpreted with caution primarily because t-statistics offer limited insight into the predictive ability of a variable.

Limitations

Certain limitations should be considered when interpreting our results. The principal limitation is perhaps the heterogeneity across the included studies, particularly in combining healthy, psychosis, and social anxiety disorder participants. We sought to mitigate this limitation by performing subgroup analyses and assessed the influence of individual studies on the main findings by conducting jack-knife leave-one-out sensitivity analysis. This procedure involved looping the analysis each time excluding 1 single study to investigate whether each cluster reported in the main analysis remained significant. Therefore, this step allowed identification of unduly influential studies. Of the 12 studies included in this analysis, 80% of all clusters survived the jack-knife, suggesting stability in the results. To further investigate the influence of heterogeneity, QH statistics were assessed in terms of a chi-square distribution and reported after

conversion to standard z values to create a map. The QH map was overlayed on top of the map of the main findings for visual inspection. There were no areas of overlap which suggests that the brain regions reported in the main findings were not affected by heterogeneity.

A further limitation is that, although we included studies that employed distinct fMRI paradigms, significant overlap was present in the participants who completed them. While solutions have been proposed for non-neuroimaging meta-analyses, such as the application of a generalised-weights meta-estimator (Bom and Rachinger, 2020), correction for correlated data in image-based meta-analyses is not trivial. Some have proposed that our approach is appropriate (Turkeltaub *et al*., 2012) given that the tasks were completely independent in their outcome measure from one another (such as reward and memory processing). Nevertheless, the use of overlapping participants may have increased rates of false positive findings and inflated effect-sizes. A separate study, using the same dataset, compared findings from an activation likelihood estimate meta-analysis with one using a modified algorithm to correct for within-group effects (Turkeltaub *et al*., 2012). While usual activation likelihood estimate functions by *summing* the probabilities within a given activation peak, per study, to produce an activation map, the modified algorithm considered only the *maximum* probability associated with an activation peak reported by each study. Turkeltaub et al. (Turkeltaub *et al*., 2012) report that although correlated datasets can influence an activation map, there was negligible difference in comparison to the modified algorithm to control for these effects.

Furthermore, there are certain limitations inherent to meta-analytic integration of neuroimaging data which we have divided into two categories, (1) design and (2) analysis. When considering our meta-analytic design, the results are based on summary data from individual studies, as opposed to imaging data obtained from individual participants. Acquiring data from individual participants would involve the same participants conducting multiple cognitive and emotional processing tasks in addition to obtaining baseline receptor data quantified using PET imaging. Although this idealised design would have allowed more direct testing of our hypotheses, collecting this type of dataset in a comparable number of participants as reported here would be both logistically and financially challenging. Therefore, the present meta-analysis provides insight into these questions by capitalising on existing available data, albeit using a less than perfect approach. When considering the second type of neuroimaging limitation related to the analysis technique, our approach used both t-maps and coordinates. The use of coordinates in the analysis, as opposed to t-maps alone, may have increased the risk of bias in our results as coordinates are reported using a family-wise error correction threshold of $p<0.05$. This stringent threshold is likely to have excluded clusters which, when pooled with other results from other studies, may have produced a significant difference in activity driven by the pharmacological effect of CBD. Nevertheless, we attempted to mitigate this issue by including as many t-maps as possible.

A further limitation of this study is that we used mRNA expression as a way to indirectly estimate receptor density. The Allen Human Brian Atlas provides an indirect measure of receptor density through an index of gene *transcriptional* activity which is governed by gene *translation*. This is notable as previous reports have highlighted difference between tissue mRNA and protein levels (Futcher *et al*., 1999; Gygi *et al*., 1999; Greenbaum *et al*., 2003). Moreover, it has been reported that gene expression (transcriptional activity) and protein abundance (translational activity) do not always have a positive correlation (Margineantu *et al*., 2007; Schwanhüusser *et al*., 2011). Furthermore, the relationship found between mRNA expression and the effect-size estimate as reported here is only an indirect evidence that complements independent evidence indicating FAAH as a molecular target for CBD and may not reflect a causal association.

Notwithstanding these limitations, the major finding of the current study extends previous evidence on the haemodynamic effects of CBD on regional brain activation signal at the meta-analytic level. We also provide preliminary evidence that suggests a negative relationship between the effect of CBD on brain signal and local FAAH expression. Together, by examining the effects of CBD on brain regions engaged across diverse cognitive and emotional processes (Shine *et al*., 2019), where its effects may also be related to FAAH availability across the brain, these findings highlight not only the neuropharmacological profile of CBD's effects across the brain but also link these (albeit indirectly) to one of the key underlying mechanisms by which CBD is proposed to exert its effects. Future studies should combine experimental CBD challenge with fMRI and PET imaging to index its effects on brain function and FAAH respectively in the same individuals to directly examine whether the effects of CBD on FAAH underlie its effects on brain function and behaviour.

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Figures

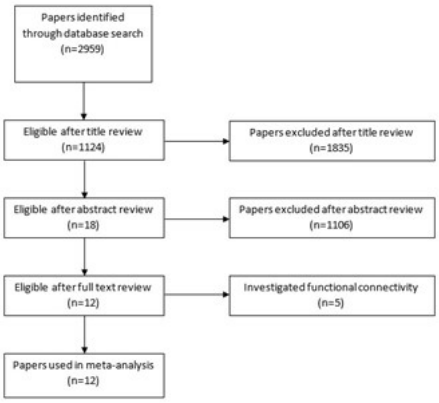

Figure 1

Prisma diagram

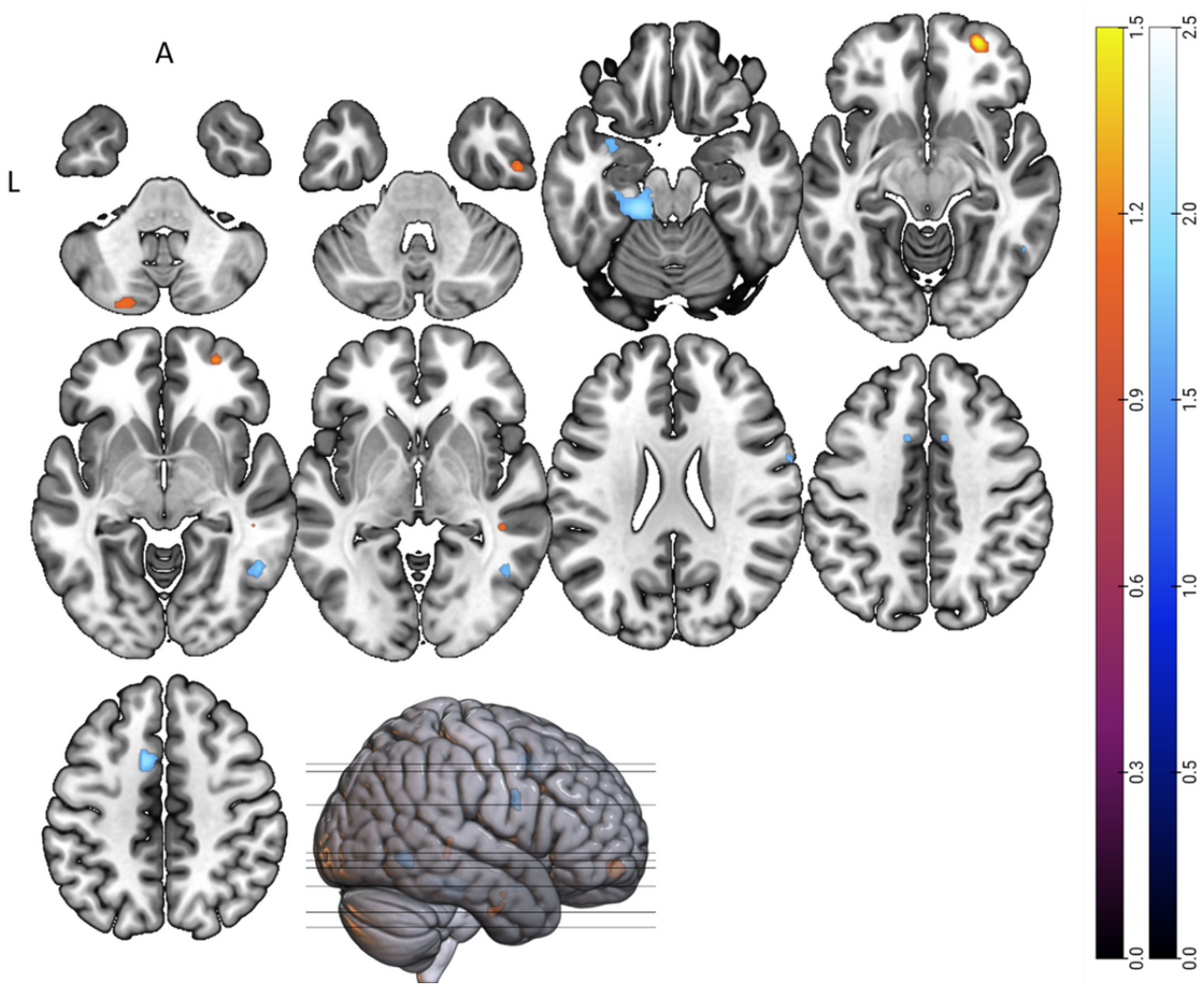

Figure 2

Comparison in brain signal between CBD and placebo. Orange= regions of augmented activation signal (CBD>placebo). Blue= regions of attenuated activation signal (CBD<placebo). L= left brain hemisphere; A= brain anterior.

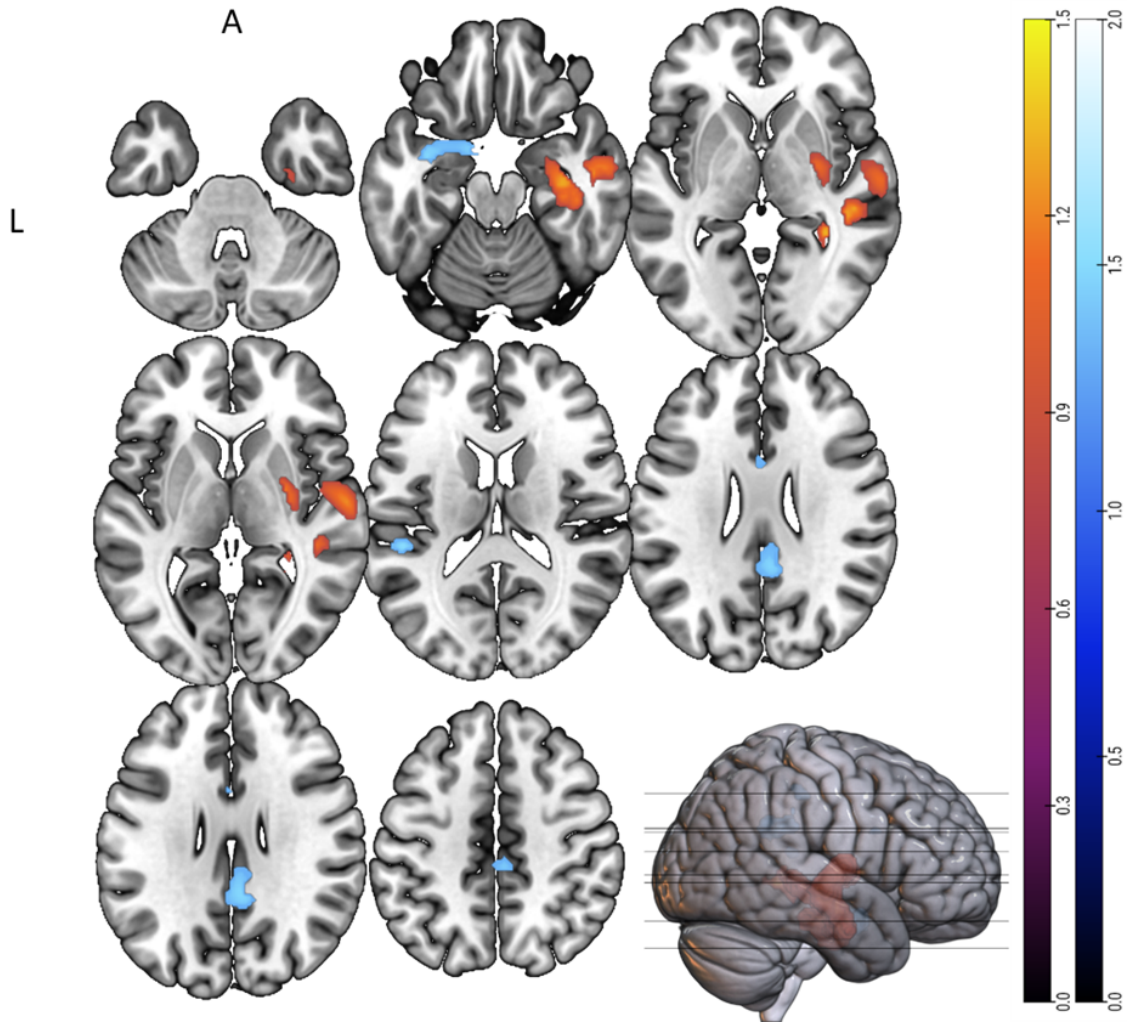

Figure 3

Brain signal differences comparing CBD with placebo within healthy participants. Orange= areas of increased activation signal (CBD>placebo). Blue= areas of attenuated activation signal (CBD<placebo). L= left brain hemisphere; A= brain anterior

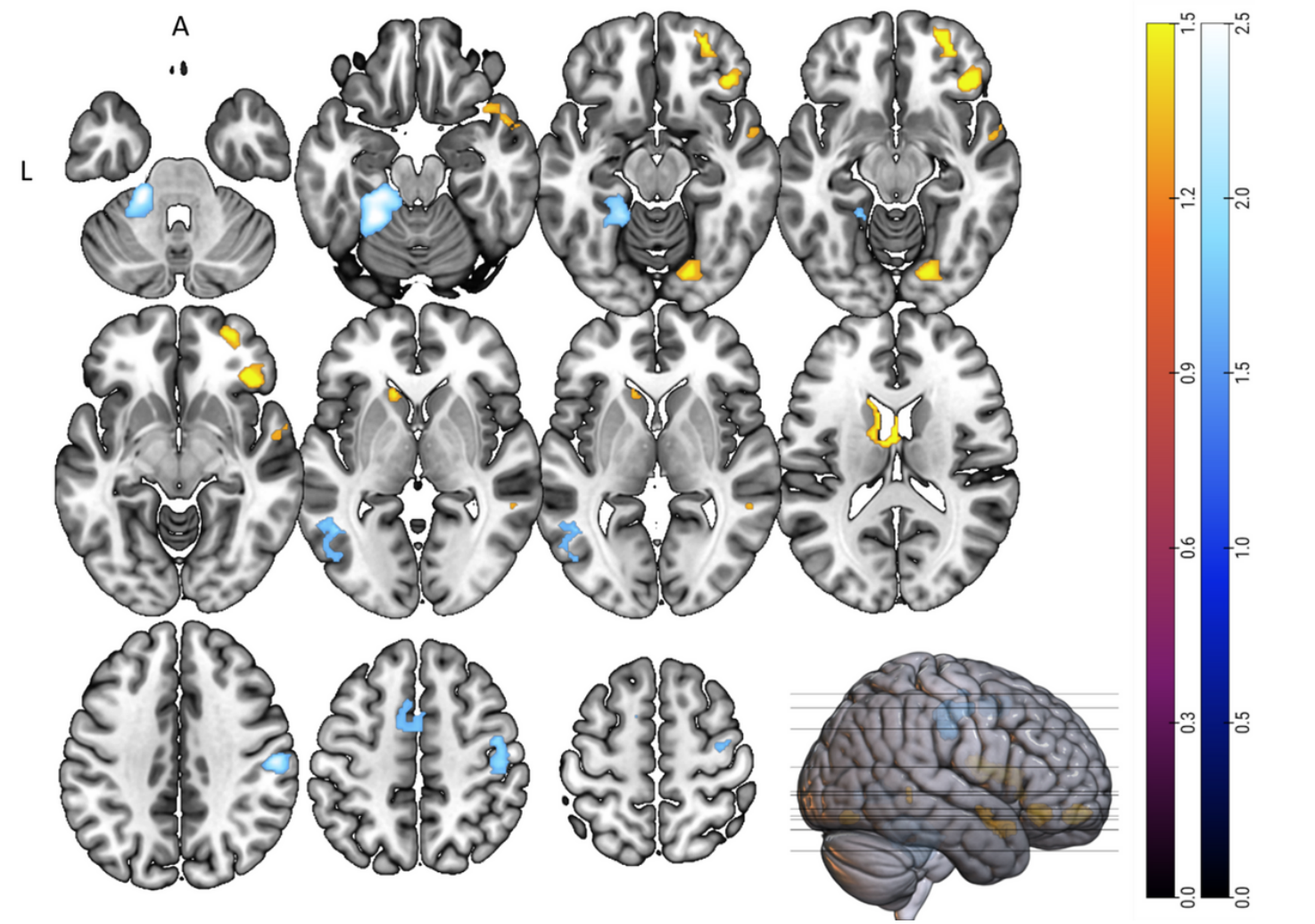

Figure 4

Brain signal differences comparing CBD with placebo within subjects at clinical high risk or early psychosis. Orange= areas of increased activation signal (CBD>placebo). Blue= areas of attenuated activation signal (CBD<placebo). L= left side of the brain; A= anterior

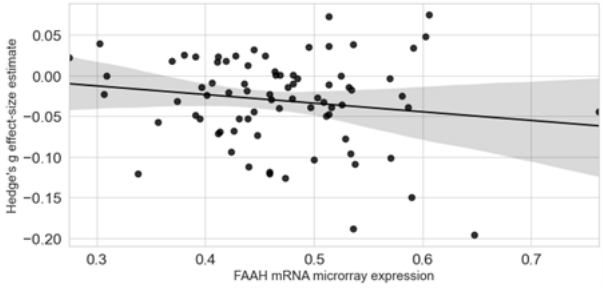

Figure 5

Scatterplot demonstrating the relationship between FAAH expression values and Hedge's g effect size estimate of CBD relative to placebo (from main meta-analytic results) across the brain, parcellated across 78 regions of the Desikan-Killiany atlas. P=0.024, t= -2.29, R2= 0.165, coefficient= -0.18, 95% CI= -0.34 to -0.024). Shaded band=95% confidence interval.

Supplementary Files

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