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Review article

Effects of cannabinoids on resting state functional brain connectivity: A systematic review

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ABSTRACT

Cannabis products are widely used for medical and non-medical reasons worldwide and vary in content of cannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Resting state functional connectivity offers a powerful tool to investigate the effects of cannabinoids on the human brain. We systematically reviewed functional neuroimaging evidence of connectivity during acute cannabinoid administration. A pre-registered (PROSPERO ID: CRD42020184264) systematic review of 13 studies comprising 318 participants (mean age of 25 years) was conducted and reported using the PRISMA checklist. During THC and THCv exposure vs placebo reduced connectivity with the NAcc was widely reported. Limited evidence shows that such effects are offset by co-administration of CBD. NAcc-frontal region connectivity was associated with intoxication levels. Cannabis intoxication vs placebo was associated with lower striatal-ACC connectivity. CBD and CBDv vs placebo were associated with both higher and lower connectivity between striatal-prefrontal/other regions. Overall, cannabis and cannabinoids change functional connectivity in the human brain during resting state as a function of the type of cannabinoid examined.

1. Introduction

Cannabinoid-based products are widely used globally and are becoming increasingly accessible, potent and diversified due to global trends towards the decriminalization of their use and sale (Scheim et al., 2020). Over the past decade, the concentration of cannabis' main psychoactive compound Δ9-tetrahydrocannabinol (THC) in cannabis products has doubled (Chandra et al., 2019; Freeman et al., 2019b). Meanwhile, the concentration of cannabidiol (CBD), a non-intoxicating cannabinoid with putative therapeutic properties (Bergamaschi et al., 2011) remain stable over time (Freeman et al., 2021). These trends are concerning: THC has addictive (Volkow et al., 2016), intoxicating (Curran et al., 2016), anxiogenic (Crippa et al., 2009) and psychotogenic properties (Hindley et al., 2020). In contrast, CBD putatively mitigates such adverse effects of THC (Englund et al., 2013; Freeman et al., 2019a). Consequently, the burden of the adverse psychosocial outcomes associated with the recent increases of THC likely represent an increasing public health, social and economic problem in the forthcoming years (Hall et al., 2019).

The effects of cannabinoid intoxication have been attributed to the influence of cannabinoids on the brain. Indeed, when cannabis is consumed, THC binds to brain cannabinoid receptors that are densely innervated in selected cortical regions (e.g., prefrontal cortex, hippocampus, cerebellum; Glass et al., 1997; Hashimotodani et al., 2007; Mackie, 2008). These brain pathways are implicated in cognitive processes that are altered with cannabinoid intoxication (e.g., disinhibition, reward processing, motor coordination; Broyd et al., 2016; Dellazizzo et al., 2022; Kroon et al., 2021; Ramaekers et al., 2021); as well as mental health symptoms which transiently increase with cannabis intoxication (e.g., anxiety and psychotic symptoms; Barrett et al., 2018; Colizzi et al., 2016). From a neurobiological perspective, we are yet to uncover in detail the brain pathways underlying cannabinoid

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intoxication. Notably, the development of functional Magnetic Resonance Imaging (MRI) tools that map brain function in-vivo has generated increasingly sophisticated efforts to identify the neurobiology of cannabinoid intoxication.

Several systematic reviews have integrated findings from experimental fMRI studies in humans during THC and/or CBD intoxication, showing changes in prefrontal, striatal and other regions (Bloomfield et al., 2019; Freeman et al., 2019a; Gunasekera et al., 2020). However, findings have varied significantly across studies, with inconsistent direction and location of the findings (Bloomfield et al., 2019; Freeman et al., 2019a; Gunasekera et al., 2020). The inconsistent results might be (partly) explained by methodological issues. Specifically, several reviews have summarised findings from task-based fMRI while participants perform a variety of cognitive tasks, which may have introduced confounding due to the cognitive demands associated with the task (e.g. cognitive domain examined, task performance, strategy and effort) from that of cannabinoid intoxication (Fox and Greicius, 2010).

Other reviews have synthesised evidence that used heterogeneous neuroimaging techniques (e.g. fMRI, positron emission tomography, single photon emission computed tomography, arterial spin labelling). Thus, they cannot readily disentangle the impact of cannabinoids from that of distinct measures of brain functional integrity (Bloomfield et al., 2019; Freeman et al., 2019a; Gunasekera et al., 2020). In addition, the most up to date search in previous reviews include publications up to July 2019 (Gunasekera et al., 2020) and several new studies have been published since then (Mason et al., 2021; Pretzsch et al., 2019; Wall et al., 2022; Zaytseva et al., 2019).

We conducted the first systematic review of studies that investigated the brain functional changes that occur during acute cannabinoid intoxication by using resting state functional connectivity fMRI – which measures how strongly the function of different brain areas regions is correlated over time without cognitive confounds (van de Ven et al., 2004) - in contrast to task-based fMRI or other functional neuroimaging techniques. Indeed, resting-state fMRI measures spontaneous fluctuations of brain function while people do not overtly perform any cognitively demanding tasks, while they are at rest but awake in the scanner (van de Ven et al., 2004). This technique has been used to identify large-scale neural networks in normative samples and core alterations underlying disease (Fox and Greicius, 2010; Philippi et al., 2020). Resting state fMRI thus holds promise to unpack fundamental functional brain changes that occur with cannabinoid intoxication.

We selected the studies which have been published thus far, that investigated subjects of any age who are psychiatrically, neurologically healthy, and free of regular substance use (other than alcohol and nicotine). We paid specific attention to the influence of cannabinoids and their administration (type, dosage, routes of administration) on the putative resting state functional connectivity phenotype of cannabinoid intoxication (Freeman et al., 2020). We also overviewed the associations between the level of functional connectivity alterations and self-reported intoxication or cognitive performance or both. Finally, we detailed the methodologies used to examine resting state functional connectivity during cannabinoid intoxication to evaluate the standards of research in this area and inform directions for future work.

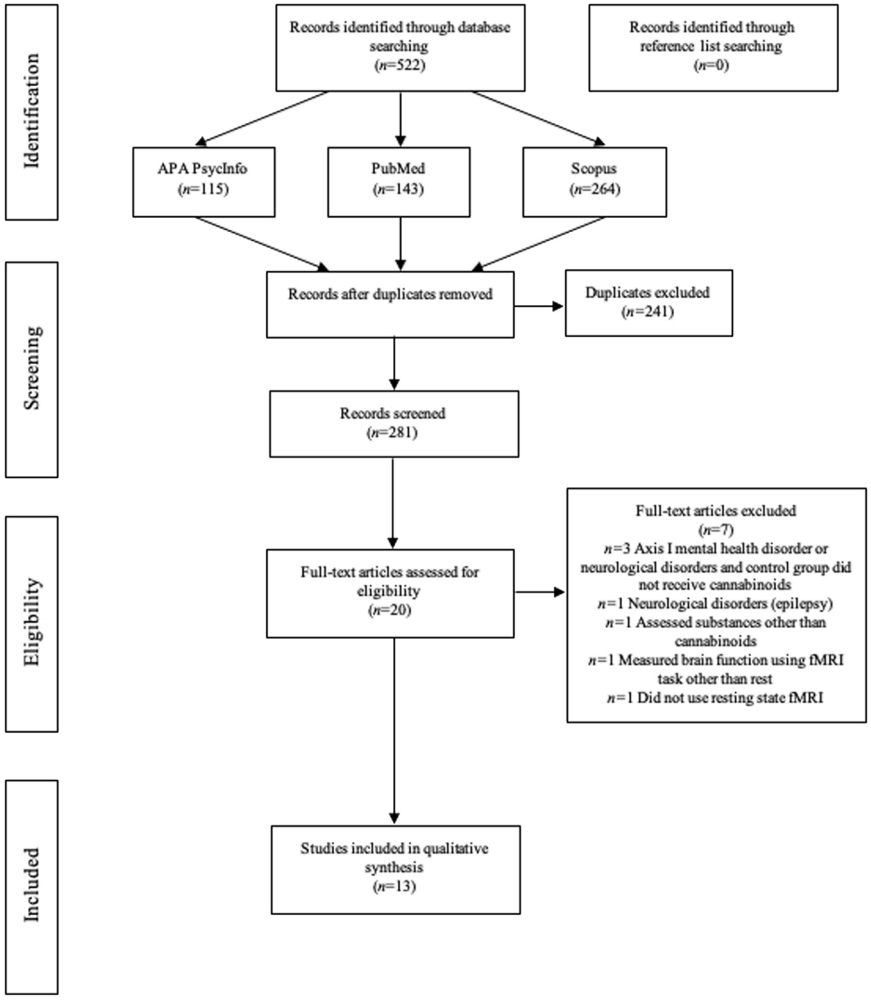

Fig. 1. PRISMA flowchart of the search strategy and number of studies eligible for review at each stage.

2. Method

2.1. Pre-registration and protocol

This systematic literature review was pre-registered on PROSPERO (CRD42020184264) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Fig. 1, see checklist in Supplementary Table 1; Moher et al., 2009).

2.2. Literature search

On May 25, 2022, the APA PsycINFO, PubMed and Scopus databases were searched using the following terms: "(cannabi* OR marijuana OR hashish OR cbd OR *thc OR *tetrahydrocannabinol) AND ("resting state" OR "functional connectivity")". The reference lists of the included studies were cross referenced also.

The searches retrieved 522 studies, 241 of which were duplicates that were removed. We screened studies against the following inclusion and exclusion criteria. Inclusion criteria were: (i) human sample; (ii) assessment during intoxication with cannabinoids, (iii) use of resting state fMRI, (iv) measurement of resting-state functional connectivity. Exclusion criteria were: (i) measure of brain integrity other than function (e.g. volumes); (ii) measure of brain function using an imaging technique other than fMRI (e.g., PET, SPECT, EEG), (iii) measured brain function using fMRI task other than rest, (iv) confirmed lifetime history of serious mental health disorders at a group level (e.g. psychotic disorders, bipolar disorder), or neurological disorders (e.g. epilepsy), (v) non-experimental study (e.g., observational studies, case studies, reviews, meta-analyses, commentaries), (vi) animal sample, (vii) not published in a peer-reviewed journal (e.g., dissertation, conference presentation, book chapter).

Using these criteria, we screened titles and abstracts, and selected 19 studies for full-text screening, of which 13 were included (Bossong et al., 2019; Crane and Phan, 2021; Grimm et al., 2018; Klumpers et al., 2012; Mason et al., 2021, 2019; Pretzsch et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019; Zaytseva et al., 2019).

2.3. Data extraction

Results were summarised by counting the number of studies the data of which endorsed specific features. We extracted data about the characteristics of the publication (first author, year), sociodemographic data of the sample (size, sex composition, age), additional sample characteristics (location, recruitment, handedness) and inclusion/exclusion criteria (Table 1), experimental design (Table 2); and results on resting state functional connectivity in relation to acute cannabinoid intoxication and their association with the level of self-reported intoxication and cognitive performance (Tables 3–5). Specifically, Table 3 includes results from studies that assessed connectivity during intoxication with THC, THCv and cannabis plant matter with known and set quantities of THC (Wall et al., 2022, 2019). Table 4 overviews results from studies that assessed connectivity during intoxication with cannabis plant matter, including multiple cannabinoids known to affect the central nervous system (e.g., THC and CBD) (Wall et al., 2022, 2019). Table 5 overviews results from studies that assessed connectivity during intoxication with CBD, CBDv and cannabis plant matter with known and set quantities of CBD.

2.4. Risk of bias assessment

We evaluated studies' risk of bias using the Centre for Evidence-Based Medicine (CEBM) critical appraisal tool shown in Supplementary Table 5. The CEBM tool entails five criteria: (i) Participants are randomly assigned to treatment conditions, (ii) Groups are similar at the outset of the trial, (iii) Groups are treated equally, other than that required for the treatment allocation, (iv) Minimal attrition, (v) Participants and/or researchers were blinded to the treatment/s.

3. Results

The review included 13 studies, the key characteristics of which are outlined in Table 2 (Bossong et al., 2019; Crane and Phan, 2021; Grimm et al., 2018; Klumpers et al., 2012; Mason et al., 2021, 2019; Pretzsch et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019; Zaytseva et al., 2019). All studies were published within ten years of the date of this review (i.e., 2022), with ten published between 2018 and 2022.

Table 1
Overview of methodological characteristics of the studies.

Author (Year)	Location	Recruitment	Handedness	Cannabis use level		Required Abstinence		Screen for abstinence from illicit drugs
				Duration, yrs	Days used/ week	Cannabis use days	Illicit drugs, days	
Wall (2022a)*	UK	–	L/R	–	2	1	1	–
Wall (2022b)	UK	General community	R	–	–	–	–	Urine, Breath
Pretzsch (2021)	UK	–	–	–	–	30	30	–
Crane (2021)	US	General community	R	0	1.5 lifetime	30	1	Urine, Breath
				0	1.7 lifetime			
Bossong (2019)	NL	General community	R	–	0.5	14	–	–
Mason (2021)	NL	University	L/R	5.40	3.5	7	7	Urine
Mason (2019)	NL	University	L/R	4.9	1	7	7	Urine
Pretzsch (2019)	UK	–	L/R	–	–	30	30	Urine
Wall (2019)*	UK	–	L/R	–	2	1	1	–
Zaytseva (2019)	CZ	General community	L/R	–	44.8 lifetime uses	7	–	Blood
Grimm (2018)	DE	General community	L/R	–	–	–	–	Urine
Ramaekers (2016)	NL	General community	L/R	7	4	–	–	Urine
Rzepa (2015)	UK	University	R	–	–	–	–	Urine
Klumpers (2012)	NL	–	R	≥ 1	–	14	–	Urine

Abbreviations: CZ, Czech Republic; DE, Germany; L, left; NL, The Netherlands; R, right; UK, United Kingdom; yrs, years. * Participants were the same across studies

Table 2
Overview of double-blind fMRI studies' designs, sample demographics, cannabinoid, and placebo.

1st author (year)	N total (female)	Age, yrs	Design	Cannabinoids/ placebo		Dosage	Route	Method
Wall (2022a) * study 1	17(9)	26	Cross-over	Plant matter	THC	1.6 standard THC units	Inhalation	Vaporizer
					THC+CBD	1.6 standard THC units		
					Placebo			
Wall (2022b) study 2	23(11)	24	Cross-over	CBD		600 mg	Oral	Capsule
				Placebo				
Pretzsch (2021)	15	29	Cross-over	CBDV		_	Oral	Liquid
				Placebo		_		
Crane (2021)	24(14)	26	Between-subject	THC (marinol)		1.5 standard THC units	Oral	Capsule (00)
	22(14)	24		Placebo (dextrose)				
Bossong (2019)	34(0)	23	Cross-over	THC		1.2 standard THC units (+ 2-to-3 uploads of 0.2 standard THC units)	Inhalation	Vaporizer
				Placebo		_		
Mason (2021)	12(7) occasional users	23	Cross-over	THC 13.5% (bedrobinol)		3.72 standard THC units for a 62kg person	Inhalation	Vaporizer
				Placebo		_		
	12(3) chronic users	23		THC 13.5% (bedrobinol)		3.72 standard THC units for a 62kg person		
				Placebo		_		
Mason (2019)	10(4)	23	Cross-over	THC 13.5% (bedrobinol)		3.72 standard THC units for a 62kg person, full dose	Inhalation	Vaporizer
				Placebo		one dose		
	10(4)	21		THC 13.5% (bedrobinol)		3 divided doses of 1.24 standard THC units, for a 62kg person		
				Placebo		3 divided doses		
Pretzsch (2019)	17(0)	29	Cross-over	CBD		600 mg	Oral	Liquid
				Placebo		–		
Wall (2019)*	17(9)	26	Cross-over	Plant matter	THC	1.6 standard THC units	Inhalation	Vaporizer
					THC+CBD	1.6 standard THC units		
				–	Placebo	_		
Zaytseva (2019)	19(12)	26	Cross-over	Plant matter		Self-dosed	Inhalation	Joint
				Passive control		_		
Grimm (2018)	16(0)	–	Cross-over	THC		2 standard THC units	Oral	Capsule
				CBD		600 mg		
				Placebo (Saline)		–		
Ramaekers (2016)	39 *	23	Cross-over	THC Plant matter		3.72 standard THC unit + upload of 1.86 standard THC units, for a 62kg person	Inhalation	Vaporizer
				Placebo		–		
Rzepa (2015)	19(9)	25	Cross-over	THCv		2 standard THC units	Oral	_
				Placebo		–		
Klumpers (2012)	12(3)	22	Cross-over	THC		0.4 standard THC units + 2 uploads of 1.2 standard THC units	Inhalation	Vaporizer
				Placebo (ethanol)		200 µl		

Abbreviations: %, percent; CBD, cannabidiol; CBDV, cannabidivarin; THC, tetrahydrocannabinol; THCv, tetrahydrocannabivarin; yrs, years; µg/kg, microgram per kilogram; *Did not report the gender split of the final sample following dropouts. Initial sample(pre-dropouts) included 96 females and 26 males. One Standard THC unit = 5 mg of THC.; Standard THC units per kilograms were computed by measuring the ratio of standard THC unit per average per kilo for average for people of the relevant age and sex (i.e., 62 kilos; Walpole et al., 2012). Mason (2021, 2019) and Ramaekers (2016), administered 0.06 Standard THC Unit /kg, from 300 µg THC/kg ; additionally Ramaekers (2016) administered an upload of 0.03 Standard THC Units/kg, from 150 µg/kg; and Mason (2019) administered 3 successive doses of 0.02 Standard THC Units/kg, from 100 µg/kg in a separate group.
* Participants were the same across studies

3.1. Sample characteristics

The studies comprised a total of 318 participants. The size of the samples ranged from 10 to 39 participants; and ten studies included < 20 participants. The total sample contained 95 females and had a mean age of 25 years.

3.1.1. Overview of levels of exposure and inclusion of cannabis use

Cannabis exposure levels varied due to heterogeneous inclusion and exclusion criteria for participants' substance use varied across studies (Table 1). Examples of inclusion criteria across the studies were (i) minimum thresholds for cannabis use (e.g., one study included participants that used cannabis at least twice in the three months prior to the study) and (ii) duration of abstinence from substances (e.g., three studies included participants that abstained from cannabis for seven days prior to the study) (see also Table 1 for actual abstinence durations and methods of testing for abstinence). Examples of exclusion criteria across the studies were maximum thresholds for cannabis use (e.g., two studies excluded participants who had used cannabis more than four times in the year prior to the study).

3.1.1.1. Cannabis exposure levels. Two out of the 12 studies set minimum thresholds for including cannabis use. One study sought participants who used cannabis at least 16 times per month in the past year (Mason et al., 2021) and another sought regular users who had used cannabis at least twice in the past three months (Ramaekers et al., 2016). Abstinence from cannabis was required by six studies to be of varying durations: one day (n = 1), to seven days (n = 3), to 14 days (n = 1), to 30 days (n = 2). Seven out of the 13 studies set maximum thresholds for cannabis use, excluding participants who had used cannabis more than

Table 3
Results on fMRI resting state functional connectivity changes occurring during THC intoxication compared to placebo.

Author	Subjective effects	Analysis method	Seed	Direction	Regions	Correlations rsFC & intoxication, cognitive performance
Crane (2021)	↑Euphoria (VAS)	Seed-whole brain	NAc	↑	dmPFC, medPFC	**Pos. Cor.** NAc-dmPFC & euphoria (VAS) **N.S. Cor.** drug liking (DEQ)
			Putamen, Caudate	=	_	_
Bossong (2019)	↑Dysphoria ↓Perception, relaxation	Seed-whole brain	mOFC	↓	ACC (mid)/precuneus	**N.S. Cor.** Perception, relaxation, dysphoria (VAS)
			Insula, IFG, Frontal cortex (med sup)	=	_	_
Klumpers (2012)	_	Seed-whole brain	Dorsal-visual (right)	↓	Frontal pole (inf, sup), IFG, MFG, dlPFC, vlPFC, MedFG	_
				↑	Frontal pole, SFG, dmPFC	
			Dorsal-visual (left)	↓	PCC	
				↑	Occipital (lat, pole), precentral, PCC, postcentral,	
			Visual (medial)	↓	ACC (dorsal), occipital, temporal, SFG, fusiform	
			Visual (lateral)	↓	Occipital (lat, pole), precuneus, precentral	
				↑	Occipital, temporal, MFG, fusiform, cerebellum (ventro-med)	
			Auditory	↓	ACC (mid, sup), frontal pole, parietal lobule (sup), precentral, temporal (mid, sup, inf), MFG, SFG, dmPFC, OFC (lat), parahippocampus, supramarginal, temporal pole, vmPFC	
				↑	PCC, parahippocampus, retrosplenial, caudate	
			Sensorimotor	↓	Precuneus, parietal (sup, post), postcentral	
				↑	Cerebellum (antero-ventral, ventro-med), midbrain	
			Executive	↓	Precuneus	
			Default mode	↑	Frontal pole, calcarine (intra), dlPFC	
Mason (2021)	↑Feeling high (VAS), more in occ ↑RT & N attentional lapses on psychomotor vigilance task^ in occ	Seed-whole brain	NAc	↓	ACC (mid), occipital (mid), precuneus, parietal lobule (inf), precentral, MFG, SFG, postcentral, SMA, rolandic operculum, supramarginal, calcarine	**Pos. cor.** NAc-MFG & feeling high (VAS) **&** sustained attention (N attentional lapses on psychomotor vigilance task) **Pos. cor.** NAc-SFG/OFC & sustained attention (N attentional lapses on psychomotor vigilance task) N.S. cor. RT on psychomotor vigilance task
		Seed-to-seed	NAc	↓	Thalamus (med dorsal), pallidum	**N.S. cor.** Feeling high (VAS), sustained attention (N attentional lapses & RT on psychomotor vigilance task)
			Pallidum (ventral)	↓	Thalamus (med dorsal)	
			ACC (mid)	↓	Thalamus (med dorsal), NAc	
Mason (2019) Full dose	↑ Feeling high (VAS) ↑N attentional lapses on psychomotor vigilance task^ =RT	Seed-whole brain	NAc	↓	ACC (mid), occipital (sup), precuneus, parietal lobule (inf), IFG (pars opercularis), precentral, temporal (mid, sup, transverse), postcentral, SMA, fusiform, insula, rolandic operculum, paracentral, angular, lingual	**Neg. Cor.** NAc-cuneus & feeling high (VAS) **Pos. Cor.** NAc-SFG & attentional lapses **Pos. Cor.** NAc-SFG & glutamate changes in the striatum
Mason (2019) Divided dose	= Feeling high (VAS), sustained attention (RT, N attention lapses on psychomotor vigilance task)	Seed-to-seed	NAc	=	_	_
		Seed-whole brain	NAc	=	_	_
Ramaekers (2016)	_	Seed-whole brain	NAc	↓	ACC, occipital, temporal (mid), thalamus, insula, cerebellum, frontal lobe/cortex, claustrum, limbic	**Neg. Cor.** NAcc-striatum, NAcc-thalamus & Impulsivity (MFFT)
Rzepa (2015)	_	Seed-whole brain	Amygdala	↓	Occipital (lat), precuneus, PCC	_
				↑	ACC (dorsal), SMA	
			dmPFC	↑	IFG, MFG	
			mOFC, Insula	=	_	
Wall (2019)[THC-CBD]	_	Seed-whole-brain	PCC	↓	Precuneus, parietal lobule, PCC	_
				↓ Neg	IFG, SFG	_
			Insula (anterior)	↓	Frontal pole, frontal lobe (inf)	_
Wall (2022a)[THC-CBD]	_	Seed-whole-brain	Striatum (pre-comm. dorsal putamen, post-comm. caudate)	↓	Frontal operculum, insula	_
			Striatum (ventral pallidum, substantia nigra)	↓	Insula, frontal operculum	
			Striatum (post-comm. putamen)	↓	Parietal/central operculum, postcentral/supramarginal gyrus, planum temporale, Heschl's gyrus, motor/somatosensory cortex	

Bold text indicates that the pair survived multiple corrections; ↑, higher; ↓, lower; ↓Neg, lower negative rsFC; ^Attentional lapses measures on a sustained attention task (Dinges & Powell, 1985).
Abbreviations: ACC, anterior cingulate cortex; cor, correlation; DEQ, drug effects questionnaire; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus; inf, inferior; lat, lateral; med, medial; med dorsal, medial dorsal; medFG, medial frontal gyrus; medPFC, medial prefrontal cortex; MFFT, matching familiar figures test; mid, middle; MFG, middle frontal gyrus; mOFC, medial orbitofrontal cortex; N.S., non-significant; NAc, nucleus accumbens; occ, occasional; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; pos, positive; post, posterior; post-comm, post-commissural; pre-comm, pre-commissural; rsFC, resting state functional connectivity; RT, response time; SFG, superior frontal gyrus; SMA, supplementary motor area; sup, superior; VAS, visual analogue scale; ventro-med, ventro-medial; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

Table 4
Results on fMRI resting state functional connectivity changes occurring during acute intoxication with cannabis plant matter compared to placebo.

Author	rsFC analysis method	Seed	Direction	Regions	Correlations rsFC & level of intoxication, cognitive performance
Wall (2022a) THC+CBD	Seed-whole-brain	Striatum (pre-comm. dorsal putamen, pre-comm. dorsal putamen, post-comm. caudate)	↓	Dorsal anterior cingulate, frontal opercular cortex/sensorimotor region	-
		Striatum (ventral pallidum, substantia nigra)	=	-	-
		Striatum (post-comm. putamen)	↓	Parietal/central operculum, postcentral/ supramarginal gyrus, planum temporale, Heschl's gyrus, motor cortex	-
Wall (2019) THC+CBD	Seed-whole brain	PCC	↓	Parietal, hippocampus	**Neg. Cor.** PCC-PCC & feeling stoned, high, drug effects, dry mouth, enhanced colour/sound perception (VAS) **N.S. Cor.** alert, happy, anxious, mentally impaired, stoned, like drug effects, want to listen to music, food or more cannabis (VAS)
			↓ Neg	IFG	**N.S. Cor.** VAS
		Insula (anterior)	↓	Frontal pole, precentral	**Neg. Cor.** Insula-dmPFC & Paranoia (VAS) **N.S. Cor.** Alert, happy, anxious, mentally impaired, stoned, like drug effects, want to listen to music, food or more cannabis
Zaytseva (2019)	ICA	Stationary rsFC	↑	Between the precuneus and sensory cortices (auditory, somatosensory, visual)	**N.S. Cor.** Dread of ego dissolution & visionary re-structurization
Plant matter		Dynamic rsFC, state 1	↑	Sensory cortices	
		State 1	↑ Neg	Sensory cortices - subcortex, insula, cerebellum	
		State 6	↑	Inhibitory control network - auditory/ somatomotor cortices and higher negative with the caudate).	**Pos. Cor.** State 6 duration & oceanic boundlessness, THC plasma concentration
		State 6	↑	Inhibitory control network - auditory/ somatomotor cortices and higher negative with the caudate).	
			↓		

Bold text indicates that the pair survived multiple corrections; ↑, higher; ↓, lower; ↑ Neg, higher negative rsFC.

Table 5
Results on fMRI resting state functional connectivity changes occurring during acute intoxication with CBD or CBDv compared to placebo.

Author	rsFC analysis method	Seed	Direction	Regions
Wall (2022b)	Seed-whole-brain	Striatum (pre-comm. dorsal putamen, pre-comm. dorsal putamen, post-comm. caudate)	↑	Posterior parietal lobe, parieto-occipital sulcus, posterior cingulate
		Striatum (ventral pallidum, substantia nigra)	↓	Insula, lateral frontal cortex
		Striatum (post-comm. putamen)	↓	Cerebellum
Pretzsch (2021)	Seed-whole brain	Striatum	↓	Paracentral lobule
		Striatum (inferior ventral)	↓	ACC
		Putamen (ventral rostral)	↑	Temporal (sup)
		Caudate (dorsal)	=	-
		Putamen (caudal)	=	-
		Putamen (dorsal rostral)	=	-
Pretzsch (2019)	Seed-whole brain	Cerebellum (vermis), fusiform	=	-
Grimm (2018)	Seed-to-whole brain	Putamen	↑	MFG, SFG, frontal pole
		Caudate	=	-

↑, higher; ↓, lower.
Abbreviations: ACC, anterior cingulate cortex; MFG, middle frontal gyrus; post-comm, post-commissural; pre-comm, pre-commissural; rsFC, resting state functional connectivity; SFG, superior frontal gyrus; sup, superior.

10 times in their lifetime (Crane and Phan, 2021), more than four times per month in the previous year (Bossong et al., 2019; Klumpers et al., 2012), participants who had used cannabis more than 12 times per month in the previous year (Mason et al., 2021, 2019; Wall et al., 2019), and participants who used cannabis more than eight times per month (Zaytseva et al., 2019).

Additional inclusion and exclusion criteria are outlined in Table 1 and Supplementary Materials, about (i) presence of mental health disorders and/or neurological disorders, (ii) use of specified medications, and (iii) use of illicit substances other than cannabis.

3.2. Overview of characteristics of the experiments

As presented in Table 2, all studies used a double-blind placebo-controlled crossover design with randomised condition allocation, except for one study that was unblinded (Zaytseva et al., 2019) and one study that used a between-subjects design (Crane and Phan, 2021). The time interval between experimental sessions for studies with a crossover design ranged from one week in most studies, to two weeks (Bossong et al., 2019; Pretzsch et al., 2019) and four weeks (Zaytseva et al., 2019).

3.3. Cannabinoid administration

3.3.1. Types of cannabinoids and placebo administered

All studies had a condition where cannabinoids were administered and a control condition. Most studies (11 of 13 studies) administered pure cannabinoids, including THC (6 studies), CBD (3 studies; Grimm et al., 2018; Pretzsch et al., 2019; Wall et al., 2022), tetrahydrocannabivarin (THCv; 1 study; Rzepa et al., 2015), cannabidivarin (CBDv; 1 study; Pretzsch et al., 2021). Four studies administered cannabis plant matter with set concentration of THC and/or CBD (3 studies; Ramaekers et al., 2016; Wall et al., 2022, 2019) or was brought by participants (Zaytseva et al., 2019).

All studies included a placebo condition, with one exception which did not (Zaytseva et al., 2019). The type of placebo administered was reported in only four studies: dextrose (Crane and Phan, 2021), ethanol (Klumpers et al., 2012), saline (Grimm et al., 2018) and placebo cannabis (Bossong et al., 2019; Mason et al., 2021, 2019; Pretzsch et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019).

3.3.2. Dosage of the administered cannabinoids

The dosage of cannabinoids given was fixed in all but 3 studies (THC, THCv, CBD, CBDv). The minimum dosage ranged from 1.2 Standard THC Unit (i.e., 6 mg) to 2.8 Standard THC Units (i.e., 14 mg) (Bossong et al., 2019; Crane and Phan, 2021; Grimm et al., 2018; Klumpers et al., 2012), 10 mg for THCv (Rzepa et al., 2015) and 600 mg for CBD (Grimm et al., 2018; Pretzsch et al., 2019; Wall et al., 2022) and CBDv (Pretzsch et al., 2021).

The dosage varied in studies that administered cannabis plant matter (4 studies). Participants were administered plant matter containing fixed levels of 10 mg of CBD and/or 8 mg of THC (Wall et al., 2022, 2019), a total of 450 μg/kg of THC (Ramaekers et al., 2016) or were asked to bring and self-administer their own type and preferred quantity of cannabis based on their usual cannabis use (Zaytseva et al., 2019).

THC was given as microgram (μg) per kg of body weight in 3 studies. Two studies administered 300-μg/kg of THC (Mason et al., 2021, 2019), and of these one study manipulated THC administration as a single dose (i.e., one administration of 300-μg/kg) and as a divided dose (i.e., three administrations of 100-μg/kg) (Mason et al., 2019). The third study administered 300-μg/kg of THC followed by a 150-μg/kg upload dose, totalling 450-μg/kg of THC (Ramaekers et al., 2016).

3.3.3. Method of administration

Cannabinoids and placebo were most consistently administered via vaporizers (7 studies; Bossong et al., 2019; Klumpers et al., 2012; Mason et al., 2021; Mason et al., 2019; Ramaekers et al., 2016; Wall et al., 2022, 2019), capsules (3 studies; Crane and Phan, 2021; Grimm et al., 2018; Wall et al., 2022), liquid (2 studies; Pretzsch et al., 2021; Pretzsch et al., 2019), a joint (1 study; Zaytseva et al., 2019), or by unspecified means (1 study; Rzepa et al., 2015).

3.4. Experimental contrasts

All studies but one (Zaytseva et al., 2019) contrasted resting state functional connectivity between intoxication with cannabinoids (i.e., THC, THCv, CBD, CBDv, cannabis) versus placebo.

The cannabinoids compared to placebo were THC in 6 studies (Bossong et al., 2019; Crane and Phan, 2021; Grimm et al., 2018; Klumpers et al., 2012; Mason et al., 2021, 2019), CBD in 3 studies (Grimm et al., 2018; Pretzsch et al., 2019; Wall et al., 2022), and THCv and CBDv in individual studies (Pretzsch et al., 2021; Rzepa et al., 2015). Other comparisons included: cannabis plant matter versus placebo, cannabis plant matter with CBD versus placebo, cannabis plant matter without CBD versus placebo; THC versus CBD; cannabis plant matter versus no cannabis (Grimm et al., 2018; Ramaekers et al., 2016; Wall et al., 2022, 2019; Zaytseva et al., 2019).

We extracted additional data shown in Supplementary Materials. Supplementary Table 1 overviews the PRISMA checklist. Supplementary Table 2 overviews when MRI scanning, subjective and objective measures of intoxication occurred in relation to cannabinoid intake and peak intoxication. Supplementary Table 3 summarises the MRI methodologies used (i.e., MRI scanner brand/strength, number of head coil channels, fMRI task duration, eyes open/closed).

3.5. Overview of fMRI methods used

Table 3 overviews the methods used to analyse the fMRI data and the results about the resting state functional connectivity changes noted in relation to cannabinoid exposure, and in association with the level of intoxication and of cognitive performance.

Twelve of the 13 studies examined resting state functional connectivity using seed-based connectivity, with one exception (Zaytseva et al., 2019). Seed-based connectivity measures the average time-course between a priori selected brain regions (termed ROI or “seed”, which comprises a cluster of voxels) and yields a map from cross-correlations coefficients between each seed voxel and all other voxels (Goebel et al., 1998). Thirteen studies measured positive resting state functional connectivity (henceforth termed resting state functional connectivity), which measures positive correlations between the time-course of distinct brain regions. One study (Wall et al., 2019) measured also negative resting state functional connectivity, which indexes negative correlations between the time-course of different brain areas.

Twelve of the 13 studies used a seed-to-whole brain approach, which measures the connectivity between a seed and the whole brain (Bossong et al., 2019; Crane and Phan, 2021; Grimm et al., 2018; Klumpers et al., 2012; Mason et al., 2021, 2019; Pretzsch et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019). Two studies used a seed-to-seed approach (in addition to a seed-to-whole brain approach), to measure the connectivity between two or more seeds (Mason et al., 2021, 2019). One study measured stationary and dynamic resting state functional connectivity using independent component analysis (ICA) (Zaytseva et al., 2019). ICA is a black-box data driven method that groups all voxels into different resting-state brain network based on their temporal and special information (Bartels and Zeki, 2004).

3.6. Overview of examined ROIs

Overall, twelve studies used a seed-based approach and selected a total of 34 distinct ROIs, comprising individual regions in eleven studies and networks in a single study (Klumpers et al., 2012). Across all cannabinoids examined, the most consistently examined ROIs were the NAc (4 studies; Crane and Phan, 2021; Mason et al., 2021; Mason et al., 2019; Wall et al., 2022), the putamen (3 studies; Crane and Phan, 2021; Grimm et al., 2018; Pretzsch et al., 2021), and the insula (3 studies; Bossong et al., 2019; Rzepa et al., 2015; Wall et al., 2019).

Studies that compared brain function during THC vs placebo used a seed-to-whole brain approach. Seeds included the following regions: NAcc (4 studies; Crane and Phan, 2021; Mason et al., 2021; Mason et al., 2019; Ramaekers et al., 2016; Wall et al., 2022), insula (3 studies; Bossong et al., 2019; Rzepa et al., 2015; Wall et al., 2019), medial OFC (2 studies; Bossong et al., 2019; Rzepa et al., 2015), other frontal regions (3 studies; Bossong et al., 2019; Mason et al., 2021; Rzepa et al., 2015) and other regions (single studies; Mason et al., 2021; Rzepa et al., 2015; Wall et al., 2019).

3.7. Results on resting state functional connectivity during acute intoxication with cannabinoids

All but two of the 13 studies (Mason et al., 2019; Pretzsch et al., 2019) reported altered connectivity following cannabinoid administration. Of these, all studies reported altered connectivity, one study found

altered negative connectivity (Wall et al., 2019) and one study reported altered stationary and dynamic resting state functional connectivity (Zaytseva et al., 2019).

Overall, 130 distinct region-pairs were reported to have altered functional connectivity during one of the following contrasts: THC vs placebo (103 region pairs), cannabis plant matter vs placebo (14 pairs), CBD vs placebo (11 pairs) and THC vs CBD (2 pairs).

3.7.1. Resting state functional connectivity during intoxication with THC or THCv versus placebo

Nine of the 12 studies that compared connectivity between THC and placebo found different connectivity in 103 region pairs (Bossong et al., 2019; Crane and Phan, 2021; Klumpers et al., 2012; Mason et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019). The results are summarised in Fig. 2.

The direction of the difference was most consistently lower functional connectivity in all studies (74 pairs), and three of these studies also noted higher functional connectivity in addition to lower functional connectivity (29 pairs; Crane and Phan, 2021; Klumpers et al., 2012; Rzepa et al., 2015).

3.7.1.1. Results from seed based connectivity studies of THC versus placebo. Five studies used NAcc as a seed (Crane and Phan, 2021; Mason et al., 2021, 2019; Ramaekers et al., 2016; Wall et al., 2022). They most consistently reported lower connectivity between the NAcc and several regions: the postcentral gyrus (3 studies; Mason et al., 2021; Mason et al., 2019; Wall et al., 2022), the insula (3 studies; Mason et al., 2021; Ramaekers et al., 2016; Wall et al., 2022), the ACC and the occipital cortex (3 studies; Mason et al., 2021; Mason et al., 2019; Ramaekers et al., 2016). The second most consistently reported change was lower functional connectivity between the NAc and the supramarginal gyrus (2 studies; Mason et al., 2021; Wall et al., 2022); and other regions: precuneus; precentral gyrus; inferior parietal lobule; supplementary motor area; and rolandic operculum (2 studies; Mason et al., 2021; Mason et al., 2019). Single studies reported different connectivity between the NAcc and other regions, or between other seed regions and other parts of the brain (Bossong et al., 2019; Crane and Phan, 2021; Mason et al., 2021, 2019; Ramaekers et al., 2016; Rzepa et al., 2015; Wall et al., 2022, 2019).

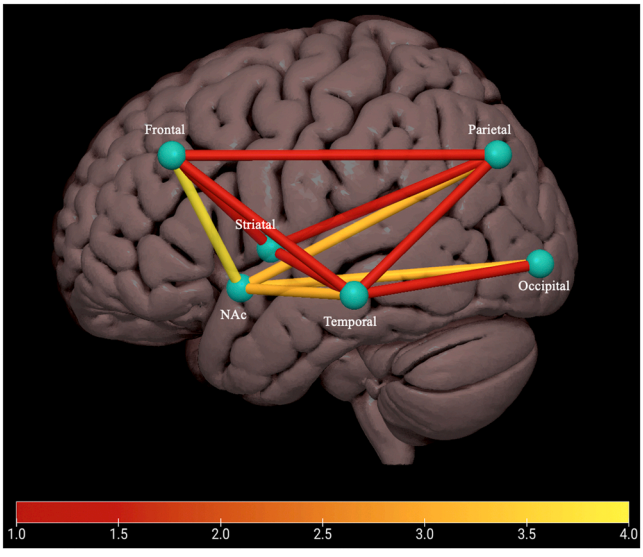

Fig. 2. Overview of location of region-pairs with lower resting state functional connectivity during THC intoxication compared to placebo. The color gradient (red-to-yellow) represents the number of studies reporting different connectivity, the spheres represent the location of the region-pairs. Specifically, 3 studies reported lower connectivity between the striatum and the postcentral gyrus (parietal cortex); 3 studies reported lower connectivity in the NAcc-insula (temporal cortex), NAcc-ACC (frontal cortex), and NAcc-Occipital; 2 studies reported lower connectivity in the NAcc-supramarginal gyrus, as well as between the NAcc and other regions: precuneus; precentral gyrus; inferior parietal lobule; supplementary motor area; and rolandic operculum.

3.7.1.2. Network based differences during THC versus placebo. Only one study examined and found differences in functional connectivity between 62 networks-pairs, of which 10 survived multiple corrections (Klumpers et al., 2012). Lower functional connectivity was most frequently found between the (i) dorsal visual/auditory network and frontal regions, (iii) auditory network and temporal regions, (iv) auditory network and fronto-parietal regions, and (v) sensorimotor network and parietal regions. Higher functional connectivity emerged between the dorsal visual network and occipito-frontal regions, and sensorimotor network and the cerebellum.

3.7.1.3. Correlations between THC-related brain function and behavioral measures. Table 3 shows positive correlations between THC (versus placebo) brain function and behavioral measures. Greater self-reported intoxication was correlated with greater NAc-middle frontal resting state connectivity (Mason et al., 2021); and a greater number of attentional lapses was associated with higher connectivity between the NAc and the frontal cortex (Mason et al., 2021). Two studies explored and found significant correlations between cognitive performance during intoxication and the connectivity between the NAc and frontal regions (MFG, SFG/OFC, SFG) (Mason et al., 2021, 2019). One study found that higher impulsivity scores (on a matching familiar figures task) correlated with lower striatal-thalamus connectivity (Ramaekers et al., 2016).

3.7.1.4. Resting state functional connectivity during intoxication with THCv versus placebo. An individual study compared connectivity between THCv and placebo, and found different connectivity between the amygdala and other regions: occipital, precuneus, PCC, ACC and SMA; as well as between the dmPFC and the IFG/MFG. No correlations were reported in this study.

3.7.2. Resting state functional connectivity during intoxication with cannabis plant matter versus placebo

During acute intoxication with cannabis plant matter versus placebo, resting state connectivity was lower in 14 different region-pairs (Wall et al., 2022, 2019) - most consistently between cortico-striatal pairs, fronto-temporal to posterior cingulate pairs, and fronto-insular pairs.

3.7.2.1. Correlations between cannabis plant matter-related brain function and behavioural measures. Single studies reported significant correlations between connectivity pairs altered with cannabis plant matter and behavioural measures (Table 4). A separate study reported that greater self-reported intoxication correlated with lower posterior cingulate-to-posterior cingulate connectivity; and that greater self-reported paranoia correlated with lower insula-dmPFC connectivity (Wall et al., 2019). Further, greater self-reported cannabis intoxication (versus placebo) (i.e., Oceanic Boundlessness – a loss of boundaries and altered sense of body; Dittrich, 1998) was associated with dynamic functional connectivity: longer durations of state 6 (i.e., higher functional connectivity between somatosensory, auditory and visual cortices) and shorter durations of state 2 (i.e., higher and lower rsFC between various regions across the whole brain; Zaytseva et al., 2019).

Abbreviations: Cor, correlation; dmPFC, dorsomedial prefrontal cortex; ICA, independent component analysis; IFG, inferior frontal gyrus; N.S., non-significant; NAc, nucleus accumbens; neg, negative; PCC, posterior cingulate cortex; pos, positive; post, posterior; post-comm, post-commissural; pre-comm, pre-commissural; rsFC, resting state functional connectivity; VAS, visual analogue scale.

3.7.3. Resting state functional connectivity during Intoxication with CBD or CBDv versus placebo

As shown in Table 5, four studies examined differences in functional connectivity during CBD or CBDv versus placebo conditions using a seed-to-whole-brain approach. Single studies reported higher and lower connectivity between distinct region pairs, most consistently striatal and frontal or other regions. One study found greater connectivity between the putamen and 3 frontal regions: (MFG, SFG, and frontal pole; Grimm et al., 2018). A separate study reported both greater and lower connectivity between the striatum (i.e., associative, limbic, and sensorimotor) and other regions (Wall et al., 2022). Lower connectivity emerged between the striatum and three regions: insula, lateral frontal cortex, and cerebellum (Wall et al., 2022). Greater connectivity emerged between the striatum and three parieto-cingulate regions (posterior parietal, parietal occipital and posterior cingulate cortices). A third study found lower connectivity in 3 region pairs, using seeds in the ventral striatum and putamen: lower ventral striatum-paracentral lobule connectivity; lower ventral striatum-ACC connectivity, and greater putamen-temporal gyrus connectivity (Pretzsch et al., 2021). A fourth study found no significant changes in connectivity between the cerebellum or fusiform gyrus and other brain areas (i.e., cerebellum, fusiform gyrus; Pretzsch et al., 2019). Correlations between CBD-related connectivity and behavioral measures were not reported.

3.7.4. Connectivity during THC intoxication versus CBD, and during non-intoxication

Single studies examined resting state functional connectivity during THC intoxication versus CBD, and during non-intoxication. THC versus CBD was associated with higher connectivity in two region pairs: putamen-frontal pole, and putamen-paracingulate cortex (frontal pole and paracingulate; Grimm et al., 2018). During placebo non-intoxication there were changes in dynamic connectivity (Zaytseva et al., 2019). Specifically, authors reported higher and lower connectivity during state 2 and state 3 across the brain, and within the somatomotor cortex. No correlations between brain function and behavioral measures were reportedly run. Different connectivity in overlapping pathways emerged in two studies examined resting state functional connectivity during two conditions: intoxication with THC and CBD, and THC without CBD (Wall et al., 2022, 2019). In one study both conditions were associated with lower connectivity between the paracingulate – parietal pairs and anterior insula – frontal pairs, and lower negative connectivity between the paracingulate cortex and the IFG (Wall et al., 2019). In another study, both conditions were associated with lower connectivity observed in selected regions pairs: striatal – frontal operculum, striatal – parietal (parietal operculum, postcentral gyrus, supramarginal gyrus) and striatal – temporal (planum temporale, Heschl's gyrus; Wall et al., 2022).

4. Discussion

The emerging evidence shows that acute cannabinoid administration causes changes in resting state functional connectivity in distinct brain pathways and as a function of the type of cannabinoid administered. The most consistent finding was lower connectivity during THC intoxication versus placebo, between the NAcc and various regions: the postcentral gyrus (3 studies; Mason et al., 2021; Mason et al., 2019; Wall et al., 2022), insula, ACC and the occipital cortex (3 studies each); followed by the supramarginal gyrus and other cortical regions (2 studies). Lower connectivity between individual cortical regions emerged during intoxication with cannabis plant matter versus placebo(2 studies; Ramaekers et al., 2016; Wall et al., 2022). Instead, both greater and lower connectivity was reported during intoxication with CBD versus placebo, in single pairs involving mostly the NAcc and frontal regions. Early evidence from studies that administered THC or cannabis plant matter showed correlations between NAcc-frontal connectivity, and greater self-reported intoxication, but the direction and the location of the findings was inconsistent.

The most consistent emerging finding is that compared to placebo, exposure to THC was associated with lower connectivity of the NAcc with parietal regions (i.e., postcentral gyrus, supramarginal gyrus), and the insula. This finding mirrors that from resting state functional connectivity following a single dose of cocaine and methylphenidate (Ramaekers et al., 2013, 2016). Notably, all regions are implicated in cognitive processes associated with cannabis intoxication. The NAcc is a key node for reward processing (Galtress and Kirkpatrick, 2010; Sesack and Grace, 2010) and addiction. The postcentral gyrus is implicated in somatosensory processing, where it receives most of the somatic sensory relay from sensory receptors via the spinal cord before projecting to the thalamus (DiGuiseppi and Tadi, 2021). Of relevance, cannabinoid intoxication can be associated with somatosensory alterations and perceptual distortion (e.g., sensation of floating, dry mouth; American Psychiatric Association, 2013; Ramaekers et al., 2021). Meanwhile, the supramarginal gyrus is ascribed to interpreting tactile sensory data, space perception and to empathy (Carlson, 2012; Hoffmann et al., 2016; Reed and Caselli, 1994) which are all cognitive processes reportedly altered during cannabis intoxication (e.g., psychomotor coordination; American Psychiatric Association, 2013; Broyd et al., 2016; Kroon et al., 2021; Ramaekers et al., 2021). Third, the insula is implicated in interoception – the awareness of bodily sensations as well as the subjective experience of time (Vicario et al., 2020; Wang et al., 2019) – both of which are altered during cannabis intoxication (e.g., sensation of slowed time, increased feeling of hunger; American Psychiatric Association, 2013; Ramaekers et al., 2021). THC may target NAcc-insular connectivity by altering neural transmission from insular neurons to the NAc shell (Berendse and Groenewegen, 1990; Brog et al., 1993; Reynolds and Zahm, 2005).

Administration of THC versus placebo also caused reductions in striatal-ACC connectivity (Ramaekers et al., 2016; Wall et al., 2022). (Russo, 2011, 2018)Perhaps, route of administration (inhalation) and dose (ranging from 0.05 Standard THC Units [+ upload of 0.025 Standard THC Units] to a 1.6 Standard THC Unit) may explain engagement of NAcc-frontal pathways. The ACC is implicated in conflict monitoring and decision-making (Kennerley et al., 2006), the impairment of which has been reported in people while intoxicated with cannabis. Therefore, altered connectivity in this region pair may partly contribute to impaired decision-making associated with cannabinoid intoxication (Ramaekers et al., 2021). Further, both the NAcc and the ACC are part of the salience network (Seeley, 2019). Thus, intoxication with THC may interfere with sustained vigilance, which the salience network is ascribed to (Seeley, 2019).

Another emerging trend was that the connectivity between the NAcc and frontal regions correlated with self-reported intoxication with THC (e.g., euphoria, feeling high). These frontal regions (i.e., medial prefrontal cortex, OFC and medial frontal gyrus) underlie disinhibition, which has been previously reported with cannabinoid intoxication (Ramaekers et al., 2009, 2021). Further, greater self-reported intoxication was associated with connectivity alterations between the striatum and other regions, during intoxication with THC and cannabis plant matter (Mason et al., 2021, 2019; Wall et al., 2019; Zaytseva et al., 2019). The direction of the correlations was inconsistent across studies, and the location of the region pairs was only partly consistent (i.e., for striatal and frontal regions). These early findings suggest that altered resting state functional connectivity in NAcc-frontal pathways are associated with increased intoxication levels. However, more evidence is required to confirm the findings and to understand the implications of connectivity alterations for behavior.

Three studies examined brain function during CBD exposure and reported different connectivity between ventral/dorsal striatum regions and prefrontal areas (e.g., lateral, ACC, frontal pole, middle and superior frontal gyrus) (Grimm et al., 2018; Pretzsch et al., 2021; Wall et al., 2022). The direction of the alteration was mixed, with both evidence of greater and lower connectivity. The location of CBD related alteration

partly overlaps with that reported in studies of cannabis plant matter (i.e., striatum-ACC). Potentially, CBD administered alone and when in cannabis plant matter, may target similar brain pathway also to those targeted from THC and therefore reportedly counteract the effects of THC on brain and related behaviors (Englund et al., 2017).

Overall, the reviewed literature comprises a relatively small sized/low powered studies, and report wide range of different cortical and subcortical brain areas. It is plausible that literature results, overall, reflect somewhat different aspects of the same global underlying disruptive effect of cannabinoid intoxication on multiple brain systems. Indeed, recent work on the acute effects of psychedelics, show that they produce large-scale and almost universal network dysfunctions (Luppi et al., 2021). Future work is warranted to test this notion in resting state functional connectivity fMRI studies of cannabinoid intoxication via utilising global integration/modularity measures of functional connectivity (Petri et al., 2014).

The reviewed findings must be interpreted in light of methodological limitations of the literature. First, most studies used a-priori seed-based connectivity to focus on hypothesis-driven, a priori regions of interest. The most consistently used seed was the NAcc, which was the most reported altered region in this review. Thus, the literature findings may be biased towards selected brain regions such as the NAcc. We recommend future studies to complement seed-based approaches with data-driven whole-brain approaches to confirm the same pathways are implicated (e.g., NAcc). Second, most studies relied on low sample sizes, as < 20 participants in 10 of 13 reviewed studies. Thus, the literature may be underpowered to detect subtle cannabinoid-related changes in connectivity and the role of moderators including but not limited to: age, sex, personality (Ramaekers et al., 2021), history of early adverse experiences, family history of mental health disorders and regular cannabis exposure. Yet, most studies utilised robust designs with placebo-controlled condition, thereby enabling systematic assessment of brain functional changes.

Third, only less than half of the studies (6 of 13) examined correlations between brain function and inconsistent and few measures of intoxication, mental health and cognition (Bossong et al., 2019; Crane and Phan, 2021; Mason et al., 2021, 2019; Ramaekers et al., 2016; Wall et al., 2019). Thus, the most consistently reported brain-behavior correlations pertained to intoxication with THC ($n = 4$) and cannabis plant matter ($n = 2$). Therefore, it is unclear how resting state connectivity alterations during cannabinoid intoxication relate to: (i) people' reported level of intoxication, (ii) intoxication-related mental health symptoms (e.g., psychosis, anxiety, depression); and (iii) altered cognitive performance while people are intoxicated - disinhibition, cognitive disorganisation, attention, episodic and working memory, psychomotor function that could lead to impaired driving (Arkell et al., 2020; Curran et al., 2016; Ramaekers et al., 2021). To elucidate this issue, we suggest that future studies should examine how mental health and cognitive measure relate to brain function during intoxication.

Fourth, the concentration of THC, CBD, other cannabinoids and terpenoids contained in cannabis plant matter samples was not systematically reported, therefore the neurobiological mechanisms of distinct cannabinoid and terpenoid are unclear. Future studies that have technical feasibility should examine and report samples of the cannabinoids contained in the administered plant matter. Fifth, participant's history of cannabis exposure and of exposure to other substances may have affected the literature findings. Specifically, emerging evidence shows that participants' level of cannabis exposure modulate the impact of cannabinoid on resting state functional connectivity (Mason et al., 2021). Also, partially overlapping cortico-striatal brain pathways have been shown to be different in observational fMRI studies of cannabis users compared to controls (Thomson et al., 2021) and in users of other substances compared to controls (Wilcox et al., 2019). Thus, history of substance exposure might have caused tolerance and neuroadaptations in striatal-cortical pathways in selected samples and thus lowered neural responses to acute cannabinoid intoxication. As history of substance use was inconsistent in the examined samples, and given the low number of samples examined, future work is required to systematically disambiguate the effect of cannabinoid exposure from the confounding influence of history of cannabis and substance use.

Further, it remains unclear whether resting state functional connectivity changes reflect peak intoxication or other parts of the time-effect profile of intoxication. Indeed, studies conducted fMRI scans at different times post cannabinoid intake (e.g., 5–150 min, see Supplementary part 3 and Table 3). All but two studies implemented protocols to measure brain function during acute intoxication (scanning ~120-to-150 min post intake via capsules, ~15-to-30 min post intake via vaporisers or smoking joints, or top up cannabinoid administration to aid continued intoxication). A part of the studies used biological or subjective measures to validate intoxication during/right before fMRI scanning, and in particular one study reported low THC plasma levels (e.g., (Grimm et al., 2018). Future neuroimaging studies of cannabinoid intoxication are required to map with precision the functional correlates at different times of the intoxication timecourse, using robust methodologies. They include: (i) the measurement of subjective rating of intoxication and objective measures of acute intoxication immediately before and after the MRI scan and at different stages of intoxication to map precisely the timecourse of intoxication during scanning; (ii) the use of pilot data to informs the specific time-course of intoxication specific to the study methodology and cannabinoid type/administration method. More evidence is required to build a sufficient body of work to enable systematic data analysis including meta-regressions to examine how the timing of intoxication map onto brain functional connectivity. Finally, females were underrepresented in the reviewed samples. All studies but one examined more males than females, and three studies specifically excluded females (Bossong et al., 2019; Grimm et al., 2018; Pretzsch et al., 2019). Future work is required to examine sex differences in the neurobiology of cannabis intoxication, particularly as females have been reported to be more sensitive to adverse effects of cannabinoid exposure (Craft et al., 2013). As cannabis use is more prevalent in males than females, future studies should implement recruitment strategies to include both sexes, and multi-site studies may allow for greater power to examine effects of interest.

The main limitation of this systematic literature review is in the small number of reviewed studies ($n = 13$). Two studies have been authored by the same group of researchers who may be likely to have used the same (or similar) participant samples in multiple studies (Mason et al., 2021, 2019). In addition, two studies report findings from the same study and participants (Wall et al., 2022, 2019). This may compromise the generalizability of the results. More work is required in other to confirm which region-pairs are robustly altered by cannabinoid intoxication. However, the reviewed body of work is relatively recent: the earliest study was published in 2012 (Klumpers et al., 2012), six studies were published in 2019 (Bossong et al., 2019; Mason et al., 2021, 2019; Pretzsch et al., 2019; Wall et al., 2019; Zaytseva et al., 2019) and three studies in 2021 and 2022 (Crane and Phan, 2021; Pretzsch et al., 2021; Wall et al., 2022). Thus, our review provides preliminary insight on how cannabinoids affect brain functional connectivity at rest.

5. Conclusion

Emerging evidence shows that intoxication with THC and cannabis plant matter lowers resting-state functional connectivity between striatal and parieto-insular pathways implicated in cognitive processes altered during cannabinoid intoxication (e.g., reward processing, disinhibition and sensorimotor function). Such alterations may be associated with self-reported intoxication. CBD may have more complex effects (e.g., higher and lower connectivity) on partially overlapping striatal-prefrontal pathways. Interestingly, resting state fMRI evidence has shown that THC and CBD affect neurobiological pathways implicated in prominent neuroscientific theories of addiction. More robust and large-scale studies are required to further uncover how brain

functional changes relate to people's own intoxication, mental health and cognition, in order to increase knowledge and raise awareness about the risks and benefits of cannabinoids.

Conflicts of interest

The authors declare no conflict of interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.105014.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Arlington, VA.
Arkell, T.R., Vinckenbosch, F., Kevin, R.C., Theunissen, E.L., McGregor, I.S., Ramaekers, J.G., 2020. Effect of cannabidiol and Δ9-tetrahydrocannabinol on driving performance: a randomized clinical trial. Jama 324, 2177–2186.
Barrett, F.S., Schlienz, N.J., Lembeck, N., Waqas, M., Vandrey, R., 2018. "Hallucinations" following acute cannabis dosing: a case report and comparison to other hallucinogenic drugs. Cannabis Cannabinoid Res. 3, 85–93.
Bartels, A., Zeki, S., 2004. The chronoarchitecture of the human brain–natural viewing conditions reveal a time-based anatomy of the brain. NeuroImage 22, 419–433.
Berendse, H.W., Groenewegen, H.J., 1990. Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J. Comp. Neurol. 299, 187–228.
Bergamaschi, M.M., Queiroz, R.H., Chagas, M.H., de Oliveira, D.C., De Martinis, B.S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., Nardi, A.E., Martín-Santos, R., Hallak, J.E., Zuardi, A.W., Crippa, J.A., 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology 36, 1219–1226.
Bloomfield, M.A., Hindocha, C., Green, S.F., Wall, M.B., Lees, R., Petrilli, K., Costello, H., Ogunbiyi, M.O., Bossong, M.G., Freeman, T.P., 2019. The neuropsychopharmacology of cannabis: a review of human imaging studies. Pharmacol. Ther. 195, 132–161.
Bossong, M.G., van Hell, H.H., Schubart, C.D., van Saane, W., Iseger, T.A., Jager, G., van Osch, M.J., Jansma, J.M., Kahn, R.S., Boks, M.P., 2019. Acute effects ofΔ 9-tetrahydrocannabinol (THC) on resting state brain function and their modulation by COMT genotype. Eur. Neuropsychopharmacol. 29, 766–776.
Brog, J.S., Salyapongse, A., Deutch, A.Y., Zahm, D.S., 1993. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. J. Comp. Neurol. 338, 255–278.
Broyd, S.J., van Hell, H.H., Beale, C., Yucel, M., Solowij, N., 2016. Acute and chronic effects of cannabinoids on human cognition-a systematic review. Biol. Psychiatry 79, 557–567.
Carlson, N.R., 2012. Physiology of Behavior. Pearson.
Chandra, S., Radwan, M.M., Majumdar, C.G., Church, J.C., Freeman, T.P., ElSohly, M.A., 2019. New trends in cannabis potency in USA and Europe during the last decade (2008-2017). Eur. Arch. Psychiatry Clin. Neurosci. 269, 5–15.
Colizzi, M., McGuire, P., Pertwee, R.G., Bhattacharyya, S., 2016. Effect of cannabis on glutamate signalling in the brain: a systematic review of human and animal evidence. Neurosci. Biobehav Rev. 64, 359–381.
Craft, R.M., Marusich, J.A., Wiley, J.L., 2013. Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? Life Sci. 92, 476–481.
Crane, N.A., Phan, K.L., 2021. Effect of Δ9-Tetrahydrocannabinol on frontostriatal resting state functional connectivity and subjective euphoric response in healthy young adults. Drug Alcohol Depend. 221, 108565.
Crippa, J.A., Zuardi, A.W., Martin-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., Fusar-Poli, P., 2009. Cannabis and anxiety: a critical review of the evidence. Hum. Psychopharmacol. 24, 515–523.
Curran, H.V., Freeman, T.P., Mokrysz, C., Lewis, D.A., Morgan, C.J., Parsons, L.H., 2016. Keep off the grass? Cannabis, cognition and addiction. Nat. Rev. Neurosci. 17, 293–306.
Dellazizzo, L., Potvin, S., Giguere, S., Dumais, A., 2022. Evidence on the acute and residual neurocognitive effects of cannabis use in adolescents and adults: a systematic meta-review of meta-analyses. Addiction.
DiGuiseppi, J., Tadi, P., 2021. Neuroanatomy, Postcentral Gyrus. StatPearls, Treasure Island (FL).
Dittrich, A., 1998. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry 31 (Suppl 2), 80–84.
Englund, A., Morrison, P.D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., Stone, J.M., Reichenberg, A., Brenneisen, R., Holt, D., Feilding, A., Walker, L., Murray, R.M., Kapur, S., 2013. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J. Psychopharmacol. 27, 19–27.
Englund, A., Freeman, T.P., Murray, R.M., McGuire, P., 2017. Can we make cannabis safer? Lancet Psychiatry 4, 643–648.
Fox, M., Greicius, M., 2010. Clinical applications of resting state functional connectivity. Front. Syst. Neurosci. 4.
Freeman, A.M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H.V., Saunders, R., Freeman, T.P., 2019a. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neurosci. Biobehav Rev. 107, 696–712.
Freeman, T.P., Groshkova, T., Cunningham, A., Sedefov, R., Griffiths, P., Lynskey, M.T., 2019b. Increasing potency and price of cannabis in Europe, 2006-16. Addiction 114, 1015–1023.
Freeman, T.P., Hindocha, C., Baio, G., Shaban, N.D.C., Thomas, E.M., Astbury, D., Freeman, A.M., Lees, R., Craft, S., Morrison, P.D., Bloomfield, M.A.P., O'Ryan, D., Kinghorn, J., Morgan, C.J.A., Mofeez, A., Curran, H.V., 2020. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. Lancet Psychiatry 7, 865–874.
Freeman, T.P., Craft, S., Wilson, J., Stylianou, S., ElSohly, M., Di Forti, M., Lynskey, M.T., 2021. Changes in delta-9–tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. Addiction 116, 1000–1010.
Galtress, T., Kirkpatrick, K., 2010. The role of the nucleus accumbens core in impulsive choice, timing, and reward processing. Behav. Neurosci. 124, 26.
Glass, M., Faull, R.L.M., Dragunow, M., 1997. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77, 299.
Goebel, R., Linden, D.E., Lanfermann, H., Zanella, F.E., Singer, W., 1998. Functional imaging of mirror and inverse reading reveals separate coactivated networks for oculomotion and spatial transformations. Neuroreport 9, 713–719.
Grimm, O., Löffler, M., Kamping, S., Hartmann, A., Rohleder, C., Leweke, M., Flor, H., 2018. Probing the endocannabinoid system in healthy volunteers: cannabidiol alters fronto-striatal resting-state connectivity. Eur. Neuropsychopharmacol. 28, 841–849.
Gunasekera, B., Davies, C., Martin-Santos, R., Bhatthacharyya, S., 2020. The Yin and Yang of Cannabis-a systematic review of human neuroimaging evidence of the differential effects of delta-9-tetrahydrocannabinol and cannabidiol. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.
Hall, W., Stjepanović, D., Caulkins, J., Lynskey, M., Leung, J., Campbell, G., Degenhardt, L., 2019. Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. Lancet 394, 1580–1590.
Hashimotodani, Y., Ohno-Shosaku, T., Kano, M., 2007. Endocannabinoids and synaptic function in the CNS. Neuroscientist 13, 127–137.
Hindley, G., Beck, K., Borgan, F., Ginestet, C.E., McCutcheon, R., Kleinloog, D., Ganesh, S., Radhakrishnan, R., D'Souza, D.C., Howes, O.D., 2020. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. Lancet Psychiatry 7, 344–353.
Hoffmann, F., Koehne, S., Steinbeis, N., Dziobek, I., Singer, T., 2016. Preserved self-other distinction during empathy in autism is linked to network integrity of right supramarginal gyrus. J. Autism Dev. Disord. 46, 637–648.
Kennerley, S.W., Walton, M.E., Behrens, T.E.J., Buckley, M.J., Rushworth, M.F.S., 2006. Optimal decision making and the anterior cingulate cortex. Nat. Neurosci. 9, 940–947.
Klumpers, L.E., Cole, D.M., Khalili-Mahani, N., Soeter, R.P., Te Beek, E.T., Rombouts, S. A., van Gerven, J.M., 2012. Manipulating brain connectivity with δ⁹-tetrahydrocannabinol: a pharmacological resting state FMRI study. NeuroImage 63, 1701–1711.
Kroon, E., Kuhns, L., Cousijn, J., 2021. The short-term and long-term effects of cannabis on cognition: recent advances in the field. Curr. Opin. Psychol. 38, 49–55.
Luppi, A.I., Carhart-Harris, R.L., Roseman, L., Pappas, I., Menon, D.K., Stamatakis, E.A., 2021. LSD alters dynamic integration and segregation in the human brain. NeuroImage 227, 117653.
Mackie, K., 2008. Cannabinoid receptors: where they are and what they do. J. Neuroendocrinol. 20, 10–14.
Mason, N., Theunissen, E., Hutten, N., Tse, D., Toennes, S., Jansen, J., Stiers, P., Ramaekers, J., 2021. Reduced responsiveness of the reward system underlies tolerance to cannabis impairment in chronic users. bioRxiv, 708677.
Mason, N.L., Theunissen, E.L., Hutten, N., Tse, D.H.Y., Toennes, S.W., Stiers, P., Ramaekers, J.G., 2019. Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity. Eur. Neuropsychopharmacol. 29, 247–256.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.
Petri, G., Expert, P., Turkheimer, F., Carhart-Harris, R., Nutt, D., Hellyer, P.J., Vaccarino, F., 2014. Homological scaffolds of brain functional networks. J. R. Soc. Interface 11, 20140873.
Philippi, C.L., Floyd, T., Dahl, G., 2020. Resting-state functional magnetic resonance imaging and neuropsychiatric conditions. Wiley Encycl. Health Psychol. 131–140.
Pretzsch, C.M., Voinescu, B., Mendez, M.A., Wichers, R., Ajram, L., Ivin, G., Heasman, M., Williams, S., Murphy, D.G., Daly, E., 2019. The effect of cannabidiol

(CBD) on low-frequency activity and functional connectivity in the brain of adults with and without autism spectrum disorder (ASD). J. Psychopharmacol. 33, 1141–1148.
Pretzsch, C.M., Floris, D.L., Voinescu, B., Elsahib, M., Mendez, M.A., Wichers, R., Ajram, L., Ivin, G., Heasman, M., Pretzsch, E., 2021. Modulation of striatal functional connectivity differences in adults with and without autism spectrum disorder in a single-dose randomized trial of cannabidivarin. Mol. Autism 12, 1–14.
Ramaekers, J., Evers, E., Theunissen, E., Kuypers, K., Goulas, A., Stiers, P., 2013. Methylphenidate reduces functional connectivity of nucleus accumbens in brain reward circuit. Psychopharmacology 229, 219–226.
Ramaekers, J., van Wel, J., Spronk, D., Franke, B., Kenis, G., Toennes, S., Kuypers, K., Theunissen, E., Stiers, P., Verkes, R., 2016. Cannabis and cocaine decrease cognitive impulse control and functional corticostriatal connectivity in drug users with low activity DBH genotypes. Brain Imaging Behav. 10, 1254–1263.
Ramaekers, J.G., Kauert, G., Theunissen, E.L., Toennes, S.W., Moeller, M.R., 2009. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. J. Psychopharmacol. 23, 266–277.
Ramaekers, J.G., Mason, N.L., Kloft, L., Theunissen, E.L., 2021. The why behind the high: determinants of neurocognition during acute cannabis exposure. Nat. Rev. Neurosci. 22, 439–454.
Reed, C.L., Caselli, R.J., 1994. The nature of tactile agnosia: a case study. Neuropsychologia 32, 527–539.
Reynolds, S.M., Zahm, D.S., 2005. Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. J. Neurosci. 25, 11757–11767.
Russo, E.B., 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br. J. Pharm. 163, 1344–1364.
Russo, E.B., 2018. The case for the entourage effect and conventional breeding of clinical cannabis: no “strain,” no gain. Front. Plant Sci. 9, 1969.
Rzepa, E., Tudge, L., McCabe, C., 2015. The CB1 neutral antagonist tetrahydrocannabivarin reduces default mode network and increases executive control network resting state functional connectivity in healthy volunteers. Int J. Neuropsychopharmacol. 19.
Scheim, A.I., Maghsoudi, N., Marshall, Z., Churchill, S., Ziegler, C., Werb, D., 2020. Impact evaluations of drug decriminalisation and legal regulation on drug use, health and social harms: a systematic review. BMJ Open 10, e035148.
Seeley, W.W., 2019. The salience network: a neural system for perceiving and responding to homeostatic demands. J. Neurosci. 39, 9878–9882.
Sesack, S.R., Grace, A.A., 2010. Cortico-basal ganglia reward network: microcircuitry. Neuropsychopharmacology 35, 27–47.
Thomson, H., Labuschagne, I., Greenwood, L.M., Robinson, E., Sehl, H., Suo, C., Lorenzetti, V., 2021. Is resting-state functional connectivity altered in regular cannabis users? A systematic review of the literature. Psychopharmacology (Berl).
van de Ven, V.G., Formisano, E., Prvulovic, D., Roeder, C.H., Linden, D.E., 2004. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum. Brain Mapp. 22, 165–178.
Vicario, C.M., Nitsche, M.A., Salehinejad, M.A., Avanzino, L., Martino, G., 2020. Time processing, interoception, and insula activation: a mini-review on clinical disorders. Front. Psychol. 11, 1893.
Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic advances from the brain disease model of addiction. New Engl. J. Med. 374, 363–371.
Wall, M.B., Pope, R., Freeman, T.P., Kowalczyk, O.S., Demetriou, L., Mokrysz, C., Hindocha, C., Lawn, W., Bloomfield, M.A., Freeman, A.M., 2019. Dissociable effects of cannabis with and without cannabidiol on the human brain’s resting-state functional connectivity. J. Psychopharmacol. 33, 822–830.
Wall, M.B., Freeman, T.P., Hindocha, C., Demetriou, L., Ertl, N., Freeman, A.M., Jones, A. P., Lawn, W., Pope, R., Mokrysz, C., Solomons, D., Statton, B., Walker, H.R., Yamamori, Y., Yang, Z., Yim, J.L., Nutt, D.J., Howes, O.D., Curran, H.V., Bloomfield, M.A., 2022. Individual and combined effects of cannabidiol and Δ(9)-tetrahydrocannabinol on striato-cortical connectivity in the human brain. J. Psychopharmacol. 36, 732–744.
Walpole, S.C., Prieto-Merino, D., Edwards, P., Cleland, J., Stevens, G., Roberts, I., 2012. The weight of nations: an estimation of adult human biomass. BMC Public Health 12, 439.
Wang, X., Wu, Q., Egan, L., Gu, X., Liu, P., Gu, H., Yang, Y., Luo, J., Wu, Y., Gao, Z., Fan, J., 2019. Anterior insular cortex plays a critical role in interoceptive attention. Elife 8.
Wilcox, C.E., Abbott, C.C., Calhoun, V.D., 2019. Alterations in resting-state functional connectivity in substance use disorders and treatment implications. Prog. Neuro Psychopharmacol. Biol. Psychiatry 91, 79–93.
Zaytseva, Y., Horáček, J., Hlinka, J., Fajnerová, I., Androvičová, R., Tintěra, J., Salvi, V., Balíková, M., Hložek, T., Španiel, F., 2019. Cannabis-induced altered states of consciousness are associated with specific dynamic brain connectivity states. J. Psychopharmacol. 33, 811–821.