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Effects of Cannabis on Impulsivity: A Systematic Review of Neuroimaging Findings

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Abstract: We conducted a systematic review to assess the evidence for specific effects of cannabis on impulsivity, disinhibition and motor control. The review had a specific focus on neuroimaging findings associated with acute and chronic use of the drug and covers literature published up until May 2012. *Seventeen* studies were identified, of which 13 met the inclusion criteria; three studies investigated acute effects of cannabis (1 fMRI, 2 PET), while six studies investigated non-acute functional effects (4 fMRI, 2 PET), and four studies investigated structural alterations. Functional imaging studies of impulsivity studies suggest that prefrontal blood flow is lower in chronic cannabis users than in controls. Studies of acute administration of THC or marijuana report increased brain metabolism in several brain regions during impulsivity tasks. Structural imaging studies of cannabis users found differences in reduced prefrontal volumes and white matter integrity that might mediate the abnormal impulsivity and mood observed in marijuana users. To address the question whether impulsivity as a trait precedes cannabis consumption or whether cannabis aggravates impulsivity and discontinuation of usage more longitudinal study designs are warranted.

Keywords: Cannabis, marijuana, cannabinoids, impulsivity, inhibition, neuroimaging, magnetic resonance imaging, MRI, fMRI.

INTRODUCTION

Cannabis sativa is a widely used drug comprising a broad spectrum of usage ranging from recreational users to chronic addicts [1, 2]. Over the last years, accumulating evidence revealed that cannabis use leads to structural and functional brain abnormalities in cannabis users [3, 4]. For example, neuroimaging data has shown that cannabis use reduces grey and white matter volumes in cannabinoid-receptor rich areas, as well as changes functional activity in the prefrontal and anterior cingulate cortex [5]. Furthermore, pharmacological neuroimaging studies of healthy volunteers has shown brain functional mechanisms underlying the effects of cannabis [6-14]. Although research on the neurobiological effects of cannabis is increasing, how it affects the neuronal correlates underlying cognitive control remain still poorly understood, in particular the interlacement of cannabis use and impulsivity. In this review, we provide an overview about the effects of cannabis has on impulsivity, a key function in cognitive self-control and goal-directed behavior. Abnormal impulsivity as a compromised ability to exert control over drug urges or to inhibit compulsive drug-driven behavior has repeatedly been reported because of drug abuse. Thus, this systematic review incorporates studies addressing the effects of cannabis on the modulation of impulsive behavior by revisiting behavioral, as well as functional and structural neuroimaging findings.

Impulsive Behavior

Although impulsive behavior is a pre-existing personality trait that may promote the usage of drugs, consuming cannabis may result in behavioral changes including alterations of impulsivity [15]. According to Durana and Barnes [16], impulsivity is defined as "actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences". As such, it is part of normal behavior, but the multifaceted construct as well encompasses behavioral characteristics contributing to different psychopathological symptoms in a broad spectrum of neuropsychiatric disorders [17], and is a core deficit in substance abuse disorders [18]. Furthermore, impulsivity has been regarded as a lack of "executive control", including deficits in higher-order cognitive functions such as inhibition, shifting and updating of information and behavior [19]. There is robust evidence that impulsive behavior reflects neurodevelopmental processes mediated in distinct brain networks (i.e. frontal cortex) contributing to its cognitive, clinical and behavioral aspects [20]. Behaviorally, impulsivity can be operationalized as a `predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others` [21]. Two domains are of relevance: the choice of a smaller, immediate reward over a larger, delayed reward [22] or the inability to inhibit behavior by changing the course of action or to stop a response once initiated [23].

Role of the Prefrontal Cortex in Neurocognitive Networks of Impulsivity and the Transition to Addiction

A key role has been ascribed to the prefrontal cortex (PFC) in its regulation of reward and its involvement in higher-order executive functions such as cognitive self-control (goal-directed behavior, response inhibition etc.), salience attribution and awareness. Goldstein and Volkow [24] reviewed neuroimaging data of distinct PFC regions and their roles in the neuropsychological mechanisms that underlie the relapsing cycle of addiction. Based on that data, with a focus on inhibitory control and emotion regulation, the iRISA-model of Goldstein and Volkow [24] distinguishes between dorsal PFC regions including the dorsolateral PFC, dorsal ACC, and the IFG, which are implicated in higher-order cognitive processes ("cold" processes), and ventral PFC regions subsuming the ventral OFC, ventromedial PFC, and rostroventral ACC, which are engaged during emotion-related "hot" processes. In the healthy state, automatic drug-related responses are suppressed by the input from dorsal PFC regions. During the state of withdrawal or craving, drug-related functions start to eclipse non-drug related functions, leading to a conflict situation with increasing drug-biased cognition and cue-induced craving. When the drug is reinstated, higher-order non-drug related cognitive functions are overrun by the input from PFC regions involved in drug-related `hot` processes. Thus, attention narrows to drug-related cues, impulsivity increases and basic emotions are unleashed resulting in automatic, stimulus-driven behavior.

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Table 1. Impulsivity instruments used in the reviewed neuroimaging studies

Response inhibition: Commission errors, reaction time, competing responses	Go-/No-Go task
	Stop signal reaction time task (SSRTT)
	(EFT)
Motor control accuracy, errors, and reaction time	Critical tracking task Self-paced finger-tapping task
Interference: incongruent/ congruent	STROOP task The multi-source interference task
Attention: -divided -sustained	Divided attention task, Stop signal task The multi-source interference task SAT, WCST, MicroCogTM) Self-paced counting task
Decision making and risk taking:	Iowa gambling task
Cognitive flexibility: -shifting -perseveration	Wisconsin Cart sorting test
Delay discounting	Barratt Impulsivity Scale - BIS-11

Operationalization of Impulsivity

There are several tasks and subjective questionnaires to measure impulsivity. Here, we specifically focused on reviewing seven subdomains of impulsivity, namely response inhibition, motor control, interference/incongruity, attention, decision making/ gambling, cognitive flexibility and delay discounting. Table **1** gives an overview of the tasks used in the reviewed neuroimaging studies.

In addition, other studies' designs often use psychometric impulsivity measures as a trait using self-reporting scales like the Barratt Impulsivity Scale (BIS-11)[25], the UPPS-P Impulsive Behavior Scale (IBS) [26], and the Kirby test of delayed discounting [27]. Psychometric measurements of impulsivity often fail to show clear correlations with objective methods and it has been suggested that self-report scales may reflect subjective commentaries on impulsive-like behavioral output [21].

METHODS

Selection Procedures and Search Strategy

We performed a PUBMED database search including all entries until the end of May 2012 on the following blocks of search terms: "Cannabis", "Cannabinoid", "THC", "Marihuana" OR "Marijuana" AND "Impulsivity", "Motor Control", "Motor Inhibition" OR "Disinhibition". We aimed to provide an overview on research of impulsivity and cannabis use, we arranged all included studies in tables. Thus, we differentiated neuroimaging and epidemiological studies in humans from behavioral studies in animals and humans, and genetic studies, again in animals and humans. In this review, we want to focus on disinhibition and task-related brain alterations of functional and structural neuroimaging data in cannabis users. We reviewed studies in English, German and Spanish. Two researchers were responsible for study selections: Johannes Wrege (JW) and Stefan Borgwardt (SB). Initially, selection was independent, then screening and full-text assessment were carried out via group discussion.

Selection Criteria and Recorded Variables

We hand-searched all publications in order to find studies investigating the effects of cannabis use on impulsivity or studies trying to elucidate the influence of the endocannabinoid system on inhibition and motor control. We also searched the references of all included manuscripts for further relevant publications. In order to be included, studies had to have a parallel, crossover or case-control design with an appropriate control group of healthy controls, placebo or baseline comparisons and an original publication in a peer-reviewed journal. To address the principal aim of this review, studies had to include an impulsivity measure or task in at least one of the above-mentioned domains. The outcome measures had to be valid neuropsychological tests (see operationalization of impulsivity section). Studies with subjects of co-use had to have a "pure" group of "cannabis users" only. Furthermore, studies had to address other potential substance use, potential history of neurological or psychiatric problems, or had to report length of abstinence from Cannabis before testing. Exclusion criteria were any psychiatric or neurological disorder with the exception of substance use disorders when providing a Cannabis group only.

The final selection of systematically reviewed studies consists of neuroimaging studies in humans. We reviewed 13 neuroimaging studies between 2003 and 2012 on the effects of cannabis on impulsivity. Of these studies, only three tested acute effects and 11 non-acute effects, with either structural or functional imaging methods. We chose to present the reviewed studies in informative tables in order to provide a comprehensible interpretation of the main findings and conclusions drawn.

In these tables, we differentiated between chronic and recreational users, abstinent and non-users, acute and non-acute effects, functional and structural studies, the type of comparison, type of administration: delta-9-THC, Cannabis, the route of drug investigated, the study design and more, see Table **2** for further information.

We included three studies of acute administration of cannabis or delta-9-THC on different types of subjects and tasks (Go-/No-Go task/stop-signal task, self-paced counting task/ virtual psycho-motor task, attention task). Two studies assessed cannabis users (occasional vs. heavy users, regular users - 1 joint per day) and only one study assessed healthy non-using volunteers [14]. This is the only study which assessed the different effects of the two main psychotropic ingredients of cannabis, cannabidiol in comparison to tetrahydrocannabinol. Three out of six reviewed non-acute functional studies applied an interference task, two a Go/No-Go task and one study a decision making gambling task. The five reviewed structural study designs used the BIS-11 (three studies) impulsivity questionnaire, and the stroop and Wisconsin Card sorting test as a measure of impulsivity and executive control.

RESULTS

We found 774 entries listed in Pubmed until May 2012 with the above depicted search terms. Neuroimaging studies on impulsivity and cannabis are limited, whereas, historically reasoned, there is a large number of behavioral studies on cannabis use with systematic reviews on cognitive functions, but not specifically on impulsivity or inhibitory control.

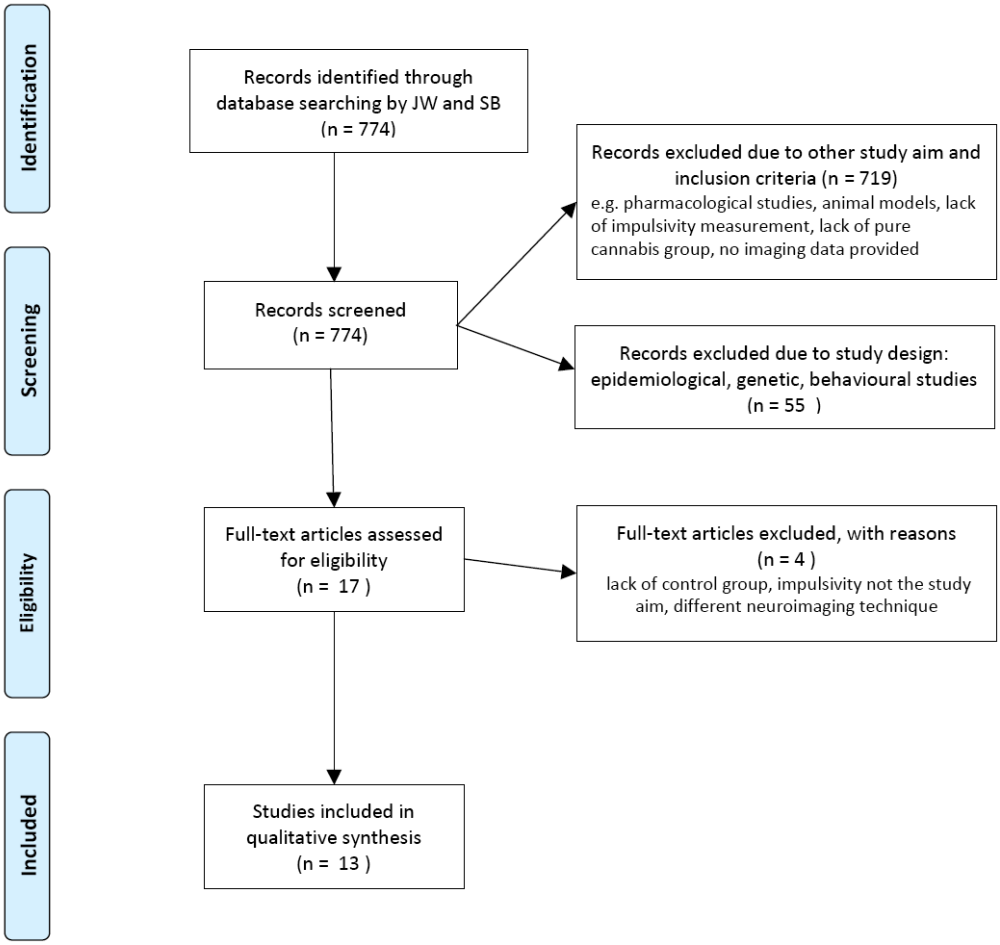
Identified Studies

Seventeen neurophysiological and neuroimaging studies published between 2003 and 2012 met the inclusion criteria and were reviewed. One study was excluded due to a missing control group [28], one due to other study aim [29], and two due to different neuroimaging techniques: event related potential EEG [30], and transcranial magnetic stimulation combined with electromyography [31]. Among the remaining 13 neuroimaging studies, three studies investigated acute effects of either healthy volunteers and occasional or heavy cannabis users (1 fMRI, 2 PET). 10 non-acute studies were included with different abstinence periods ranging from 12 hours up to 28 days, while six studies investigated non-acute functional impacts (four fMRI, two PET), and four studies investigated non-acute structural alterations of cannabis use. One study provided both functional and structural data [41] which sums up the structural data to five studies. We sorted the final number of reviewed studies in acute functional, non-acute functional and non-acute structural studies as you can see in Table **2**. It lists all included studies and contains an overview for better orientation. The following flow chart (in Fig. **1**) illustrates the selection process.

Behavioral Findings in Neuroimaging Studies

Two out of the three reviewed studies of acute administration of either cannabis or delta-9-THC reported an impact on the behavioral level. Weinstein and colleagues [32] found significant more virtual wall hits in a reality maze after smoking 17mg delta-9-THC cigarettes in regular users, and subjects in the study of O`Leary *et al*. [33] showed increased rates of self-paced counting after smoking marijuana in both recreational and heavy users.

All included studies of non-acute functional designs found no significant differences in inhibitory task performance. However, despite comparable inhibitory performances between users and non-users, marijuana users tended to have faster reaction times and



(Fig. **1**).

Table 2.

	Author		Journal	Study aim	POPULATION C / Usertype		SPECIFICATION OF STUDIE DESIGN Parallel, crossover, placebo / abstinence time		Tests/ measurements of Impulsivity and Motor Control
acute effects	Borgwardt *et al*. 2008		Biological Psychiatry	fMRI, acute effects of THC on motor inhibition in healthy volunteers	-	15 healthy male volunteers (<15 times use in lifetime)	double-blind, pseudo-random., placebo-contr. rep. meas. within-sub.	1 month	Go/No-Go-task
	Weinstein *et al*. 2007		Psychopharmacology	^{18}FDG-PET, acute 17mg THC on motor control in regular marijuana users	-	12 regular users (1 joint per day at least 5 years)	Double-blind, placebo-controlled, cross-over	Requested only, the night before	Psycho-motor(virtual maze) task; WCST, IGT, estimates of time and distance of a car
	O'Leary *et al*. 2003		NeuroReport	$H_2{}^{15}O$-PET, acute effects of THC, perfusion and internal timing in heavy compared to moderate use	-	12 heavy(daily 1.8 joints since 5.4y) / 12 moderate (once a week since 3.9y)	Double-blind placebo-controlled counterbalanced design	-	Self-paced counting task Self-paced finger-tapping task
non-acute effects	functional	Gruber *et al*. 2012	Neuroscience Letters	fMRI, inhibiting impulsive behaviors in early (<16y) vs. late onset MJs	16 <15x	**23**heavy (2500+joint)MJ (n=9 <16y/ n=15 +16y) / 16 non-smoking HC	Cross-sectional	12h	MSIT
		Hestor *et al*. 2009	Neuropsychopharmacology	fMRI, inhibitory control and error awareness in chronic MJ	16	16 chronic users (500+ joints, 5-7x/week for 2y)	Cross-sectional	-	Go/No-Go-task; EAT
		Tapert *et al*. 2007	Psychopharmacology	fMRI, go/no-go task in adolescent marijuana users after 28 days of abstinence.	17	16 recreational (+60 lifetime)	Cross-sectional	28 days	Go/No-Go-task
		Bolla *et al*. 2005	NeuroImage	$H_2{}^{15}O$-PET, 25-day abstinent MJ users dose-related alterations in the Iowa Gambling (IGT)	11	11 heavy chronic users (4/w for 2y) (8-35j/w vs. 53-84j/w)	Cross-sectional	28 days	IGT, resting state, sensorimotor Control-task
		Gruber *et al*. 2005	Cognitive brain research	fMRI, DTI, frontal dysfunctions & structural changes in heavy cannabis use in modified Stroop task	9	9 chronic users (4000+ joints)	Cross-sectional	Urine+/- for THC, but not others	STROOP-task
		Eldreth *et al*. 2004	NeuroImage	PET 15O, modified Stroop task, 25-day abstinent, heavy MJ users, executive cognitive functioning	11	11 chronic users (4/w for 2y)	Cross-sectional	23d MJ 3d Controls Urine sample time range	Rest-R (eyes fixated on a target); Active Task-A (Conflict condition STROOP);Control Task-C (sensorimotor No Conflict condition)
	structural	Gruber *et al*. 2011	Experimental and Clinical Psychopharmacollogy	DTI, impulsivity measures in chronic heavy MJ smokers, white matter microstructure	15	15 chronic users	Cross-sectional	-	BIS-11

(Table 2) Contd….

	Author	Journal	Study aim	POPULATION C / Usertype		SPECIFICATION OF STUDy DESIGN Parallel, crossover, placebo / abstinence time		Tests/ measure-ments of Impulsivity and Motor Control
	Siveri *et al.* 2011	Psychiatry Research	MRSI in MJ-dependence	11	15 chronic users MJ 1.use=15.7±2.2y for 5.5±2.6y; 5.6±1.7/week	Cross-sectional	Non Urine+/-	BIS-11, +3 affect/mood scales
	Churchwell *et al.* 2010	Frontiers in Psychology	MRI, functional integrity of moPFC, reward perception, substance abuse, and dependence.	18	18 recreational users	Cross-sectional	Continued use until study visit	BIS-11
	Hermann *et al*. 2007	Biological Psychiatry	^{1}H-MRS, Cannabinoids neurotoxic and neuroprotective properties inconsistent alterations neuropsychological deficits, neuropsychological testing	13	14 chronic recreational users	Cross-sectional	Non Urine+/-	WCST, TMT, D2
	Gruber *et al*. 2005	Cognitive brain research	DTI, heavy cannabis smokers performing a modification of the classic Stroop task.	9	9 chronic users (4000+ joints)	Cross-sectional	Urine+/- for THC, but not others	STROOP

BIS-11: Barratt Impulsivity Scale-11; **C:** Controls; **DTI**: Diffusion tensor imaging technique; **EAT**: Error Awareness Task; **IGT**: Iowa Gambling task; **MJ**: Marijuana user; **MRSI**: proton magnetic resonance spectroscopic imaging; **MSIT**: Multi-Source Interference Task; PET: positron emission tomographic imaging; **STROOP**: Stroop Colour Word Test; **WCST**: Wisconsin card sorting test, (Heaton, 1999);

higher rates on commission errors [34]. This was even more pronounced in early onset than in late onset of cannabis use, albeit not statistically underpinned. Hester *et al*. [35] found that earlier onset of cannabis use was associated with poorer inhibitory control, but this association only approached significance. Their cannabis-using subjects showed significantly decreased error awareness. One study used the decision-making Iowa Gambling task (IGT) and found abnormal performance in marijuana-smoking subjects who had chosen more risky cards with higher reward opportunities [36]. Heavy unlike moderate users showed significant performance abnormalities and developed no learning behavior over two trials, which indicates a missing adaptive shift in decision-making and the ability to balance reward and punishment. Studies measuring impulsivity with self-rating questionnaires such as BIS-11 found significantly higher BIS-11 scores in marijuana using subjects. Further studies revealed higher total scores [37, 38], higher cognitive and motor impulsivity subscores [38], and decreased future orientation indexed in the non-planning subscale of the BIS-11 [39].

Neuroimaging Findings

Table **3** depicts the details of higher or lower brain activation in terms of BOLD response contrasts, greater or less regional volume or modified regional cerebral blood flow after the administration of cannabis or within the cannabis-user group. In general, significant PFC activation during inhibitory control and cognitive control of impulsivity were found in the ACC, the left and right DLPFC, the inferior and medial PFC and the OFC. In addition, significant activation patterns were observed in parietal, temporal, hippocampal, occipital or cerebellar regions depending on the task used.

Acute Effects of Cannabis on Functional Brain Activity in Users and Healthy Volunteers

Healthy volunteers administered delta-9-THC acutely showed a decreased BOLD signal (fMRI) in the ACC and in the inferior frontal gyrus during No-Go conditions [14]. O'Leary *et al*. [33] found by using ^{15}O-PET that cannabis resulted in increased rCBF in several regions including the anterior cingulate, mesial and orbital frontal lobes, insula, temporal poles, and cerebellum compared to placebo. These subjects of occasional vs. regular users (daily usage) had to attend to a finger tapping and self-paced counting task and revealed significant group differences. After smoking marijuana, occasional user showed decreased rCBF in cerebellar vermis and the thalamus, whereas chronic user showed less frontal lobe activation. This corresponds to the results of Borgwardt *et al*. [14] with decreased BOLD signaling under No-Go conditions. Nevertheless, a greater rCBF increase from pre- to post-smoking in the chronic compared to occasional user group has been found in thalamus and cerebellum. Regular cannabis users [40] underwent an ^{18}FDG-PET scan analysis while applying a virtual reality maze task after the administration of 17mg delta-9-THC or placebo. More virtual wall hits under delta-9-THC have been accompanied by an increased brain metabolism during task performance in the middle and medial frontal cortices and anterior cingulate, while a reduced metabolism was found in the occipital lobes.

Non-acute Effects of Regular Cannabis use on Functional Brain Activity

Five (out of six) functional neuroimaging studies applied an inhibition task and revealed different BOLD responses during the No-Go conditions or during suppression of interfering information in cannabis users. During the task, marijuana users showed significantly higher ACC activity compared to healthy controls [40]. Furthermore, an earlier onset of cannabis use was associated with more commission errors compared to late onset users concomitant with more focal clusters. Gruber *et al*. [41] further revealed reduced activity during the Stroop task in focal areas of the ACC, but more activation in the middle cingulate and a more diffuse and bilateral pattern in the dorso-lateral PFC during interference condition in the marijuana-using group, while healthy controls showed only right dorso-lateral PFC activation during interference.

Hestor *et al*. [35] showed significant stop-related activity in right prefrontal, parietal and anterior cingulate regions. In the group comparison, cannabis users showed significantly greater activations in the right inferior parietal lobe, right putamen, and right middle cingulate gyrus. They combined the Stroop and Go/No-Go task to compare the BOLD signals of aware and unaware inhibition errors and found decreased activity in the ACC and right insula when errors were unaware. Pearson`s correlation analysis revealed that higher levels of cannabis use were associated with a lower BOLD signal in the right ACC and right insula in the marijuana group.

Tapert *et al*. [42] revealed that the cannabis-related BOLD signal increased during No-Go conditions in the right dorso-lateral PFC, bilaterally in middle frontal, inferior and superior parietal lobes and in the right occipital gyrus after 28 days of abstinence, indicating a greater brain effort while having same behavioral performance. Results remained significant after controlling for lifetime usage and alcohol use. Duration of regular marijuana use was negatively related to the activity in the right anterior superior frontal gyrus (BA 10), right superior middle frontal gyrus (BA 6), and left anterior superior frontal gyrus (BA 10) in response to No-Go conditions. Similarly, an early onset of regular marijuana use and more lifetime marijuana use episodes were related to less inhibitory responses in the right anterior superior frontal gyrus (BA 10). The number of marijuana hits per month was also negatively related to brain responses in the right anterior superior frontal gyrus (BA 10), right superior middle frontal gyrus (BA 6), left anterior superior frontal gyrus (BA 10), and left posterior parietal cortex.

Eldreth and colleagues [43] applied a modified stroop task during a PET scan after 25 days abstinence and revealed decreased activation in the left perigenual ACC, left lateral PFC and hippocampus bilaterally.

Bolla *et al*. [44] found decreased activation in the right lateral OFC, right dorso-lateral PFC and left cerebellum when cannabis users had to make decisions in a gambling task after 25 days of abstinence. A second-step analysis with a comparison between heavy and moderate use revealed decreased activity in the left medial OFC and an increase in left cerebellum in the heavy-user group.

Non-acute Effects of Regular Cannabis use on Brain Structures

Gruber *et al*. [37] found reduced fractional anisotropy (FA) of left frontal lobe in chronic heavy users and positive correlations with BIS-11 total and motor sub-scores, together with reduced FA and enhanced diffusivity in right genu of corpus callosum. Left frontal and right callosal alterations correlated with age of onset and duration of cannabis use. Without significant structural group difference, there was a correlation between right frontal diffusion tensor imaging (DTI) measures and BIS-11 total and attention subscore. A reduced volume in medio-orbital PFC has been shown by Churchwell *et al*. [39], which was correlated with age of first usage. These occasional users scored more on non-planning subscale of the BIS-11. Two studies did not find regional specific structural alterations, but a different slope of metabolism of white matter fiber tracts and a trend towards an increase of non-parallel hence therefore non-directional diffusivity which is a sign of reduced integrity in frontal brain areas in dependent heavy marijuana using subjects [38, 41]. Two structural studies found positive correlations between age of onset of Marijuana use and frontal brain areas: [37] [39].

DISCUSSION

The aim of this systematic review was to assort the recent literature addressing the effect of cannabis use on impulsivity, disinhibition, and motor control. To the best of our knowledge, this is the first systematic review specifically disentangling the effect of cannabis on impulsivity or disinhibition.

Because impulsivity is a multifaceted construct (cf. [45]), comparisons between different study designs have to address the different operationalization used in that construct. Two facets of impulsivity often predominate research on impulsivity in the context of drug abuse [46], namely impulsive choice and impaired inhibition (see also [47]). In the current review, we included studies on cannabis and impulsivity measuring the following domains: response inhibition, motor control, interference/suppression of information, and executive functions of divided/sustained attention and decision making/risk taking. Neurophysiological definitions of impulsivity share all these aspects (see introduction). The focus of this review was to assess structural and functional imaging studies examining the effect of cannabis on impulsivity. We analyzed a broad cross-section of studies which each applied at least one impulsivity measure. These included acute and non-acute designs, different abstention periods and different consumption intensities.

On the behavioral level, the included studies did not find performance differences on inhibition in cannabis users, but trends towards faster reaction times and higher rates on commission errors were observed [34]. In contrast, behavioral studies of inhibitory and motor control found deficits of inhibitory control in cannabis users under acute exposure [48] [49, 50] [32, 51, 52] [53], and in regular users after abstention of use [36, 54] [55]. Duration, time of onset and total lifetime amount of cannabis use, as well as hits per month have a detrimental impact on executive functions [56] [57] [58]. Earlier onset, longer duration, and heavier usage have been associated with altered structural frontal integrity and decreased activations in users compared to non-users in the superior and middle frontal gyrus [34, 37]. Behavioral studies showed impulsive decision-making in cannabis users under acute [32, 50, 59] and non-acute conditions [54] [60], while others did not find significant differences [61] [62] [53]. In recreational users a positive correlation between reduced volume in the medial prefrontal cortex and age of first marijuana use was found [39] while chronic users reported higher scores on the "non-planning" but lesser scores on the "motor impulsivity" subscale of the BIS-11 [38]. Put together, mere behavioral studies show detrimental effects of cannabis consumption on different domains of impulsivity even after prolonged abstention. While the behavioral data of neuroimaging studies show only trends, there are correlations between severity of consumption and structural and functional alterations in these studies.

Beyond behavioral findings, we also reviewed neuroimaging data with a focus on alterations in dorsal and ventral PFC regions including the dorsolateral (dl-), ventrolateral (vl-), ventromedial (vm-)PFC, subgenial, dorsal, or rostral ACC, inferior frontal gyrus (IFG), and orbital frontal cortex (OFC), because these brain regions have been proposed to be critically implicated in drug addiction [24].

PET studies of acute administration of cannabis or delta9-THC found pre- and post-treatment increases in rCBF and brain metabolism in the PFC (mesial, orbital, middle and medial frontal cortices) and ACC during task performance (O'Leary *et al*.,2003, Weinstein et. al., 2007), indicating an increased brain effort to perform equally (see also [63]). The only fMRI study we reviewed here found significant BOLD signal decreases after delta-9-THC and CBD administration among healthy non-smoking volunteers in the ACC and in the inferior frontal gyrus during response inhibition [14]. These functional brain imaging data suggest that delta-9-THC acutely attenuates the engagement of brain regions that mediate response inhibition. Independent from pre- to post-treatment increases in rCBF, between-group comparison showed significant less frontal activations in chronic versus occasional users [33]. These results support the iRISA model proposed by Goldstein and Volkow [24] models by showing that acute cannabis exposure reduced frontal activations in chronic users and that delta9-THC has a direct diminishing impact on brain areas relevant for executive control.

With respect to non-acute studies of cannabis administration in two fMRI studies, chronic and recreational cannabis users showed

Table 3.

Comparison: MJ vs. NC			author & year of publication		PFC: dlPFC, mPFC, IFG	ACC	OFC
acute	User		O'Leary *et al*., 2003	cannabis	ventral frontal lobe ↓ in chronic compared to occasional users after smoking	R/L Activation ↑ in occasional and chronic users after smoking	L Activation ↑ in occasional and chronic users after smoking
	Non-user		Borgwardt *et al*., 2008	THC	right inferior frontal lobe ↓	Activation ↓	No results
				CBD	No results	No results	No results
	user		Weinstein *et al*., 2007	THC	Voxelwise: in mid, sup frontal, medial frontal gyrus↑ ROI: superior, frontal regions ↑	↑	No results
non-acute	functional	chronic	Gruber *et al*., 2012		No results	R More Voxel/ cluster↑	No results
		Chronic	Hester*et al*., 2009		No results between groups	less error awareness in cannabis users: right ACC↓ (BOLD)	No results
		Recreational	Tapert *et al*., 2007		R dlPFC BOLD↑ L/R middle frontal ↑	No results	No results
		Chronic	Bolla *et al*., 2005		R dlPFC ↓ (VVOI templates vs. NC)	No results	R Lat. OFC↓ (VVOI templates vs. NC) heavy vs. moderate use: L medial OFC ↓
		Chronic	Gruber *et al*. 2005		more bilateral-diffuse pattern of BOLD↑ in dlPFC (vs. NC only fokal rightsided dlPFC)	L / R BOLD↓ (2 fokal ROI of ACC) during interference	No results
		chronic	Eldreth *et al*. 2004		L dlPFC Activation ↓ (a priori) R ant. dlPFC (within BA10) (post hoc) R ant. ventromedial PFC (post hoc)	L perigenual Activation ↓ (a priori)	No results
	author & year of publication				PFC : dlPFC/mPFC	ACC	OFC / Corpus C. -Genu
	structural	chronic	Gruber *et al*., 2011		Left frontal: FA↓	No results	No results / R FA↓
		chronic	Silveri *et al*., 2011		did not address regionally specific marijuana-related alterations		
		recreational	Churchwell *et al*., 2010		moPFC: Vol↓	No results	No results

(Table 3) Contd…..

Comparison: MJ vs. NC			author & year of publication	PFC: dlPFC, mPFC, IFG		ACC	OFC
		chronic	Hermann *et al*., 2007	lower ratios of NAA/tCr and- NAA/Cho in cannabis users	lower ratios of NAA/tCr and NAA/Cho in cannabis users	No results	No results
		chronic	Gruber *et al*., 2005	no difference in FA but a trend towards increased trace	no difference in FA but a trend towards increased trace	no diff. in FA but a trend towards incr. trace	no difference in FA but a trend towards increased trace

greater activation and a more diffuse and bilateral activation pattern of the dlPFC and middle frontal gyrus during inhibition compared to non-users [41, 42]. More diffuse and bilateral activations in users compared to more focal and lateralized cluster in non-using controls may reflect a compensatory brain effort mechanism [42] to achieve similar inhibitory control.

Attentional functions involved in error detection, interference and stop signaling are mediated mainly by the ACC. Reduced ACC activity has been linked with altered metabolisms in cingulate cortex (e.g. [79, 80]). There is evidence for reduced focal ACC activity during task performance in chronic cannabis users [35, 41, 43]. Chronic users also show a more diffuse activation pattern in the cingulum among different research groups with greater activations in the middle compared to the anterior cingulate cortex, and together with activations in parietal regions [34, 35, 41, 42]. This favors the hypothesis of additional recruitment of parietal cortices to maintain attentional competence in order to equally perform during task. Garavan *et al*. [79] proposed two interacting cortical systems of response inhibition based on fMRI and EEG data depending on high- or low-absent-mindedness: recruitment of right prefrontal and parietal regions on the one hand, and activation of cingulate regions on the other hand. Hence, different cingulum activations and additional parietal activation in cannabis users would represent difficulties or inefficacies to sustain sufficient attention when inhibiting responses.

Abnormal monitoring abilities may furthermore affect decision-making [34, 35, 41, 42] and this corresponds with reduced activations in right dlPFC and right lateral OFC [44]. Cannabis users also show diminished choice optimization and decreased functional activation of orbital prefrontal regions during performance of the IGT [81]. Regions of interest in fMRI research of the IGT are the OFC and dlPFC [82, 83]. The OFC is involved in reward attribution and altered in addiction [84, 85]. Poor decision-making is a hallmark of addiction, and the IGT can discriminate controls from patients also with ventral medial lesions [86, 87], substance-dependence, or pathological gamblers [44, 88, 89].

Frontal correlates of response inhibition are linked to the pre-supplementary motor cortex to simply suppress unwanted movements, while the dlPFC needs to be recruited during tasks involving higher working memory load [64, 65]. Inhibition-related functions have been found to be significantly heritable [66-68] [69]. It has been shown, by using a variety of imaging modalities, that the prefrontal cortex (most prominently the inferior prefrontal cortex and the supplementary motor area (SMA), as well as subcortical striato-thalamic projection targets), represents a neural correlate of response inhibition [70-78]. The neuroimaging findings reviewed here indicate both reduced task-specific and predefined region-specific (region of interests - ROI) activations in PFC, OFC and ACC in acute as well as non-acute studies, and greater activations in a more diffuse, bilateral pattern together with supplementary parietal cortex recruitments. On the behavioral level, neuroimaging data showed no significant differences, but tendencies in impairments towards task complexities as well as correlations with earlier onset and heavier consumption. Thus, cannabis under acute and non-acute condition attenuates the focal engagement of inhibitory networks, namely the right dorsolateral and inferior as well as the orbital prefrontal cortex and ACC. To perform equally as a compensatory mechanism, cannabis leads to bilateral and broader, more diffuse activations depending on the specific task. To maintain attentional competence, greater activation occurs in the middle, while a broader, more diffuse pattern of activity is found within the anterior cingulum. Supplementary parietal activations have also been found. When cognitive load in the task is higher, chronic users decompensate and have less PFC activation (hence prefrontal control) than occasional users. Impulsive decision-making is associated with reductions in dlPFC and OFC.

Out of the five structural imaging studies one found a reduction in the medial prefrontal cortex in recreational users [39]. Recently, findings from structural neuroimaging studies have found positive, negative or even inverse results of persisting alterations on brain morphology after long-term marijuana use that underlies deficits in attention, learning, memory, executive functions and emotional processes [5, 90, 91], for review see [92]. Abnormalities in neuropsychological testing and fMRI activation are consistent with imaging studies demonstrating morphological changes in cannabis users [5]. Some reports have described reduced grey matter in limbic areas [92, 93] and abnormal gyrification [94]. Recent reviews of structural neuroimaging studies revealed no significant differences on global measures of brain volume following cannabis use [5]. Region-specific brain volume alterations have been found in different areas, most consistently in hippocampal and parahippocampal regions, but were not consistent across studies [92, 95]. Inconsistencies might arrive from different imaging modalities, as well as from different analysis approaches such as region-of-interest (ROI) or whole brain voxel-based morphometry.

DTI of white matter microstructures has identified reduced fractional anisotropy (FA) in cannabis users [37, 41]. In accordance, increases of axonal diffusivity have also been found in fronto-temporal brain connections [96]. Furthermore Arnone *et al*. [97, 98] found a marijuana-related damage in the corpus callosum. Chronic marijuana use may result in reduced FA and increased diffusivity, which may be associated with increased impulsivity, and ultimately contribute to the initiation of marijuana use or the inability to discontinue use [37].

Morphological changes of neuronal structures that are rich in cannabinoid receptors have been reported most consistently in the hippocampus [99] [100, 101] and the cerebellum [102, 103]). However, Zalesky *et al*. [104] found no evidence for brain-wide cannabis-induced shortening of axonal fibers except in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum and commissural fibers. Another study used (^{1}H-MRS-)markers to investigate neurogenesis, synaptogenesis (NAA), and synaptic plasticity (Cho) in recreational cannabis users and found reduced neuronal and axonal integrity in the dlPFC and ACC. Thus, there is growing evidence of structural disintegration after prolonged cannabis exposure not only in whole-brain analyses, but also specifically in brain regions that are crucial for impulse control [29]. Whether structural alterations remain persistent after prolonged discontinuation of cannabis use is still in debate. There are hazardous white matter connectivity impacts when the developing brain is exposed to long-term cannabis usage, but these alterations could be reversible after abstinence or functional adaptation [104].

In general, reviews show either the effects of cannabis on brain structures in psychiatric patients, individuals at a high risk of developing psychosis, or the interplay between psychosis and comorbidities. These data may be distinct from non-psychiatric samples [5,91,95,105]. Nevertheless, cannabis use in clinical subjects is associated with decreases in some brain regions, particularly those rich in CB_1–receptors such as the cingulum, the dlPFC, the cerebellum, and striatum. According to the iRISA model, the cingulum, PFC and striatum are crucial regions of the inhibition network required to monitor, suppress and countermand hot drives and to instill cold, volitional control. Chang and Chronicle [106] reviewed the chronic effects in cannabis users and found equivocal evidence that it might result in structural brain changes, blood-oxygenation-level-dependent-fMRI studies consistently show alterations, or neuroadaptation, in the activation of brain networks responsible for higher cognitive functions, but whether changes are reversible with abstinence was unclear. Likewise Chang and Chronicle [106], Batalla and colleagues [107] reviewed neuroimaging data in chronic adolescent and adult cannabis users with no other psychiatric disorder. Probands had to have consumed cannabis at least several times per week for a minimum of two years. Morphological alterations were found in medial, temporal and frontal cortices, as well as in the cerebellum. They also found different patterns of resting in global and brain activity during different task performances, which may also have indicated compensatory effects in chronic exposure. In contrast to that review, we focused on the impact of cannabis use on impulsivity measures and included acute and non-acute studies of recreational drug users and drug-naïve individuals. Comparisons of studies are often limited because of the differing definitions of cannabis exposure. Only a few studies provide absolute numbers of consumption in order to use cannabis abuse as a continuous variable. This is important when taking into account the possibility of a threshold effect of cannabis on brain morphology. Furthermore, we reviewed the literature with respect to impulsivity, using the iRISA model as a framework, to provide a conclusive overview of neuroimaging data regarding the impact of cannabis on brain structures and the functionality of habitual control networks in humans.

Impulsivity is a proposed endophenotype for substance dependence as well as a possible consequence of prolonged drug use [108]. Drugs of addiction and subconscious craving are likely to increase impulsiveness due to the loss of frontal cortical inhibition of impulses and increased limbic drive (see [24] [109]). Neural substrates of impulsivity encompass circuitry involving both cortical (top-down volitional control) and subcortical mechanisms, particularly within the basal ganglia, and have mainly been studied on response inhibition in humans and experimental animals. Although there are insights into the interplay of compulsive stimulant taking and impulsivity, this remains unclear in the case of cannabis. However, there are behavioral and epidemiological findings, which emphasize such a relationship, as well as the fact that cannabis use may lead to a loss of attention, reflection and inhibitory control. Associated cerebral activations consist of "right lateralized fronto-parietal" attentional or response selection mechanisms, as well as "midline performance monitoring processes" (ACC). To stop already pre-processed activation inferior frontal region are involved to countermand responses (see [80]). Thus, giving the broad epidemiological "burden of society" cannabis leads to dose-related impairments of psychomotor performance with implications for car driving, and personal health risk [110].

Limitations of this review include the analysis of different user types (heavy vs. recreational), small study groups, and a failing to control for co-use between studies. Whole brain search strategies often fail to show significant results, but localized differences may be found in connectivity analyses in future structural and functional neuroimaging studies.

SUMMARY AND CONCLUSION

This systematic review provides evidence that acute administration of cannabis increases regional CBF and brain metabolism, which might indicate an increase in brain effort during task performance.

Neuroimaging data provide evidence of detrimental effects of cannabis on inhibitory control. There is a threshold effect with alterations being found preferably in heavier and more regular users. When subjects showed an early onset of use, especially during brain maturation (before age of 16), structural brain alterations seem to be stronger. Research on the acute impacts of cannabis is limited and should be further engaged. As yet, there is no longitudinal study addressing the question whether impaired inhibition is due to a preceding trait of impulsivity and therefore leads to cannabis use, or whether it represents a result of use, and is therefore intertwined with difficulties to discontinue usage (see [111]). There is evidence of region-specific reduced volume and white matter integrity of the PFC, which leads to increased diffusivity and different metabolism in CB_1-receptor-rich brain areas that might mediate the abnormal impulsivity and mood observed in marijuana users.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

ACC	=	Anterior cingulate cortex
BIS-11	=	Barratt Impulsivity Scale-11
C	=	Controls
CBD	=	cannabidiol
DTI	=	Diffusion tensor imaging technique
EAT	=	Error Awareness Task
IGT	=	Iowa Gambling task
FA	=	fractional anisotropy e.g.
IFG	=	inferior frontal cortex
DLPFC	=	Dorso-lateral prefrontal cortex
MJ	=	Marijuana user
L	=	left
MRSI	=	Proton magnetic resonance spectroscopic imaging
MSIT	=	Multi-Source Interference Task
OFC	=	Orbital frontal cortex

PET	=	Positron emission
PFC	=	Prefrontal cortex; tomographic imaging
rCBF	=	Regional cerebral blood flow
Stroop	=	Stroop Colour Word Test
R	=	right
THC	=	delta-9-tetrahydrocannabinol
WCST	=	Wisconsin card sorting test

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