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REVIEW

Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults

Florian Ganzer[1] · **Sonja Bröning**[1] · **Stefanie Kraft**[1] · **Peter-Michael Sack**[1] · **Rainer Thomasius**[1]

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Abstract Findings on neurocognitive effects of sustained cannabis use are heterogeneous. Previous work has rarely taken time of abstinence into account. In this review, we focus on understanding sustained effects of cannabis, which begin when clinical symptoms of the drug have worn off after at least 14 days. We conducted a search between 2004 and 2015 and found 38 studies with such a prolonged abstinence phase. Study-design quality in terms of evidence-based medicine is similar among studies. Studies found some attention or concentration deficits in cannabis users (CU). There is evidence that chronic CU might experience sustained deficits in memory function. Findings are mixed regarding impairments in inhibition, impulsivity and decision making for CU, but there is a trend towards worse performance. Three out of four studies found evidence that motor function remains impaired even after a time of abstinence, while no impairments in visual spatial functioning can be concluded. Functional imaging demonstrates clear differences in activation patterns between CU and controls especially in hippocampal, prefrontal and cerebellar areas. Structural differences are found in cortical areas, especially the orbitofrontal region and the hippocampus. Twenty studies (57 %) reported data on outcome effects, leading to an overall effect size of r_{mean} = .378 (CI 95 % = [.342; .453]). Heavy use is found to be more consistently associated with effects in diverse domains than early age of onset. Questions of causality—in view of scarce longitudinal studies, especially those targeting co-occurring psychiatric disorders—are discussed.

Keywords Cannabis · THC · Marijuana · Cognitive effects · Neuropsychology · Systematic review

Introduction

Cannabis use – the generic term we use throughout this article for all non-medical prescription forms of hashish, marijuana or synthetic cannabinoid consumption – is widespread in European countries, as it is in the United States and other Western civilizations such as Australia or Canada (Roncero et al. 2015). Over the past 20 years, cultivation and plant-breeding techniques have greatly increased the potency of cannabis products. Thus, the modern cannabis smoker may be exposed to doses of Δ9-tetrahydrocannabinol (*THC*) many times greater than his or her counterpart in the 1960s and 1970s (Ashton 2001). The consumed THC concentration varies among different sources and preparations of cannabis.

Regular cannabis use is significantly associated with increased health problems, e.g., respiratory symptoms, general indisposition, or neurocognitive impairments (Hall and Degenhardt 2014; Hoch et al. 2015). Furthermore, it is well documented that cannabis use can increase psychosocial difficulties such as academic underachievement and/or school dropout (Brook et al. 2008; Silins et al. 2014). Since most cannabis users (*CU*) start consuming during adolescence or emerging adulthood, impaired educational attainment plays an especially critical role (Hall and Degenhardt 2014; Johns 2001). THC users also increase their risk of developing psychotic symptoms and disorders (Di Forti et al. 2007), especially if there is a family history of these mental illnesses (Moore et al. 2007). In turn, a

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✉ Florian Ganzer
f.ganzer@uke.de

[1] Deutsches Zentrum für Suchtfragen des Kindes- und Jugendalters (DZSKJ; German Center for Addiction Research in Childhood and Adolescence), University Medical Center Hamburg-Eppendorf (UKE), Martinistrasse 52, 20246 Hamburg, Germany

number of mental health disorders such as depression, anxiety, schizophrenia, bipolar disorder and obsessive-compulsive disorder are associated with high rates of comorbid substance use (Barnes et al. 2006; Saban et al. 2014, Scott et al. 2014). This association appears to be independent of culture (Wu et al. 2013). Current statistics show that about one of ten chronic CU develops a dependence syndrome (Budney et al. 2007; Hall 2015). Dependency symptoms appear progressively and treatment for cannabis dependence is complex (Danovitch and Gorelick 2012). While loss of control over cannabis use and continued cannabis use against better knowledge emerge earlier, self-reported withdrawal symptoms tend to emerge later and for a much smaller proportion of users (Rosenberg and Anthony 2001).

Cannabis and the Brain

The pharmacokinetics of cannabinoids are reviewed by Agurell et al. (1986) and Khiabani and Mørland (2007). Effects and adverse effects are versatile (Ashton 1999; Maykut 1985), in fact, the use of cannabinoids has been advocated for several medical indications (Radbruch and Nauck 2003; Whiting et al. 2015). Cannabinoids exert their effect by interaction with specific endogenous cannabinoid receptors, discovered by Devane et al. (1988). Neuronal cannabinoid receptors termed cannabinoid type 1 (*CB1*) receptor have been found in high density both in animal and human cerebral cortices, particularly for the frontal regions, i.e. in regions involved in processing emotional inputs, rewarding stimuli, habit formation, and higher cognitive functions (Herkenham et al. 1990; Pertwee 2005). The response of cannabinoid receptors to THC exposure varies depending on the brain area (Romero et al. 1995). The impact of cannabis on high-density CB1 areas (such the frontal lobe, hippocampal/temporal regions, basal ganglia, and cingulate cortices) and on associated cognitive functions (such as memory and attention) was already observed in early cannabis research (Herkenham et al. 1990).

The endocannabinoid system appears to be functionally linked to the extended dopamine reward pathway involving the ventral tegmental area, nucleus accumbens, prefrontal cortex (including the orbitofrontal and dorsolateral prefrontal cortex), and anterior cingulate, viewed as central to the development of addictive behavior (Volkow et al. 1996). With repeated dosage, high levels of cannabinoids accumulate in the body and continue to reach the brain. Animal studies show reversible downregulation of brain CB1 receptors after chronic exposure to cannabis (Gonzalez et al. 2005; Sim-Selley 2003). Once the adult cannabinoid receptor levels are reached, binding activity in the nervous system neither increases nor declines during the normal aging process in rats (Belue et al. 1995). Animal research also indicates that brain regions that are rich in cannabinoid receptors are more susceptible to the effects of cannabis (Freedland et al. 2002; Pontieri et al. 1999; Zimmer et al. 1999; Schneider 2008). The relative absence of the cannabinoid receptors from brainstem nuclei may account for the low toxicity of cannabinoids when given in overdose (Iversen 2003). Frequently, the onset of THC consumption occurs during adolescence and therefore, in a sensitive period of brain maturing. The prefrontal brain cortex is one of the last regions of maturation during adolescence (Gogtay et al. 2004; Lenroot and Giedd 2006; Sowell et al. 2004a, b) and is one of the densest CB1 parts of the human brain. Therefore, it is likely to be particularly vulnerable to the early effects of heavy marijuana exposure (Egerton et al. 2006; Horti and Van Laere 2008; Lubman et al. 2015; Lorenzetti et al. 2014, Quickfall and Crockford 2006).

Research on Neurocognitive Effects of Cannabis use

Research on cannabis and neurocognitive impairments has studied acute and persistent effects of cannabis use. Acute effects of cannabis reported in studies occurred in diverse areas such as general intellectual function, memory, abstraction ability, sustained attention, verbal fluency, and the ability to learn and recall new verbal and visuospatial information (for an overview see Ranganathan and D'Souza 2006; Iversen 2005; Pope et al. 2001a, b; Earleywine 2002; Gruber et al. 2011). Persistent effects of cannabis use have also been widely studied. Table 1 provides an overview of 31 reviews we found in the time period between 2004 and 2015 that had their main focus on residual/long-term effects of cannabis use on neurocognitive functioning. These reviews report impaired performance on a variety of attention, memory (Solowij and Battisti 2008) and executive function tasks (Wrege et al. 2014) as well as alterations in blood flow and brain tissue density (e.g., Yucel et al. 2007). They also point to a considerable variability of findings (e.g., Crane et al. 2013). A possible link between residual impairments and the duration and quantity of cannabis use is frequently mentioned (e.g., Crean et al. 2011; Hall 2015). Early age of onset is discussed as an especially critical factor in the development of cannabis-related neurocognitive impairments (e.g., Schweinsburg et al. 2008a; Lisdahl et al. 2013). In their systematic review, Batalla et al. (2013) conclude that neuroimaging studies provide evidence of morphological brain alterations particularly in the medial temporal and frontal cortices as well as in the cerebellum both in adolescents and adults. Only few reviews report evidence levels of studies or effect sizes. Through meta-analytic research, Grant et al. (2003; 11 studies) found evidence for deficits in learning ($r = .104$) and forgetting domains ($r = .134$) but non-significant confidence intervals for other neurocognitive domains. In a replication to this study (Schreiner and Dunn 2012; 33 studies), a significant overall effect of $r = .144$ is reported. Rocchetti et al. (2013; 14 studies) observed alterations in structural imaging studies of $r = .222$ [r-transformations: these authors]. In sum, although evidence

Table 1 Reviews on long-term effects of neurocognitive domains and functional/structural imaging

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
1	2013	Batalla A, Bhattacharyya S, Yücel M, Fusar-Poli P, Crippa JA, Nogué S, Torrens M, Pujol J, Farré M, Martin-Santos R	Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings.	neuroimaging studies on chronic cannabis users with matched KG	43	Evidence of morphological brain alterations in adolescents and adults, particularly in the medial temporal and frontal cortices, as well as the cerebellum.	l	12 h or longer
2	2007	Chang L, Chronicle EP	Functional imaging studies in cannabis users.	PET and MRI studies on acute effects and effects of chronic Cannabis use	9 acute, 8 chronic	Consistent alterations in the activation of brain networks responsible for higher cognitive functions in chronic users.	a/l	4 h or longer
3	2013	Crane NA, Schuster RM, Fusar-Poli P, Gonzalez R.	Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences.	acute and non-acute effects of cannabis use since 2007, sex differences, early vs. late onset	n/a	Evidence of problems with episodic memory is one of the most consistent findings reported; memory deficits more pronounced in adolescents; however, several other neurocognitive domains appear to be adversely affected by cannabis use under various conditions. There is significant variability in findings across studies, thus a discussion of potential moderators is increasingly relevant.	a/l	8 h or longer
4	2011	Crean RD, Crane NA, Mason BJ	An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions.	acute and non-acute effects/ 7 h-20 days after use	n/a	Recently abstinent cannabis users may experience impairment in certain aspects of executive functioning. In contrast to the acute effects of cannabis in working memory, deficits as a function of residual cannabis effects have not been found. Studies showing the greatest deficits in executive functioning used subjects who had been smoking heavy amounts of cannabis for long periods of time. It is likely that residual impairments are linked to the duration and quantity of cannabis use. Cannabis appears to continue to exert impairing effects in executive functions even after 3 weeks of abstinence and beyond.	a/l	7 h or longer
5	2007	Di Forti M, Morrison PD, Butt A, Murray RM	Cannabis use and psychiatric and cognitive disorders: The chicken or the egg?	recent literature on the effects of cannabis on mental health and cognition	n/a	Cannabis use in adolescence increases the risk of later schizophrenia-like psychoses,	n/a	n/a

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
						especially in genetically vulnerable individuals. There is less evidence of cannabis playing an aetiological role in other mental disorders including depression, but there have been far fewer studies. Heavy cannabis use has also been shown to affect memory and learning performance, both in healthy individuals and in patients suffering from psychosis.		
6	2007	Gonzales R	Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance.	review on acute and non-acute effects	n/a	Clear evidence for changes in brain functioning among acutely intoxicated and abstinent cannabis users. Changes do not necessarily translate to functional impairment. Poorer performances on measures of neuropsychological functioning also observed among cannabis users, especially poorer memory. Deficits most commonly seen in frequent and heavy users.	a/l	n/a
7	2011	Hermann D	Wirkung von Cannabinoiden auf das Gehirn: Ein Überblick über MRI Befunde.	MRI studies on Cannabis effects on the brain	37	Studies including cannabis users revealed contradicting results of fMRI activation pattern, and only allowed the conclusion that neural plasticity is altered by chronic cannabinoid use. Whether these alterations are harmful or beneficial cannot be judged.	l	n/a
8	2005	Iversen L	Long-term effects of exposure to cannabis.	long-term effects of cannabis use	n/a	A subgroup seems at risk: individual who have psychotic thought tendencies and individuals consuming large doses of the drug on a regular basis. Little evidence of persisting adverse effects after drug use stops.	l	n/a
9	2009a	Jacobus J, Bava S, Cohen-Zion M, Mahmood O, Tapert SF	Functional consequences of marijuana use in adolescents.	studies on neuropsychological functioning, brain structure and function, measures of sleep in adolescent marijuana users	n/a	Adolescents who use marijuana heavily tend to show disadvantaged attention, learning, and processing speed; subtle abnormalities in brain structure; increased activation during cognitive tasks despite intact performance; and compromised objective indicators of sleep	l	n/a

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
						quality. Some abnormalities appear to persist beyond a month of abstinence, but may resolve within three months if cessation is maintained.		
10	2014	Jacobus J, Tapert SF	Effects of Cannabis on the Adolescent brain.	review on neuroimaging, neurocognitive, and preclinical findings regarding the effects of cannabis on the adolescent brain	n/a	The article points out neurocognitive disadvantages of heavy cannabis use in the domains of attention and memory that persist beyond abstinence. Findings suggest possible macrostructural brain alterations, changes in white matter tract integrity and abnormalities of neural functioning.	a/l	n/a
11	2013	Lisdahl KM, Gilbart ER, Wright NE, Shollenbarger S	Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function.	impact of adolescent early onset of alcohol and marijuana use on neurocognition	n/a	Early onset associated with increased deficits in poorer attention, reduced overall or verbal IQ, executive functioning. Regular use during adolescence may lead to structural changes such as abnormal gray matter pruning patterns and reduced white matter myelination. These changes have been associated with poor neuronal efficiency and poorer cognitive functioning.	l	n/a
12	2014	Lorenzetti V, Solowij N, Fornito A, Lubman DI, Yucel M	The Association between Regular Cannabis Exposure and Alterations of Human Brain Morphology: An Updated Review of the Literature.	structural neuroimaging investigations of regular cannabis users	23	Regular cannabis use is associated with alterations in medial temporal, frontal and cerebellar brain regions. Greater brain morphological alterations were evident among samples that used at higher doses for longer periods. However, the evidence for an association between brain morphology and cannabis use parameters was mixed. Further, there is poor evidence for an association between measures of brain morphology and of psychopathology symptoms/ neurocognitive performance.	a/l	12 h or longer
13	2005	Lundqvist T	Cognitive consequences of cannabis use: Comparison with abuse of stimulants and	comparing cannabis use with other drug use	n/a	Cannabis induces loss of internal control and cognitive impairment, especially of attention and	a/l	24 h or longer

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
			heroin with regard to attention, memory and executive functions.			memory, for the duration of intoxication. Heavy cannabis use is associated with reduced function of the attentional/executive system, as exhibited by decreased mental flexibility, increased perserveration, and reduced learning, to shift and/or sustain attention.		
14	2010	Martín-Santos R, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, Fusar-Poli P, Borgwardt S, Seal M, Busatto GF, McGuire P	Neuroimaging in cannabis use: a systematic review of the literature.	literature on neuroimaging studies of chronic or acute cannabis use until January 2009	41	Functional neuroimaging studies suggest a modulation of global and prefrontal metabolism both during the resting state and after the administration of THC. Results from the activation studies using a cognitive task are inconsistent.	l	12 h or longer
15	2006	Quickfall J, Crockford D	Brain neuroimaging in cannabis use: a review.	structural and functional neuroimaging studies of cannabis use	34	Structural abnormalities generally have not been identified with chronic use. Regular users demonstrate reciprocal changes in brain activity globally and in cerebellar and frontal regions. Abstinence results in decreases, and administration results in increases correlating with subjective intoxication. Chronic use and cannabis administration result in attenuated brain activity in task-activated regions or activation of compensatory regions.	l	5 days or longer
16	2009	Realini N, Rubino T, Parolaro D	Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids.	experimental data on the long-term behavioral consequences of cannabis treatment in adolescence. Animal vs. human studies	n/a	Subtle changes in the adult brain circuits after heavy cannabis consumption in adolescence. These alterations lead to impaired emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse, and may represent a risk factor for developing schizophrenia in adulthood. The few studies examining the neurobiological basis of the altered behaviors demonstrate the presence of stable alteration in the endocannabinoid system that can trigger subsequent	l	n/a

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
						alteration in synaptic protein and synaptic morphology, thus altering the responsiveness of selected brain areas to different internal and external stimuli. These pre-clinical observations are strengthened by literature in humans where longitudinal studies often support the experimental results.		
17	2013	Rocchetti M, Crescini A, Borgwardt S, Caverzasi E, Politi, P, Atakan Z, Fusar-Poli P	Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users.	studies between 2000 and 2013	14	Results suggest that in the healthy brain, chronic and long-term cannabis exposure may exert significant effects in brain areas enriched with cannabinoid receptors, such as the hippocampus, which could be related to a neurotoxic action. Limited evidence supporting a cannabis-related alteration of white and gray matter structures, however consistent smaller hippocampus in users.	l	n/a
18	2008	Rubino T, Parolaro D	Long lasting consequences of cannabis exposure in adolescence.	long-term consequences of cannabinoid exposure during adolescence including animal studies	n/a	Heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse in selected individuals, and may represent a risk factor for developing schizophrenia in adulthood.	l	n/a
19	2008	Schneider M	Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure.	residual cannabinoid effects during puberty	n/a	Findings from human retrospective studies point out the risk of early cannabis use for cognitive functioning in a similar way, they also have some limitations. Taken together, these findings from animal studies confirm the previous results from human studies and indicate puberty/mid-adolescence as a highly susceptible time window for possible residual (and also acute) effects on cognitive processing.	l	n/a
20	2013	Schoeler T, Bhattacharyya S		acute and residual effects on memory function	25	Robust evidence for acute impairment induced by a single	a/l	12 h or longer

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
			The effect of cannabis use on memory function: an update.			dose of THC on verbal and working memory. Deficits in verbal and working memory are likely to persist, particularly when heavy cannabis use is started at early age.		
21	2012	Schreiner AM, Dunn ME	Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis.	meta-analysis on residual effects after prolonged abstinence	33/13	Small negative effect for global neurocognitive performance as well for most cognitive domains assessed. In 13 studies after prolonged abstinence, results indicated no significant effect of cannabis use on global neurocognitive performance or any effect on the eight assessed domains.	l	13 h or more, 2nd analysis: 25 days or more
22	2014	Schulte MH, Cousijn J, den Uyl TE, Goudriaan AE, van den Brink W, Veltman DJ, Schilt T, Wiers RW	Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment.	reviews prospective studies on neurocognitive recovery using neuropsychological assessments before and after sustained abstinence	3	Regular heavy users scored significantly worse than never-users in overall IQ, processing speed, verbal short term memory and verbal long term memory. Former cannabis users who had been abstinent for at least 3 months did not show any cognitive impairments compared to never-users	l	1 month or more
23	2008a	Schweinsburg AD, Brown SA, Tapert SF	The influence of marijuana use on neurocognitive functioning in adolescents.	heavy marijuana use in adolescence and increased adolescent vulnerability	n/a	Adolescents are more vulnerable than adults to neurocognitive abnormalities associated with chronic heavy marijuana use; however, the impact of preexisting risk factors is unknown. Adolescents demonstrate persisting deficits related to heavy marijuana use for at least six weeks following discontinuation, particularly in the domains of learning, memory, and working memory. Further, adolescents appear more adversely affected by heavy use than adults.	l	n/a
24	2013	Sneider JT, Mashhoon Y, Silveri MM	A Review of Magnetic Resonance Spectroscopy Studies in Marijuana using Adolescents and Adults.	summary of data from MRS studies of Marijuana use in adolescents and adults	8	Converging evidence for neurochemical alterations in MJ users, with lower NAA (N-adetyl-aspartate) metabolite levels being	n/a	n/a

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
						the most frequently observed alteration.		
25	2008	Solowij N, Battisti R	The chronic effects of cannabis on memory in humans: a review.	residual effects on memory	24	Impaired encoding, storage, manipulation and retrieval mechanisms in long-term or heavy cannabis users related to duration, frequency, dose and age of onset.	l	6 h or more
26	2010	Solowij N, Pesa N	Cognitive abnormalities and cannabis use.	cognitive impairments of cannabis use	n/a	Long-term or heavy cannabis use appears to result in longer-lasting cognitive abnormalities and possibly structural brain alterations. Greater adverse cognitive effects are associated with cannabis use commencing in early adolescence.	a/l	n/a
27	2008	Trezza V, Cuomo V, Vanderschuren LJ	Cannabis and the developing brain: insights from behavior.	neurobiological effects of prenatal and adolescent exposure to cannabis	n/a	Association between early cannabis use and schizophrenic as well as psychotic symptoms.	n/a	n/a
28	2011	van Holst RJ, Schilt T	Drug-related decrease in neuropsychological functions of abstinent drug users.	neuropsychological performance in frequent users of cocaine, (meth-) amphetamines, ecstasy, opiates, alcohol, and cannabis	3	Studies published in the last five years, focusing on studies that included only adults, required at least 2 weeks of abstinence from drug use, and included a control group. There was little evidence for sustained cognitive impairments in adult abstinent cannabis users.	l	min 2 weeks
29	2014	Wrege J, Schmidt A, Walter A, Smieskova R, Bendfeldt K, Radue EW, Lang UE, Borgwardt S	Effects of cannabis on impulsivity: a systematic review of neuroimaging findings.	specific effects of cannabis on impulsivity, disinhibition and motor control	13	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.	a/l	12 h or longer
30	2007	Yücel M, Lubman DI, Solowij N, Brewer WJ	Understanding drug addiction: A neuropsychological perspective.	cannabis and other substances were reviewed regarding neuropsychological effects	16	Impaired performance on a variety of attention, memory and executive function tasks as well as in attention, verbal memory, working memory and decision making tasks, furthermore alterations in blood flow, and brain tissue density. Extent of persistence of effects or recovery of function following abstinence is uncertain with some studies suggesting no recovery after 25–28 days while	l	n/a

Table 1 (continued)

Nr.	Year	Authors	Title	Scope	Studies reviewed	Main Findings	Acute (a) vs. long-term (l) use	Abstinence period in long-term use
						others report full or partial recovery after 28 days or longer.		
31	2013	Yusoff N, Yuan J, Yang J	A Review of Neuropsychological Status in Cannabis Users.	investigates status effects of cannabis toxicity on neuropsychological performance	n/a	The domain of memory function is the area most influenced by cannabis toxicity. Domain second strong influence is exerted on executive functioning and inhibitory control. Authors underline that strong proof exists for negative effects of cannabis even though findings also exist that suggest the contrary (no effect).	l	n/a

n/a not available, *a* acute, *l* long-term

is building to suggest that cannabis use in adolescence is associated with cognitive and psychosocial and health impairment (Rubino and Parolaro 2008; Lisdahl et al. 2014; Volkow et al. 2014), the exact effects of long-term cannabis use on cognitive performance as well as the magnitude or reversibility of possible effects remain unclear to date.

The Role of Abstinence Duration

Reviews on long-term effects typically do not make a clear distinction between studies that explore effects of cannabis use in barely abstinent CU (usually starting with a minimum of 12 h of abstinence) and true sustained effects of cannabis, which begin when clinical symptoms of the drug have worn off, usually starting with 14 days (Budney et al. 2004). Instead, these reviews include studies with rather heterogeneous abstinence durations ranging from several hours to many months (see Table 1). Next to other limitations for reviews such as heterogeneity of studies, assessment methods and samples, this variability in abstinence might considerably contribute to the inconsistency of findings mentioned above. As Roten et al. (2015) stated: "Cognitive performance in certain domains […] was significantly better in those with abstinence when compared to those who were not abstinent. Results suggest an improvement in these cognitive performance domains with abstinence from marijuana" (p. 121). While it is important to assess cognitive deficits associated with each stage of abstinence, assessment during short-term abstinence presents interpretive problems. Specifically, decrements in functioning may be due to anything from alterations in the brain, residues of the drug in the brain or the withdrawal symptoms themselves. These symptoms typically appear during the first 1–2 days after cessation of THC consumption and return to baseline within 1–2 weeks (Budney et al. 2004; Wiesbeck et al. 1996). For instance, Kouri and Pope (2000) report that during this time, CU reported greater levels of anxiety, irritability, negative mood, physical symptoms, and decreased appetite. Most symptoms returned to baseline after two weeks. Only few of the 31 reviews presented in Table 1 excluded studies with very short abstinence periods: Schreiner and Dunn (2012) conducted a meta-analysis on the effects of cannabis use after 25 days of abstinence and found no significant effect of cannabis use on global neurocognitive performance or any effect on the eight assessed domains. However, due to their choice of a protracted abstinence period (25 days), they were only able to include 13 studies in their meta-analysis. Van Holst and Schilt (2011) reviewed effects of cannabis and other drugs after 14 days of abstinence but only included three studies on cannabis in their review due to a limited time scope (literature between 2005 and 2010). Earlier reports on cognitive functioning in drug users with longer-term abstinence presented mixed findings (Bolla et al. 2002; Pope et al. 2001a, b).

Objective

In this systematic review, we investigate the long-term effects of cannabis use after a prolonged duration of abstinence (at least 14 days), thus excluding possible effects resulting from drug residues or withdrawal symptoms. We choose a 14 day period to permit a larger data base than previous work along this line (Schreiner and Dunn 2012; van Holst and Schilt 2011). Our research questions are the following:

1) *What are the long-term effects of cannabis use on neurocognitive functioning after a prolonged abstinence period of at least 14 days?*
2) *What magnitude do long-term effects of cannabis use have?*
3) *Does the early onset (EO) of cannabis use exacerbate long-term effects of cannabis use?*

To answer question 1), we report the effects of cannabis use in the neurocognitive domains of attention, executive function, motor function, memory and learning, and visual spatial. We also report results in the areas of functional imaging/EEG and structural imaging. To answer question 2), we provide additional meta-analytic information on effect sizes. To answer question 3), we report our findings for a selected EO sample within the domains mentioned in 1), and consider the role of EO separately within the discussion section.

Even though no formal review protocol exists, the procedures of our systematic review are guided by the PRISMA statement (Moher et al. 2009).

Methods

Search Strategy

Electronic searches were performed using EMBASE, Ovid MEDLINER, PsycInfo, PSYNDEXplus Literature and Audiovisual Media as well as PSYNDEXplus Tests databases. Search terms used were cannabi* or THC or marijuana or marihuana AND neuro* or cognit* or assess* or abilit* or affect* or process* or function* or impair* AND residual or long-term or abstinen* or abstain* or lasting or non-acute or non-intox* or persist*. In addition, we did reference searching, and reviewed book chapters on substance abuse neuroimaging. We focused on literature published between 2004 and 2015 (a comprehensive overview about the research of cannabis and neurocognitive impairments from 1960s to 2004 can be found in Verdejo-Garcia et al. 2004), thus covering more than ten years of research. Only clinical trials with human subjects were included. This search yielded a total of 1038 studies after removal of duplicates. The title and the abstract of these studies were reviewed by two independent reviewers (FG and SK) for relevance. We included studies only on subjects with regular consumption of cannabis or marijuana. To rule out acute intoxication effects, only studies with a period of at least 14 days of abstinence were included. We excluded studies on subjects with a history of chronic medical and neurological illness or severe psychiatric disorders (like schizophrenia or mania), or with a diagnosis of additional substance use disorders (alcohol, opioids, amphetamines) defined in ICD-10 or DSM-IV as addiction (without nicotine dependence). We also excluded animal studies, case reports, expertises, commentaries, and books. Discrepancies were resolved in discussion. At the end of this process, a total of 38 studies fulfilled all of the abovementioned criteria and were included in this review.

Evidence Level

One of the authors (SB) supervised two trained University students in their 5th term who graded the evidence-level of studies according to the Scottish Intercollegiate Guidelines Network (*SIGN*) methodology (Harbour and Miller 2001; Baker et al. 2010). Differences were resolved in discussion. Since none of the studies at hand were RCTs, but all studies included control groups and were well-designed, study quality was comparatively similar, for instance with regard to sample size or blinding. Thus, all studies either received grades 2++ or 2+ within level 2 of the SIGN methodology,[1] depending on whether they had a matched or an un-matched control group. Table 2 provides an overview on study participants and methodology, neurocognitive domain and evidence levels of the studies included in this review. Studies were classified as *EO* studies if subjects started using cannabis before the age of 18.

Additional Meta-Analytic Information

Effect sizes (*ES*) were computed in terms of (unweighted) correlations *r* using Fisher's *Z*-transformation (Cohen 1988; Rosenthal and DiMatteo 2001).[2] To that end, statistical parameters reported (*F, t, d*, etc.) were converted in correlations *r*. For these and other meta-analytic computations, Psychometrica software was employed (Lenhard and Lenhard 2015; www.psychometrica.de), furthermore IBM SPSS Statistics 22 (www.ibm.com). For multiple effects studies, one mean r was computed, for zero effect studies, $r = .00$ was applied by definition, and thus, all zero

[1] 2++ = "high quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal"

2+ = "well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal" (Baker et al. 2010, p. 359)

[2] By convention, effects of $r = .10$ to .29 count as small, effects of $r = .30$ to 0.49 as medium and effects of $r = 0.50$ or more as large (Cohen 1988).

Table 2 Clinical Studies - participants characteristics and study methodology

Study			Participants		Cannabis use	
Nr	Year	Authors	Sample N (male)	Groups n (age mean/SD)	Quantity/Frequency M(SD)	Duration/Age of Onset (AO) M(SD)
1	2009	Ashtari M, Cervellione K, Cottone J, Ardekani BA, Sevy S, Kumra S	28 (28)	CU = 14 (19.3 ± 0.8 years) NC =14 (18.5 ± 1.4 years)	m = 5.8 (2.1) joints/day	5.3 years (min 1 year)AO = 13.1 (9.0–15.0) years
2	2011	Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S	28 (28)	CU = 14 (19.3 ± 0.8 years) NC =14 (18.5 ± 1.4 years)	m = 5.8 (2.1) joints/day	5.3 years (min 1 year) AO = 13.1 (9.0–15.0) years
3	2005	Bolla KI, Eldreth DA, Matochik JA, Cadet JL	22 (22)	CU =11 (26 ± 4–6) NC =11 (31 ± 9)	CU 41 (8–48) joints/ week	7.9 (4–22) years
4	2013	Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, Theunissen EL, Kuypers KP, Huestis MA, Ramaekers JG	49 (49)	CU = 19 (27.6 ± 1.5) NC = 30 (22.7 ± 0.3)	CU 10.9 (1.6) joints/day NC: limited SU	10.5(1.2) years
5	2006	Chang L, Yakupov R, Cloak C, Ernst T	43 (2)	CU = 12 (27.9 ± 10.8) FCU = 12 (29.6 ± 8.7) NC = 19 (30.6 ± 8.0)	FCU 26.7 (±1.4) days/month CU 27.9 (±1.1) days/month	CU 147.6 (±33.7) months; AO = 15.5 (±0.9) FCU 138.8 (±24.4) months; AO = 14.7 ± 0.4)
6	2009	Clark L, Roiser JP, Robbins TW, Sahakian BJ	84 (56)	EU = 46 (24.2 ± 6.7) FEU = 24 (27.9 ± 6.6) CU = 15 (22.3 ± 4.3) NC = 19 (24.0 ± 3.6)	CU 2704.2 (6221.4) life joints; 31.3 (53.7) joints last month EU 6707.7 (9244.1) life joints; 609.1 (703.2) life tablets; 53.1(80.9) joints last month FEU 10379.2 (18.546.5) life joints 1000.8 (1792.4) life tablets; 52.1(121.9) joints last month	n/a
7	2013	De Bellis MD, Wang L, Bergman SR, Yaxley RH, Hooper SR, Huettel SA	56 (56)	CU = 15 (16.4 ± .73) PSYC = 23 (15.4 ± 1.49) NC = 18 (16.0 ± 1.2)	CU max. 19 (±27.8) joints/week; max. 9.14(±11.1) joint/day	CU 1.26 years ± 0.83 AO = 14.6 ± 1.32
8	2004	Eldreth DA, Matochik JA, Cadet JL, Bolla KI	22 (22)	CU = 11 (25; 21–35) NC = 11 (29,22–34)	34.7(8–63 joints/week	CU 7.5 (2–22) AO = 15.7 (12–21)
9	2010	Fernández-Serrano MJ, Pérez-García M, Schmidt Río-Valle J, Verdejo-García A	90 (76)	SU = 60 (30.58 ± 7.08) NC = 30 (26.40 ± 8.03)	148.65 (±179.87) joints/ month	SU: 8.27 (±7.63) years
10	2010	Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA, Tapert SF	40 (33)	CU = 19 (18.1 ± 0.8) NC = 21 (17.4 ± 1.0)	CU = limited other SU 16.0 ± 9.2 CU d/30d 465.0(±294.5) LT CU episodes	CU AO = 15.6(±1.6)
11	2005	Herning, RI, Better WE, Tate K, Cadet JL	72 (52)	CU(l) = 11 (25.5 ± 6.3) CU(m) = 23 (22.6 ± 4.9) CU(h) = 20	CU (l) = 11.0 ± 3.5 joints/ week; 15.9 ± 37.d/30d CU(m) = 43.7 ± 16.4 joints/week; 24.5 ± 71	CU (l) 5.6 ± 3.8 years CU (m) 7.2 ± 5.8 years CU (h) 6.1 ± 3.1 years

Table 2 (continued)

Study			Participants		Cannabis use	
				(21.6 ± 2.8) NC = 18 (24.2 ± 3.2)	d/30d CU (h) = 130.8 ± 73.0 joints/week; 29.2 ± 3.4 d/30d	
12	2008	Herning RI, Better W, Cadet JL	108 (67)	CU = 56 (21.4 ± 3.4) LCU = 19 (24.3 ± 4.1) NC = 33 (22.8 ± 5.3)	CU = 26.0 ± 5.2 d/30d LCU = 26.4 ± 4.9 d/30d	CU 4.4 ± 1.5 years; AO = 17.2 ± 3.7 LCU 9.6 ± 1.8 years; AO = 14.6 ± 3.5 years
13	2012	Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, Pike VW, Volkow ND, Huestis MA, Innis RB	58 (58)	CU = 30 (28 ± 8) NC =28 (32 ± 10)	CU 10 ± 6 joints/day	CU 12 ± 7; AO = 15 ± 3 years
14	2014	Hooper SR, Woolley DW, De Bellis MD	113 (71)	CU = 33 (16.37 ± 0.98) NC = 16.24 ± 1.03	18.1 ± 26.4 joints/week	341.7 ± 224.2 LT CU episodes; AO = 14.5 ± 1.42 years
15	2004	Jacobsen LK, Mencl WE, Westerveld M, Pugh KR	21 (8)	CU = 7 (17.4 ± 1.0) TC or OCU =7 (17.1 ± 0.9) NC =7 (6.8 ± 1.4)	LT days CU 282.8 ± 532.1 OCU 0.6 ± 0.5	CU AO = 13.8 ± 1.9
16	2007	Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE	45 (12)	CU = 20 (17.3 ± 1.1) TU = 25 (17.0 ± 1.1)	CU 847.1 ± 872.9 LT CU TU 9.6 ± 10.8 LT CU	CU AO = 13.6 ± 1.7
17	2009b	Jacobus J, McQueeny T, Bava S, Schweinsburg BC, Frank LR, Yang TT, Tapert SF	42	BD = 14 (18.1 ± 0.7) BD + CU(h) = 14 (18.2 ± 0.7) NC = 14 (17.3 ± 0.8)	BD + CH(h): LT CU = 5.495 ± 479.2 episodes, 152.9 ± 162.2 CU episodes/past 3 months, 26.1 ± 16.1 drinks/month; BD: LT CU 2.2 ± 3.1; 19.6 ± 16.1 drinks/ months past 3 months	LT CU 180–1800 episodes
18	2012	Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF	46 (36)	CU(h) = 23 (17.1 ± 0.7) NC = 23 (17.5 ± 0.8)	CU(h) 3.98.6 ± 181.5 LT CU, 17.9 ± 9.2 d/30d; NC limited SU	n/a
19	2014	Jacobus J, Squeglia LM, Sorg SF, Nguyen-Louie TT, Tapert SF	54 (39)	CU = 24 (17. ± 0.7 years) NC = 30 (17.4 ± 0.8 years)	408.8 ± (193.1) days LT CU, 17.3 ± 9.6 times last month	AO = 15.4 ± 0.9 years
20	2004	Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, Tsuang MT	108 (108)	(monozygotic twins) CU = 54 (46.3 ± 3.1) NC = 54	CU 916 ± 1201	CU 5.8 ± 5.3 years; AO = 21.3 ± 3.8
21	2010	Mahmood OM, Jacobus J, Bava S, Scarlett A, Tapert SF	130 (98)	CU(h) = 65 (17.96 ± 0.90) NC = 65 (17.71 ± 0.93)	16.03 ± 10.19 days CU per month; LT CU 500.65 ± 398.91	CU 7.5 ± 5.5; AO = 15.7 ± 2.5
22	2005	Matochik JA, Eldreth DA, Cadet JL, Bolla KI	19 (19)	CU(h) = 11 (25.5 ± 5.0) NC = 8 (29.7 ± 4.7)	CU 34.7 ± 17.6 joints/ week	7.5+/− 5.5 years
23	2011		82 (63)	CU = 27 male (17.92 ± 0.91), 8	CU 446 (180–1800) LT CU; 12 d/30d	CU duration = 3 years

Table 2 (continued)

Study			Participants		Cannabis use	
		McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF		female (18.15 ± 0.86) NC =36 male (18.15 ± 0.86), 11 female (17.85 ± 0.73)		
25	2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	65 (48)	CU = 31 (18.2 ± 0.87) NC = 34 (17.89 ± 0.99	CU 540.64 ± 380.24 LT CU; 170.72 ± 2340.03 episodes in last 3 months	2.91 ± 2.08 years of weekly CU
24	2007b	Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF	32 (25)	CU (with MD) = 16 (18 ± .7) NC = 16 (18 ± .9)	476 ± 269 LT CU	n/a
26	2009	Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF.	32 (22)	CU = 16 (18 ± 0.7) NC = 16 (18 ± 0.9)	CU 476 ± 269 LT CU	3.4 ± 1.7 years
27	2010	Medina KL, Nagel BJ, Tapert SF	32 (22)	CU = 16 (18 ± 0.7) NC = 16 (18 ± 0.9)	CU 476 ± 269 LT CU	3.4 ± 1.7 years
28	2007	Padula CB, Schweinsburg AD, Tapert SF	34	CU (h) = 16 (18 ± 0.7) NC = 16 18 ± 0.9)	CU (h) 477.06 ± 260.07 LT CU	n/a
29	2008	Pillay SS, Rogowska J, Kanayama G, Gruber S, Simpson N, Pope HG, Yurgelun-Todd DA	27 (14)	CU (h) = 11 (37.7 ± 6.2) NC = 16 (29.7 ± 10.3)	CU (h) 17,637 ± 9744 LT CU	21 ± 4.9 years; AO = 18.75 ± 5.52
30	2014	Pujol J, Blanco-Hinojo L, Batalla A, López-Solà M, Harrison BJ, Soriano-Mas C, Crippa JA, Fagundo AB, Deus J, de la Torre R, Nogué S, Farré M, Torrens M, Martín-Santos R	57 (57)	CU(h) = 28 (21 ± 2) NC = 29 (22 ± 3)	CU(h) 5268 ± 4265 LT CU; 899 ± 560 joints/year	6.0 ± 2.5 years; AO = 14.9 ± 1.0
31	2008b	Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF	32 (23)	CU = 15 (18.1 ± 0.7) NC = 17 (17.9 ± 1.0)	CU 480.7 ± 277.2 LT CU; 13.5 ± 11.6 CU/past 3 months	2.7 ± 1.8 years of weekly CU
32	2010	Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF	44 (29)	CU (r) = 13 (17.07 ± 0.53) CU = 13 (17.58 ± 0.92) NC = 18 (17.34 ± 0.82)	CU 515.38 ± 275.67 LT CU; 16.8510.85 CU/past 3 months	CU 2.65 ± 1.71 years of weekly CU
33	2011	Schweinsburg AD, Schweinsburg BC, Nagel BJ, Eyler LT, Tapert SF	74 (56)	CU = 8 (18.1 ± 0.9) BD = 16 (18.1 ± 0.7) CU + BD = 28 (18.0 ± 1.0) NC (limited SU) = 22 (17.6 ± 0.8)	CU = 426.5 ± 280.1 LT CU, 8.4 ± 9.3 CU/past 3 months; CU + BD = 517.6 ± 451.4 LT CU, 11.8 ± 9.3 CU/past 3 months	CU AO = 14.5 ± 2.5 years; CU + BD AO = 14.9 ± 3.4 years
34	2008	Sevy S, Smith GS, Ma Y, Dhawan V, Chaly T, Kingsley PB, Kumra S, Abdelmessih S, Eidelberg D	12 (12)	CU = 6 (20 ± 1) NC = 6 (20 ± 1)	CU 16 ± 12 g/day	5 ± 2 years; AO 12 ± 2
35	2008		32 (17)	LCU = 15 (38.3 ± .56) NC = 17 (16.4 ± 3.8)	CU 20,601.3 ± 13,540.8 LT CU; 30 ± 0 d/30d	21.3 ± 5.3 years

Table 2 (continued)

Study			Participants		Cannabis use	
		Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA				
36	2007	Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT, Frank LR	33 (24)	CU = 16 (18.1 ± 0.7) NC = 17 (17.9 ± 1.0)	CU 475.6 ± 268.5 LT CU; 14.3 ± 11.6 days/ month	AO = 14.0 ± 1.6; AO (weekly) = 15.4 ± 1.7
37	2007	Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI	31 (31)	CU = 11 (25.7 ± 4.9) CCU = 12 (36.8 ± .51) NC = 14 (30.9 ± 5.9)	CCU 1.6 ± 4.3 joints/ week; CU 40.1 ± 22.3 joints/week	CU 7.9 ± 5.6 years; CCU 9.7 ± 9.4 years
38	2014	Winward JL, Hanson KL, Tapert SF, Brown SA	128 (80)	CU = 20 (17.79 ± 0.81) AA = 24 (17.9 ± 0.63) CU + AA = 29 (18.05 ± 0.83) NC = 55 (17.71 ± 0.83)	17.70 (10.76) days per month CU	CU 500.48 (289.59) LT cannabis use episodes AO = 15.27 (1.56)

Study	Cannabis use		Methodology					
Nr	Early Onset: AO <18 (y/n)	Abstinence Period M(SD)	Domain(s)	Study design	Urine control	Methods	Outcome	Evidence Level
1	yes	6.7 (3–11) months	FI	cross sectional	yes	MRI (structural) and performance	ROI Hippocampus, CVLT (verbal memory)	2+
2	yes	6.7 (3–11) months	SI, ML	cross sectional	yes	fMRI	compare white matter integrity using voxelwise and fiber tractography analysis	2++
3	no	min 25 days	FI, E	cross sectional	yes	PET	performance and brain activity during the Iowa Gambling Task-IGT (a decision-making task)	2++
4	no	1–23 days	A, M	longitudinal, two site	oral fluid and blood samples	performance	critical tracking (CTT) and divided attention (DAT)	2+
5	yes	FCU = 38 (±18) months	FI, A, E, ML	cross sectional	yes	Blood oxygenation-level dependent (BOLD) functional MRI (fMRI) and neuropsychological tests	visual-attention tasks with graded levels of difficulty	2+
6	no	min 3 weeks	E	cross sectional	no	performance	Impulsivity subscale of the Eysenck Impulsiveness-Venturesomeness-Empathy questionnaire, NART (National Adult Reading Test)	2+
7	yes	133.9 (±57.99) days	FI, E	cross sectional	yes	fMRI and behaviour	Decision-Reward Uncertainty Task	2+
8	no	min 25 days	FI, E	cross sectional	yes	PET (15)O and a modified version of the Stroop task	executive functions	2++
9	no	min 15 days, median 32 weeks	E	cross sectional	yes		executive functions performance: fluency, working memory, analogical	2+

Table 2 (continued)

Study	Cannabis use		Methodology					
							reasoning, interference, cognitive flexibility, decision-making and self-regulation	
10	yes	3 test points: 2.7, 13.3, 21.0 days	A, ML	longitudinal	yes	neuropsychological battery on three occasions	verbal learning, verbal working memory, attention and vigilance, and time estimation	2+
11	no	2 test points: 3 days, 28–30 days	FI	cross sectional	yes	transcranial Doppler sonography	blood flow velocity in the anterior and middle cerebral arteries	2+
12	no	2 test points: 72 h; 59 participants tested after 4 weeks	FI	repeated measures, two points in time	yes	EEG	the resting eyes closed EEG, EEG patterns are indicative of cerebral perfusion deficits	2+
13	no	1 day, 4 weeks	SI	repeated measures, two testing points (CU only)	yes	PET	brain cannabinoid CB(1) (cannabinoid receptor type 1) receptors after chronic exposure to cannabis	2+
14	yes	Minimum 30 days, maximum 480 days; median 110 days	ML, A, E,	cross sectional	yes	neuropsychological battery	Academic achievement, general intelligence, attention, memory and executive functions	2+
15	yes	10.1 ± 10.2 (min. 1.5 months)	A, ML	cross sectional, pilotstudy	yes	fMRI	auditory verbal working memory task (1-back and 2-back conditions) and selective attention task (binaural and dichotic stimulus presentation)	2+
16	yes	4.8 ± 7.0 months	FI, ML	repeated measures, two testing points	yes	fMRI und Behaviour	fMRI: auditory verbal working memory selective attention sustained attention selective und divided attention	2+
17	no	min 23 days (range 23–61)	SI	cross sectional	yes	fMRI and DTI	white matter integrity examination	2+
18	yes	2 test points: baseline (1–17 days abstinence), 4 weeks	FI, A, E, ML	repeated measures, 2 testing points	yes	Arterial spin labelling (ASL) characterizes neurovascular status and cerebral blood flow (CBF), potentially revealing contributors to neuropathological alterations.	executive functioning, nonverbal memory, structural verbal memory, visuospatial processing at baseline only	2+
19	yes	2 test points: baseline (5.7 ± 4.5 days last CU), follow up (29.8 ± 8.2 days last CU), min 20 days	SI, A, E, ML, VS	Repeated measures, 2 testing points	yes	MRI, neuropsychological test battery	cortical thickness, California Verbal Learning Test (CVLT), Delis-Kaplan-Executive Function System (D-KEFS), Rey-Osterrieth Complex Figure et cetera	2++
20	no	min of 1 year, mean duration last CU 27.1 ± 6.0	A, E, ML	cross sectional	no	neuropsychological test battery	general intelligence, executive functioning, attention, memory and motor skills	2++
21	yes		ML	cross sectional	yes	neuropsychological performance		2++

Table 2 (continued)

Study	Cannabis use		Methodology					
		min 22 days; mean duration last CU 52.92 ± 67.36					neuropsychological tests for visual and verbal memory (for example (CVLT)	
22	no	min 20 days	SI, ML	cross sectional	yes	fMRI	testing differences in gray matter and white matter tissue density	2++
23	yes	min 28 days	SI	cross sectional	yes	amygdala and intracranial volumes on high-resolution magnetic resonance images	relationships between amygdala volume and internalizing symptoms in teenaged chronic marijuana users	2+
25	no	min 23 days; 490.80 ± 458.18	A, E, M, ML, VS	cross sectional	yes	behaviour	psychomotor speed, complex attention, sequencing ability, verbal story memory, verbal list learning, visuo-spatial function and memory, verbal accuracy, planning and problem solving	2+
24	no	min 28 days	SI	cross sectional	yes	fMRI	white matter volume and right hippocampal volume in relation to depressive symptoms	2+
26	yes	min 30 days; 107 ± 33	SI, E	cross-sectional,	yes	MRI	prefrontal cortex (PFC) morphometry	2+
27	yes	min 30 days; 107 ± 33	SI, E, M	cross sectional	yes	fMRI and behaviour (executive functioning and psychomotor processing speed)	neuropsychological data and structural brain scans defining cerebellar volumes (including three cerebellar vermis lobes and both cerebellar hemispheres) on high-resolution T1-weighted magnetic resonance images	2+
28	yes	28 Tage/60,4	FI, ML	cross sectional	yes	fMRI	spatial working memory	2+
29	no	3 test points: baseline, day 7, day 28	FI, M	cross sectional	yes	fMRI	finger-tapping tests Differences in cerebral activation were examined in the left and right primary motor cortex (BA4), SMA (BA6), and ACC (BA24 and BA32 separately).	2+
30	yes	acute (12 h abstinence) and 28 days abstinence	FI, ML	cross sectional	yes	fMRI	brain networks relevant to self-awareness, and relation to perceived anxiety and memory performance (RAVLT).	2+
31	yes	min 28 days; 60.4 ± 54.1 days	FI, ML	cross sectional	yes	fMRI and spatial working memory (SWM)	2-back location working memory with simple detection (dot detection)	2+
32	yes	min 27 days; 38.08 ± 10.28 days	FI, VS	cross sectional	yes	fMRI	spatial working memory (SWM) task	2+
33	yes	min 22 days; CU 117.6 ± 153.9 days; CU + BD 43.4 ± 37.1 days	ML	cross sectional	yes	fMRI	verbal paired associates encoding task	2+
34	yes	15 ± 5 (12–25) weeks	FI, SI	cross sectional	yes	PET	striatal dopamine receptor (D2/D3) availability and cerebral glucose metabolism	2++

Table 2 (continued)

Study	Cannabis use		Methodology					
35	no	3 test points: baseline, 7, 28 days	FI	cross sectional	yes (only LCU)	Dynamic susceptibility contrast MRI (DSCMRI)	changes in regional blood volume in the frontal and temporal lobe, and the cerebellum	2+
36	yes	min. 28 days; 58.4 ± 52.8 days	FI, E	cross sectional	yes	fMRI BOLD	inhibitory processing go/no-go task	2+
37	no	min 25 days	E	repeated measures, two test points on one day	yes	Iowa Gambling Task (IGT)	decision-making and risk taking	2+
38	yes	35.05 days (11.90)	E, ML, VS, A, M	cross sectional	yes	neuropsychological test battery	executive functioning, attention, memory and motor skills, working memory, language, visuospatial construction	2++

Evidence Level 2++ = "high quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal" 2+ = "well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal"

A Attention, *E* Executive functions, *M* Motor function, *ML* Memory and Learning, *VS* Visual Spatial, *FI* Functional imaging, *SI* Structural Imaging, *CU* Cannabis Users, *NC* Non-using Controls, *LCU* Long-term Cannabis Users, *FCU* Former Cannabis Users, *OCU* Occasional Cannabis Users, *CU(l)* Light Cannabis Users, *CU(m)* Moderate Cannabis Users, *CU(h)* Heavy Cannabis Users, *CU(r)* Recent Cannabis Users, *EU* Ecstasy Users, *FEU* Former Ecstasy Users, *OMU* Occasional MDMA Users, *PSYC* Controls with Psychopathology but without Substance Use Disorder History, *SU* Substance Users, *TU* Tobacco Users, *BD* Binge Drinkers, *MD* Mood Disorder, *AA* Alcohol Abuse, *AO* Age of onset, *d/30d* Number of days of substance use in the last 30 days, *LT* Lifetime, *CCU* Cocaine Users, *CU + AA* Alcohol and cannabis Abusers, *n/a not available*

correlations were included in computations. This could only be done in studies supplying adequate data. Marginal effects ($p \leq .10$) were also included (Chang et al. 2006; Pujol et al. 2014; Schweinsburg et al. 2010; Sevy et al. 2008; Verdejo-Garcia et al. 2007) following the reasoning of Grant et al. (2003, p. 683) in "that in investigating the potential toxic effects of a substance such as cannabis, it [is] important to be more 'permissive' rather than 'conservative'." Via heterogeneity statistic Q and index I^2 we assessed whether the pooled effect sizes of study results measure the same underlying population effect in specific domains and in total (Rosenthal and DiMatteo 2001). Cochrane's Q, a widely used statistic, is impacted by sample size. Therefore, it is completed by I^2, which is not (Huedo-Medina et al. 2006).

Results

Of the 38 studies reviewed here, nine studies or 24 % were rated with evidence level 2++, while the others received evidence level 2+. This renders the studies fairly comparable with regard to study quality. Study characteristics, however, proved to be heterogeneous with regard to sample size, age, gender ratio, subject acquisition, comorbidities, other substance use, abstinence duration, quantity or frequency of consumption and test methods (see Table 2). Twenty-nine studies were rated as having an adolescent, 22 as having an EO study sample. Table 3 provides an overview over main results within five neurocognitive domains. Twenty-four zero effects out of 13 performance studies (Ashtari et al. 2011; De Bellis et al. 2013; Eldreth et al. 2004; Hooper et al. 2014; Jacobus et al. 2012, 2014; Lyons et al. 2004; Medina et al. 2010; Padula et al. 2007; Schweinsburg et al. 2008b; Schweinsburg et al. 2010; Schweinsburg et al. 2011; Winward et al. 2014) and 2 zero effects out of 2 imaging studies (Hirvonen et al. 2012; Jacobus et al. 2012) were found. All of them were included in further computations. As detailed in Tables 4 and 5 for studies providing sufficient data, *neurocognitive performance* ($I^2 = 55.9$ %) and *functional and structural imaging* studies ($I^2 = 62.5$ %) are both of similar medium heterogeneity. Their ES ($r_{mean} = .305$ resp. $r_{mean} = .446$) differ only by a small ES according to Cohen's $q = .165$. In all, impairment ES in CU relative to non-using controls (NC) could be overall qualified as medium to large from both perspectives, and a pooled overall ES would be $r_{mean} = .378$ (CI 95 % = [.342; .453]).

Attention

Ten studies examined differences in attention between CU and a group of NC, five of them found impairments in CU. Quantifiable data ($n = 10$ studies) rendered an overall medium ES of $r = .273$ (CI 95 % = [.109; .423]). Most of the reviewed studies provide evidence for some attention and concentration deficits in CU even after a time of abstinence. In a study by

Table 3 Clinical Studies – main findings

Year	Authors	Domain	Evidence Level	Main Findings	Early Onset (EO) (1 = yes; 0 = no)	Differences CU/NC?	Effect Sizes (r or mean r)
ATTENTION							
2013	Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, Theunissen EL, Kuypers KP, Huestis MA, Ramaekers JG	A	2+	impaired performance for divided attention at baseline, not fully recovered after 3 weeks	0	CU worse	.303
2006	Chang L, Yakupov R, Cloak C, Ernst T	A	2+	impaired on attention subtest (response reversal/visual scanning)	1	CU worse	.183
2010	Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA, Tapert SF	A	2+	attention processing speed similar between groups of users and non-users; but attention accuracy impairments	1	CU worse	.381
2004	Jacobsen LK, Mencl WE, Westerveld M, Pugh KR	A	2+	impaired attention in a selective attention task	1	CU worse	.619
2012	Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF	A	2+	no differences in attention and processing speed	1	no	0.00
2004	Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, Tsuang MT	A	2++	no differences in attention	0	no	0.00
2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	A	2+	poorer complex attention results	0	CU worse	.460
2014	Jacobus J, Squeglia LM, Sorg SS, Nguyen-Louie TT, Tapert SF	A	2++	both CU and NC improve complex attention over time, but no group differences	1	no	0.00
2014	Winward JL, Hanson KL, Tapert SF, Brown SA	A	2++	no differences in attention	0	no	0.00
2014	Hooper SR, Woolley DW, De Bellis MD	A	2+	no group differences in attention	0	no	0.00
EXECUTIVE FUNCTIONS							
2005	Bolla KI, Eldreth DA, Matochik JA, Cadet JL	E	2++	lower decision-making task performance	0	CU worse	.591
2006	Chang L, Yakupov R, Cloak C, Ernst T	E	2+	slower reaction times on a choice reaction task	1	CU worse	.204
2009	Clark L, Roiser JP, Robbins TW, Sahakian BJ	E	2+	increased reflection impulsivity and reduced information sampling	0	CU worse	.375
2013	De Bellis MD, Wang L, Bergman SR, Yaxley RH, Hooper SR, Huettel SA	E	2+	similar performance on decision making	1	no	0.00
2004	Eldreth DA, Matochik JA, Cadet JL, Bolla KI	E	2++	no difference in executive function	0	no	0.00
2010	Fernández-Serrano MJ, Pérez-García M, Schmidt Río-Valle J, Verdejo-García A	E	2+	poorer performance in the areas of fluency, self-regulation, working memory and reasoning	0	CU worse	.265
2012	Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF	E	2+	decreased performance on verbal learning and recall	1	CU worse	.240
2004	Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, Tsuang MT	E	2++	no differences in executive functioning	0	no	0.00
2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	E	2+	deficits in planning and sequencing ability	0	CU worse	n/a
2009	Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF	E	2+	among CU, smaller prefrontal cortex volume was associated with better executive functioning, opposite pattern in NC	1	interaction with prefrontal cortex volume	.313
2010	Medina KL, Nagel BJ, Tapert SF	E	2+	no difference in composite variables of executive functioning	1	no	0.00
2007		E	2+	verbal fluency impaired	1	CU worse	n/a

Table 3 (continued)

Year	Authors	Domain	Evidence Level	Main Findings	Early Onset (EO) (1 = yes; 0 = no)	Differences CU/NC?	Effect Sizes (r or mean r)
	Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT, Frank LR						
2007	Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI	E	2+	worse decision making performance	0	CU worse	.454
2014	Jacobus J, Squeglia LM, Sorg SS, Nguyen-Louie TT, Tapert SF	E	2++	both CU and NC improve executive functions over time, but no group differences	1	no	0.00
2014	Winward JL, Hanson KL, Tapert SF, Brown SA	E	2++	CU worse than NC in subtest trail making	0	CU worse	.384
2014	Hooper SR, Woolley DW, De Bellis MD	E	2+	no group differences in executive tests	0	no	0.00
MOTOR FUNCTION							
2013	Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, Theunissen EL, Kuypers KP, Huestis MA, Ramaekers JG	M	2+	impaired psychomotor performance	0	CU worse	.402
2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	M	2+	slower psychomotor speed	0	CU worse	n/a
2010	Medina KL, Nagel BJ, Tapert SF	M	2+	no differences in composite variable of psychomotor speed	1	no	0.00
2008	Pillay SS, Rogowska J, Kanayama G, Gruber S, Simpson N, Pope HG, Yurgelun-Todd DA	M	2+	worse performance in finger-tapping tasks	0	CU worse	.515
2014	Winward JL, Hanson KL, Tapert SF, Brown SA	M	2++	worse psychomotor speed results in subtest	0	CU worse	.327
MEMORY AND LEARNING							
2011	Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S	ML	2++	no difference in performance on memory tests	1	no	0.00
2006	Chang L, Yakupov R, Cloak C, Ernst T	ML	2+	no difference in visual memory task	1	no	n/a
2010	Hanson KL, Winward JL, Schweinsburg AD, Medina KL, Brown SA, Tapert SF	ML	2+	poorer verbal learning, verbal working memory	1	CU worse	.392
2004	Jacobsen LK, Mencl WE, Westerveld M, Pugh KR	ML	2+	worse performance on working memory task	1	CU worse	.657
2007	Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE	ML	2+	poorer verbal delayed recall, persistent deficits in verbal working memory under high working memory load	1	CU worse	.345
2012	Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF	ML	2+	no differences in verbal learning test	1	no	0.00
2004	Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, Tsuang MT	ML	2++	no differences in memory function	0	no	0.00
2010	Mahmood OM, Jacobus J, Bava S, Scarlett A, Tapert SF	ML	2++	greater alcohol hangover symptoms predicted worse verbal learning and memory scores for NC, but not for CU	1	interaction with binge drinking	.099
2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	ML	2+	poorer story memory	0	CU worse	.410
2007	Padula CB, Schweinsburg AD, Tapert SF	ML	2+	no difference on behavioral measures of task performance	1	no	0.00
2014	Pujol J, Blanco-Hinojo L, Batalla A, López-Solà M, Harrison BJ, Soriano-Mas C, Crippa JA, Fagundo AB,	ML	2+	higher anxiety scores, reduced verbal memory span and delayed recall, and increased forgetting rate	1	CU worse	.297

Table 3 (continued)

Year	Authors	Domain	Evidence Level	Main Findings	Early Onset (EO) (1 = yes; 0 = no)	Differences CU/NC?	Effect Sizes (r or mean r)
	Deus J, de la Torre R, Nogué S, Farré M, Torrens M, Martín-Santos R						
2008b	Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF	ML	2++	no difference on spatial working memory task	1	no	0.00
2011	Schweinsburg AD, Schweinsburg BC, Nagel BJ, Eyler LT, Tapert SF	ML	2+	no differences in performance on a testing verbal paired associates encoding task	1	no	0.00
2014	Jacobus J, Squeglia LM, Sorg SS, Nguyen-Louie TT, Tapert SF	ML	2++	both CU and NC improve memory functions over time, but no group differences	1	no	0.00
2014	Winward JL, Hanson KL, Tapert SF, Brown SA	ML	2++	CU in one subtest worse delay cued recall	0	CU worse	0.284
2014	Hooper SR, Woolley DW, De Bellis MD	ML	2+	no group differences in memory tests	0	no	0.00
VISUAL SPATIAL							
2007a	Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF	VS	2+	CU performed better on visuo-construction than NC	0	CU better	n/a
2010	Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF	VS	2++	equivalent spatial working memory performance, no difference in vigilance reaction time between groups	1	no	0.00
2014	Jacobus J, Squeglia LM, Sorg SS, Nguyen-Louie TT, Tapert SF	VS	2++	group x time interaction for visual spatial subtest, no improvement for CU	1	CU worse	.292
2014	Winward JL, Hanson KL, Tapert SF, Brown SA	VS	2++	no differences between CU and NC	0	no	0.00
FUNCTIONAL IMAGING							
2009	Ashtari M, Cervellione K, Cottone J, Ardekani BA, Sevy S, Kumra S	FI	2+	CU had reduced fractional anisotropy, increased radial diffusivity and increased trace in fronto-temporal areas via arcuate fasciculus	1	yes	.422
2005	Bolla KI, Eldreth DA, Matochik JA, Cadet JL	FI	2++	CU showed greater activation in the left cerebellum and less activation in the right lateral orbitofrontal cortex and the right dorsolateral prefrontal cortex than NC	0	yes	n/a
2006	Chang L, Yakupov R, Cloak C, Ernst T	FI	2+	CU showed decreased activation in the right prefrontal, medial and dorsal parietal and medial cerebellar regions, but greater activation in various frontal, parietal and occipital brain regions during the visual-attention tasks	1	yes	n/a
2013	De Bellis MD, Wang L, Bergman SR, Yaxley RH, Hooper SR, Huettel SA	FI	2+	CU demonstrated distinctly different activation patterns during risky decision-making and reward processing, esp. left orbitofrontal cortex compared to NC, no areas of hypoactivation to risky decisions and executive regions in CU at whole-brain level	1	yes	.782
2004	Eldreth DA, Matochik JA, Cadet JL, Bolla KI	FI	2++	decreased left dorsolateral prefrontal blood flow during a modified Stroop task in CU as well hypoactivity in the left perigenual anterior cingulate cortex and the left lateral prefrontal cortex and hyperactivity in the	0	yes	n/a

Table 3 (continued)

Year	Authors	Domain	Evidence Level	Main Findings	Early Onset (EO) (1 = yes; 0 = no)	Differences CU/NC?	Effect Sizes (r or mean r)
				hippocampus bilaterally compared to NC			
2005	Herning, RI, Better WE, Tate K, Cadet JL	FI	2+	pulsatility index and systolic velocity significantly increased in CU	0	yes	.272
2008	Herning RI, Better W, Cadet JL	FI	2+	CU was associated with reduced EEG power in alpha and beta bands at posterior sites which was associated with changes in cerebral perfusion and/or thyroid function	0	yes	.242
2007	Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE	FI	2+	CU exhibited increased parietal activation and greater activation in posterior parietal cortex during verbal working memory test	1	yes	n/a
2012	Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF	FI	2+	no cerebral blood flow differences	1	no	0.00
2007	Padula CB, Schweinsburg AD, Tapert SF	FI	2+	CU showed performance × brain response interactions in the bilateral temporal lobes, left anterior cingulate, left parahippocampal gyrus, and right thalamus on a spatial working memory task	1	yes	.390
2008	Pillay SS, Rogowska J, Kanayama G, Gruber S, Simpson N, Pope HG, Yurgelun-Todd DA	FI	2+	Differences in cerebral activation in the contralateral supplementary motor area and partly in the dorsal anterior cingulate area	0	yes	n/a
2014	Pujol J, Blanco-Hinojo L, Batalla A, López-Solà M, Harrison BJ, Soriano-Mas C, Crippa JA, Fagundo AB, Deus J, de la Torre R, Nogué S, Farré M, Torrens M, Martín-Santos R	FI	2+	CU showed increased functional connectivity in the core of the default and Insula networks and selective enhancement of functional negative correlation between both, reduced functional connectivity for CU was observed in areas overlapping with other brain networks	1	yes	.440
2008b	Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF	FI	2++	CU was associated with lower activity in right dorsolateral prefrontal and occipital cortices	1	yes	.609
2010	Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF	FI	2++	CU had increased response in the right precentral gyrus clusters	1	yes	.629
2008	Sevy S, Smith GS, Ma Y, Dhawan V, Chaly T, Kingsley PB, Kumra S, Abdelmessih S, Eidelberg D	FI	2++	lower normalized glucose metabolism in the right orbitofrontal cortex, putamen bilaterally and precuneus in CU	1	yes	n/a
2008	Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA	FI	2+	left temporal area and cerebellum showed significantly increased cerebral blood flow values in CU	0	yes	.459
2007	Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT, Frank LR	FI	2+	CU showed activation differences in right dorsolateral prefrontal, bilateral medial frontal, bilateral inferior and superior parietal lobules, and right occipital gyri, as well as in insular and parietal cortices	1	yes	.782
STRUCTURAL IMAGING							
2011	Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S	SI	2++	CU showed significantly smaller left and right hippocampus volumes than NC, no significant differences in left and right amygdala volume	1	yes	n/a
2012		SI	2+		0	no	0.00

Table 3 (continued)

Year	Authors	Domain	Evidence Level	Main Findings	Early Onset (EO) (1 = yes; 0 = no)	Differences CU/NC?	Effect Sizes (r or mean r)
	Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, Pike VW, Volkow ND, Huestis MA, Innis RB			no difference in regionally selective downregulation of brain cannabinoid CB(1) receptors after 4 weeks of abstinence			
2009b	Jacobus J, McQueeny T, Bava S, Schweinsburg BC, Frank LR, Yang TT, Tapert SF	SI	2+	concomitant binge drinking and THC use was not associated with better white matter structure compared to controls, but higher fractional anisotropy values compared to adolescents reporting only binge drinking	0	interaction with binge drinking	n/a
2005	Matochik JA, Eldreth DA, Cadet JL, Bolla KI	SI	2++	lower gray matter density in the right parahippocampal gyrus and greater density bilaterally near the precentral gyrus and the right thalamus in CU, also lower white matter density in the left parietal lobe and higher density around the parahippocampal and fusiform gyri on the left side compared to NC	0	yes	n/a
2011	McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF	SI	2+	female CU had larger right amygdala volumes and more internalizing symptoms than female NC, while male CU had similar volumes as male NC. For female NC and males, worse mood/anxiety was linked to smaller right amygdala volume whereas more internalizing problems were associated with enlarged right amygdala only in female CU	1	yes (females)	.454
2007b	Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF	SI	2+	white matter volume was negatively associated with depressive symptoms in CU, no difference in intracranial volume, left or right hippocampal volume	0	yes	.335
2009	Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF	SI	2+	CU: smaller prefrontal cortex total volume was associated with better executive functioning while the opposite pattern was seen among NC	1	interaction with executive function	.300
2010	Medina KL, Nagel BJ, Tapert SF	SI	2+	CU: significantly larger inferior posterior (lobules VIII-X) vermis volume were associated with poorer executive functioning	1	interaction with executive function	n/a
2008	Sevy S, Smith GS, Ma Y, Dhawan V, Chaly T, Kingsley PB, Kumra S, Abdelmessih S, Eidelberg D	SI	2++	striatal dopamin2/dopamin3 receptor availability did not differ between CU and NC	1	yes	.178
2014	Jacobus J, Squeglia LM, Sorg SS, Nguyen-Louie TT, Tapert SF	SI	2++	CU demonstrated thicker cortices compared to controls: left caudal anterior cingulate cortex, left entorhinal cortex, left lingual gyrus and left pericalcarine cortex	1	interaction with life time alcohol use	.309

Evidence Level 2++ = "high quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal" 2+ = "well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal" (Baker et al. 2010, p. 359)

A Attention, *E* Executive functions, *M* Motor function, *ML* Memory and Learning, *VS* Visual Spatial, *FI* Functional imaging, *SI* Structural Imaging, *CU* Cannabis Users, *NC* Non-using Controls, *n/a* not available

Table 4 Sample sizes, effect sizes, and heterogeneity of studies with applicable information on neurocognitive functions

		Domain				
Statistic	Overall	Attention	Executive functions	Motor function	Memory + Learning	Visual Spatial
n of studies	31	10	16	5	16	4
n of effects	75	13	23	15	21	3
n of cases	1.428 [a]	528	696	183	834	160
MD of cases	32	49	32	40	42	65
range of cases	14–130	14–108	22–108	27–75	14–130	31–76
effect size (r_{mean})	.305	.273	.294	.478	.229	.094
95 % CI (r_{mean})	[.254; .358]	[.109; .423]	[.187; .394]	[.394; .555]	[.130; .323]	[−.303; .464]
Q	167.77	30.45	50.57	14.99	36.02	2.73
df_Q	74	12	22	14	20	2
p_Q	.000	.002	.001	.379	.015	.255
I^2 (%)	55.9	60.6	56.5	6.6	35.5	26.7

[a] without overlap across studies; *MD* median, *CI* confidence interval. Sample sizes only refer to actual comparisons and do not necessarily equal the sample total of a given study. All effects except visual spatial significant at $p \leq .05$

Medina et al. (2007a), CU demonstrated poorer complex attention results even after 23 days of abstinence. Jacobsen et al. (2004) reported impaired attention for CU in a selective attention task and Chang et al. (2006) in an fMRI study on visuospatial attention. Hanson et al. (2010) found similar attention processing speed between CU and NC, but attention accuracy remained deficient in users throughout a 3-week abstinence period ($p < .01$).

Within the five EO studies on attention, four studies found impairments while one study found no differences between CU and NC.

Table 5 Sample sizes, effect sizes, and heterogeneity of studies with applicable information on functional and structural imaging

	Domains		
Statistic	Overall	Functional imaging	Structural imaging
n of studies	27	17	10
n of effects	54	44	6
n of cases [a]	732	531	161
MD of cases	36	36	32
range of cases	12–108	28–108	12–58
effect size (r_{mean})	.446	.479	.287
95 % CI (r_{mean})	[.383; .505]	[.409; .554]	[.198; .371]
Q	141.23	126.88	6.22
df_Q	53	43	5
p_Q	.000	.000	.285
I^2 (%)	62.5	66.6	19.6

[a] without overlap across studies; *MD* median, *CI* confidence interval. Sample sizes only refer to actual comparisons and do not necessarily equal the sample total of a given study. All effects significant at $p \leq .05$

Executive Functions

Sixteen studies examined differences in executive functions, and ten studies found impairments. Quantifiable data ($n = 14$ studies) revealed an overall medium ES of $r = .294$ (CI 95 % = [.109; .423]). Evidence is mixed as to whether inhibition, impulsivity and decision making are impaired in abstinent CU. However, there is a trend towards worse performance even after a period of abstinence in CU groups. Executive functions, and how they are measured, are highly heterogeneous. For example Medina et al. (2007a) found deficits in planning and sequencing ability while Tapert et al. (2007) found impaired verbal fluency. Bolla et al. (2005) identified a dose-related association between increased THC use and a lower decision-making task performance (Iowa gambling task, *IGT*) and alterations in brain activity. Verdejo-Garcia et al. (2007) administered the IGT twice to 25-day abstinent cocaine and THC users and matched controls. CU performed worse than controls but this effect was not significant. They showed linear dose–response effects on IGT performance. The "number of joints" smoked prior to the period of enforced abstinence was negatively related to IGT performance. CU (abstinent for at least 3 weeks) showed significantly more impulsivity and tolerated a lower level of certainty in their decision-making compared to NC (Clark et al. 2009). On the other hand, five studies found no differences in executive function (e.g., Eldreth et al. 2004; Lyons et al. 2004), for instance in the area of decision making (De Bellis et al. 2013). Medina et al. (2009) reported an interaction effect in the way such that among CU, smaller prefrontal cortex (*PFC*) total volume was associated with better executive functioning while the opposite pattern was seen among the controls.

Within the seven EO studies on executive functioning, four studies found impairments.

Motor Function

Five studies examined differences in motor function abilities between CU and NC. Quantifiable data ($n = 4$ studies) gave an almost large ES of .478 (CI 95 % = [.394; .555]). Altogether, four out of five studies found evidence that motor function remains impaired even after a time of abstinence. It remains unclear if this result is due to reaction time (speed), or accuracy, or both. Bosker et al. (2013) assessed psychomotor function in CU and reported that sustained cannabis abstinence moderately improved critical tracking and divided attention performance in chronic, daily cannabis smokers, but that impairments were still observable compared to controls after three weeks of abstinence. Pillay et al. (2008) conducted finger-tapping tests and concluded that residual diminished brain activation in motor cortical circuits is still observed after discontinuing cannabis use for 28 days. In another study, after at least 23 days of abstinence, adolescent CU had impairments in psychomotor performance compared to controls, and there was a negative, dose-dependent association between performance and lifetime cannabis use episodes (Medina et al. 2007a).

In the only EO study on motor function, Medina et al. (2010) uncovered no significant relationships between cerebellar volume and psychomotor speed in adolescents.

Memory and Learning

Sixteen studies examined differences in memory and learning between CU and NC, seven of which found impairments. Quantifiable data ($n = 15$ studies) gave an overall medium ES of .229 (CI 95 % = [.130; .323]). There is some evidence that chronic CU might experience sustained deficits in the area of information encoding, storage and retrieval. Results for deficits in other types of memory seemed to be more nuanced when considering length of abstinence, age at which CU discontinue their use, amount and duration of cannabis use. For instance, Medina et al. (2007a) found poorer results for story memory, Jacobsen et al. (2007) demonstrated that THC users performed a working memory task less accurately than controls, and Hanson et al. (2010) demonstrated poorer verbal learning and working memory in a longitudinal study. Seven studies found no differences, for instance Lyons et al. (2004) in the area of memory function, Jager et al. (2010) in the area of associative memory or Chang et al. (2006), in whose study abstinent CU even showed a trend for better performance on one of the verbal memory tests. One study found an interaction effect with binge drinking (*n.b.* without alcohol-related addiction diagnosis; Mahmood et al. 2010), in which greater alcohol hangover symptoms predicted worse verbal learning and memory scores for NC, but not for CU.

Of the 12 EO studies examining memory and learning, seven found memory and learning deficits.

Visual Spatial

Only four studies (two EO studies) examined differences in visual spatial functioning between CU and NC. Here, two studies found differences (CU one better/one worse). From this scarce evidence only subtle impairments in visual spatial functioning can be concluded. The EO studies found inconsistent results after sustained abstinence (Schweinsburg et al. 2010, Jacobus et al. 2014), while Medina et al. (2007a) found better visual spatial functioning in CU than in NC after four weeks of abstinence.

Functional Imaging

Seventeen studies examined neurocognitive alterations in CU compared to NC with functional imaging technology, and 16 studies found neurocognitive alterations. Quantifiable data ($n = 11$ studies) resulted in a medium ES of $r = .479$ (CI 95 % = [.409; .554]). There is clear evidence for differences in activation patterns between CU and NC even after a washout period of more than 14 days. It seems that differences in activation patterns are demonstrated in prefrontal, temporal and occipital as well as cerebellar regions. Bolla et al. (2005) reported greater activation in the left cerebellum and less activation in the right lateral orbitofrontal cortex and the right dorsolateral prefrontal cortex for CU. In the study of Pujol et al. (2014), CU showed increased functional connectivity in the core of the default and insula networks and in selective enhancement of functional anticorrelation between both. Schweinsburg et al. (2010) demonstrated an increased response in the right precentral gyrus clusters for CU. Also, this group reported significantly more activity during spatial working memory (*SWM*) relative to vigilance in adolescent CU in the right parietal cluster, but less activity during the use of SWM relative to vigilance than NC in right dorsolateral prefrontal cortex (Schweinsburg et al. 2008b). Sevy et al. (2008) reported decreased glucose metabolism in CU compared to controls after more than 12 weeks of abstinence. Herning et al. (2008) found that chronic CU was associated with reduced EEG power in alpha and beta bands at posterior sites, alterations that were associated with changes in cerebral perfusion and/or thyroid function. Herning et al. (2005) reported that the pulsatility index, a measure of cerebrovascular resistance, and systolic blood flow velocity were still significantly increased in heavy CU after a month of monitored abstinence. In a visual attention study, active CU with positive urine toxicology screens evidenced greater reductions in right prefrontal fMRI response than abstinent users (Chang et al. 2006), a finding that suggests a change in neural recruitment throughout the course of abstinence. Sneider et al. (2008) also examined changes over abstinence duration and found that while

cerebral blood flow levels begin to normalize with continued abstinence from cannabis after 28 days, specifically in frontal areas, other temporal and cerebellar brain regions show slower blood flow decreases. Only one study found no functional imaging differences between CU and NC: Jacobus et al. (2012) identified no relationships between cerebral blood flow and executive functioning, nonverbal memory, structural verbal memory, or visuospatial processing.

Eleven EO studies examined neurocognitive alterations in CU compared to NC with functional imaging technology, of which 10 studies found neurocognitive alterations.

Structural Imaging

Ten studies examined structural imaging differences between CU and NC, of which nine found differences. Quantifiable data ($n = 6$ studies) gave a small mean ES of $r = .287$ (CI 95 % = [.198; .371]). Structural differences are found in cortical areas such as the limbic system, the orbitofrontal region (decision making) or the hippocampus (memories) and in subcortical areas that are involved in emotion processing such as the amygdala as well as in the nucleus accumbens, a region that is central to the reward system. These differences are indicated by volume differences (esp. white matter volume). In a positron emission tomography (*PET*) imaging study, CB1 receptor density returned to normal levels after a time of abstinence (Hirvonen et al. 2012). Medina et al. (2007b) found smaller white matter volume in CU, and other than in controls, white matter volume was negatively associated with depressive symptoms for CU. Ashtari et al. (2011) found that heavy CU had significantly smaller left and right hippocampus volumes as compared to their matched controls, but no significant changes in the left and right amygdala volume. Matochik et al. (2005) found lower gray matter density in the right parahippocampal gyrus and greater density bilaterally near the precentral gyrus and the right thalamus in CU. In the same group, lower white matter density was found in the left parietal lobe and higher density around the parahippocampal and fusiform gyri compared to controls. Longer duration of marijuana use was significantly correlated with higher white matter tissue density in the left precentral gyrus. Three studies reported interaction effects: Female CU demonstrated comparatively larger PFC volumes while male CU had smaller volumes compared with same-gender controls (Medina et al. 2009). Another study from Medina et al. (2010) found that CU exhibited a larger inferior posterior (lobules VIII-X) vermis volume, and that larger vermis volumes were associated with poorer executive functioning.

Six EO studies examined structural imaging differences between CU and NC, and all six studies found differences.

Additional Meta-Analytic Information

Neurocognitive Performance The overall data basis is $N = 1.428$. A total of 31 studies reported neurocognitive outcome effects, while concerning five studies (about 16 %) supplied no applicable data to calculate ES. In Pillay et al. (2008) (motor function), 12 effects were reported. As these proved to be homogeneous after *Q*-testing, only one pooled effect size (*ES*) has been used for this study. As shown in Table 4, mean overall ES across all studies is $r_{mean} = .305$ with CI 95 % = [.254; .358], which amounts to a significant medium sized effect. However, *Q*-testing ($p = .000$) reveals that there could be population effects which allow only for limited generalizability. ES in motor function is significantly higher than in the remaining domains ($p \leq .005$), but Cohen's $q \leq .217$ gives only small ES. In terms of I^2, heterogeneity is typically low to medium even in highly significant *Q*-measures. In sum, in quantifiable studies, CU appear to be adversely affected in neurocognitive performances compared to NC. For assessing possible publication bias, a funnel plot based on 75 observed effects is given in Fig. 1. Upon inspection, it is slightly asymmetric, but this is because zero and small ES findings have been published and this does not speak for a publication bias, unless the tendency for underpowered studies counts as "bias".

Functional and structural imaging The overall data basis is $N = 732$. Seventeen studies (11 EO studies) examined alterations in neural activity in CU compared to NC with functional imaging technology. Of these 17 studies, 16 studies (10 EO studies) found functional alterations with a medium effect size of $r = .479$ (CI 95 % = [.409; .554]), while only one study did not. Ten studies (6 EO studies) examined structural imaging differences between CU and NC. Of these 10 (6) studies, 9 (5) found differences with a mean effect of $r = .287$ (CI 95 % = [.198; .371]), while only one (0) did not. Three studies reported interaction effects, one with life-time alcohol use and two with executive functioning. ES in functional imaging is significantly higher than in structural imaging ($p \leq .006$), but again Cohen's $q = .226$ gives only a small ES. In sum, 27 studies reported functional and structural imaging outcome effects, 10 (37 %) supplied no applicable data. As shown in Table 5, mean overall ES across all studies is $r_{mean} = .446$ with CI 95 % = [.383; .505], which amounts to a significant, almost large-sized effect. Thus, findings in studies with meta-analytic information suggest that CU are adversely affected in measures of functional and structural imaging compared to NC. But again, *Q*-testing ($p = .000$) reveals that there is limited generalizability, which is confirmed by the I^2-statistic that yields a low to medium heterogeneity. Possible publication bias is negligible as assessed by the funnel plot in Fig. 2, based on 54 observed effects. The plot is slightly asymmetric, but again this is because zero and small ES findings have been published, thus not speaking for a publication bias. Again, a small-samples-size

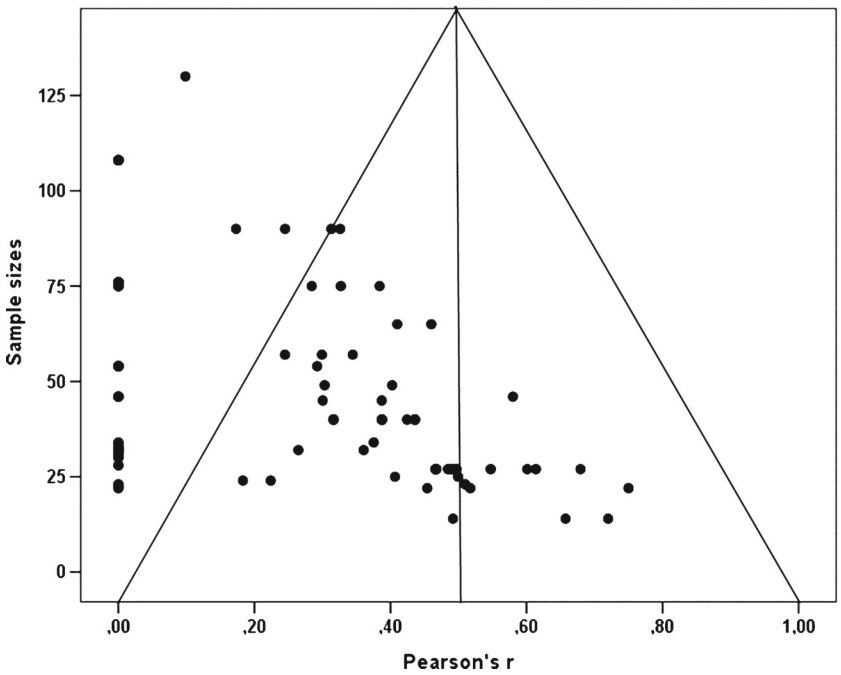

Fig. 1 Funnel plot on effect sizes of 31 peer-reviewed studies published between 2004 and 2015 comparing neurocognitive performance of cannabis users to healthy controls

Notes. Plotted are 75 effect sizes including a total sample size of $N = 1.428$.

"bias" appears, which comes as no surprise since there is considerable overlap between studies from Figs. 1 and 2.

Early versus later onset Concerning *neurocognitive performance*, EO studies (age of onset < 18 years) reveal a low heterogeneity ($I^2 = 39.4$ %) and an almost medium ES of $r_{mean} = .250$ with CI 95 % = [.173; .324], whereas studies employing subjects with a later age of onset show medium heterogeneity ($I^2 = 66.0$ %) and a medium ES of $r_{mean} = .359$ with CI 95 % = [.280; .432]. These ES differ with $q = .120$, i.e. a small ES according to Cohen's convention. Hence, in *neurocognitive performance*, neurocognitive impairment over

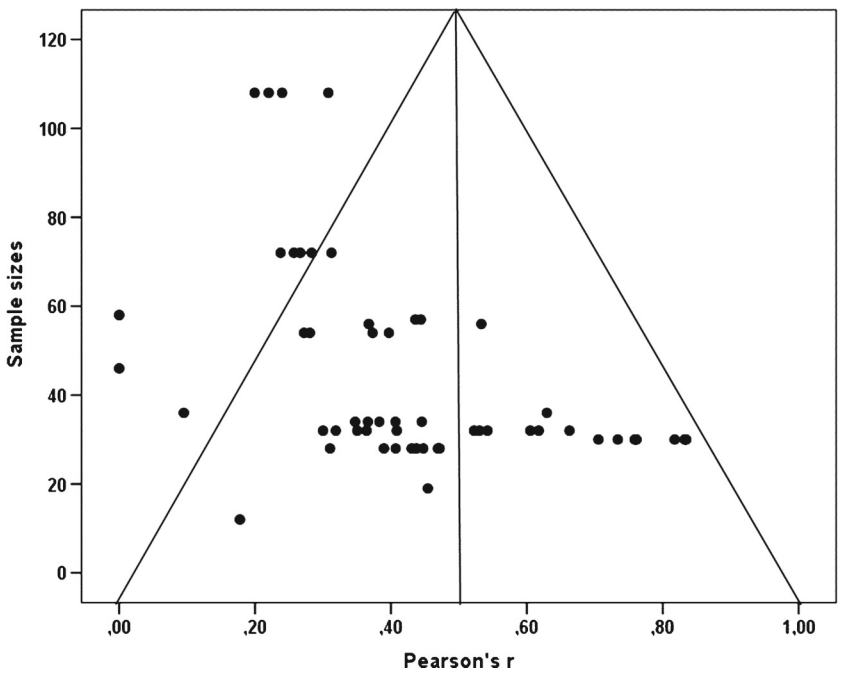

Fig. 2 Funnel plot on effect sizes of 27 peer-reviewed studies published between 2004 and 2015 comparing functional and structural imaging-data of cannabis users to healthy controls

Notes. Plotted are 54 effect sizes including a total sample size of $N = 732$.

all domains in CU with early age of onset seems *less* pronounced than in CU with later onset, compared to NC. In the area of *functional and structural imaging*, we found medium heterogeneity ($I^2 = 61.5\,\%$) and a large ES of $r_{mean} = .617$ with CI 95 % = [.487; .767] in EO studies, but in studies employing subjects with later onset we found no heterogeneity ($I^2 = 0$ % by definition; $Q = 12.50$ with $p = .641$) and a medium ES of $r_{mean} = .328$ with CI 95 % = [.246; .415]. These ES differ with $q = .380$ to medium ES. This finding is opposed to the finding in the area of neurocognitive performance because, here, differences in functional and structural imaging according ES in CU with early age of onset appear *more* pronounced than in CU with later onset, compared to NC.

Discussion

In this review, we sought to collect and report current knowledge concerning (1) the long-term effects of cannabis use on neurocognitive functioning after a prolonged abstinence period of at least 14 days, (2) the conclusiveness of findings, especially in studies providing data for meta-analysis, and (3) the question if EO of cannabis use exacerbates long-term effects of cannabis use.

Regarding (1) we conclude that findings concerning neurocognitive impairments remain heterogeneous. Most studies found some attention or concentration deficits in CU. Also, there is evidence that chronic CU might experience sustained deficits in the area of information encoding, storage and retrieval. Findings are mixed regarding impairments in inhibition, impulsivity and decision making for CU, but there is a trend toward worse performance. Four out of five studies found evidence that motor function remains impaired even after a time of abstinence, while the data basis concerning impairments in visual spatial functioning (four studies) is inconsistent. Functional imaging demonstrates clear differences in activation patterns between CU and controls. Structural differences are found in cortical areas, like the orbitofrontal and temporal region, or the hippocampus and in subcortical areas, such as amygdala and nucleus accumbens. On the whole, neurocognitive findings remain quite mixed even after our attempt to account for additional factors such as abstinence period, study quality, method, and onset of CU. This heterogeneity is more evident in some domains than in others. For example, while 16 out of 17 functional imaging/EEG studies find different brain activation patterns, blood flow or other alterations in CU, only five out of ten structural imaging studies report significant differences between CU and NC (three more report differences in interaction with confounders). This may be due to the fact that, while volumetric effects will be especially observed in heavy users, functional effects might generally be easier to detect. The heterogeneity of findings is discussed further below. In conclusion, we detected neurocognitive differences between CU in comparison to NC – mostly appearing as impairments – that lasted for more than two weeks of abstinence. Also, across all domains, functional and structural differences between CU and NC were found that persisted longer than 14 days after terminating THC consumption. Drawing associations between both domains (neuropsychological testing and imaging) is out of our scope, however this promising avenue should be pursued by further research.

Regarding (2) we conclude that, in most domains, substantial medium or large detrimental effects of cannabis use can be expected as per 20 similarly well-designed clinical trials which supply quantifiable data. ES and homogeneity measures suggest that in CU compared to NC, impairment in neurocognitive performances can be expected on a level of medium- to large-sized effects. We detected medium-sized heterogeneity/variance between populations, employed measures, and domains. About half of the studies are underpowered (Median $N = 32$). T-testing, for instance, requires a sample total of $N \geq 40$ to detect medium ES. This means that several small effects may have been overlooked and that, consequentially, the true detrimental effects of cannabis are probably still underestimated in this review due to shortcomings in respective reports.

Regarding (3), our results indicate that – in terms of ES – individuals with earlier EO of cannabis use differed more heavily from individuals with later age of onset in structural and functional imaging ($q = .380$), but comparatively less in neuropsychological tests ($q = .120$). These findings are more in accordance with a hypothesis that cannabis consumption is of serious impact in adolescence due to age-related vulnerability (Lisdahl et al. 2014; Volkow et al. 2014). We will return to the role of EO later.

All in all, the heterogeneity of findings warrants interpretation. Are some studies overrating the long-term effects of cannabis use – or were these effects not detected in some studies? In the following, we explore these possibilities further.

Why Sustained Effects of Cannabis use may be Overrated

There are two main arguments that speak for a cautious stance toward the effects we found:

First, there is the *time factor*: how long does abstinence need to persist before effects can truly be viewed as long-term? Even though our review already places a large emphasis on abstinence, it is unclear whether this suffices. Possibly, longer washout periods are required (Schreiner and Dunn 2012; Pope et al. 1995) due, for instance, to prolonged intoxication within fatty tissue (Iversen 2003). Animal studies showed reversible downregulation of brain CB1 receptors after chronic exposure to cannabis (Gonzalez et al. 2005; Sim-Selley 2003). Using positron emission tomography imaging, Hirvonen et al. (2012) detected reversible and regionally selective downregulation of brain CB1 receptors in human subjects who chronically smoked cannabis. The downregulation correlated with years of cannabis smoking and was selective

to cortical brain regions. After 4 weeks (26 ± 5 days) of continuously monitored abstinence from cannabis, CB1 receptor density returned to normal levels. This was the first direct demonstration of cortical CB1 receptor downregulation as a neuroadaptation that may promote cannabis dependence in the human brain. Therefore, reversibility may be possible after an abstinence period even longer than 14 or 28 days (as suggested by Schreiner and Dunn 2012; Grant et al. 2003), though there might be a dose-related aspect to reversibility (Verdejo-Garcia et al. 2007). In sum, study effects might still be viewed as temporary deficits due to a residue of cannabinoids in the brain, even if they cannot be attributed to acute withdrawal effects from stopping cannabis use, and not as effects of cumulative THC exposure on brain functioning.

Second, there is the question of *cause and effect*: some evidence suggests that preexisting brain abnormalities predate and predict the onset of substance use (e.g., Cheetham et al. 2012). The cross sectional nature of the studies at hand makes it impossible to judge whether chronic cannabis use impairs cognitive performance, or whether worse cognitive performance is a premorbid condition for problems with cannabis use. The same goes for the association of cannabis use with poorer educational attainment (Stiby et al. 2015). Possibly, both conditions are caused by common factors rooted in cognitive deficiencies (e.g., Gonzalez 2007). But not only cognitive deficits may influence an individual's development of dependency symptoms. The "pre-existing conditions", meaning state of health before first episode of THC could be influenced by a widespread conglomerate of factors: certain premorbid personality characteristics such as neuroticism, risk-taking or sensation-seeking as well as deficits in inhibitory control and affect regulation may also precede regular cannabis use (e.g., Crane et al. 2013; Gonzalez 2007; Jacobus et al. 2009a) and then be falsely attributed to cannabis consumption in neurocognitive tests. For example, could a correlation between craving and amygdala volume in abstinent cannabis users be mediated by frustration tolerance or inhibition control? And: should it be explained by focal damage specific to the amygdala through THC or are there more widespread alterations to brain networks involved like the reward system or emotional regulation (Padula et al. 2015)? Only few studies did control for family history of substance use disorders, early school dropouts, uncertain family structures or instable family situations as well as different sexual or cultural health awareness. Only incompletely did studies exclude subjects with Axis I comorbid psychiatric disorders. Thus, more evidence from longitudinal studies is needed to determine whether brain and cognitive abnormalities may have predated the onset of drug use, evidence gained by thoroughly controlling for a variety of potential confounders, e.g., pre-existing or current mood disorder, prodromal psychosis, other drug use, etc.

Why Sustained Effects of Cannabis use may Have Gone Undetected

There are three essential arguments that speak for taking the effects we found seriously:

First and foremost, there is the issue of deficient *methodology*. The studies at hand utilized advanced electrophysiological or imaging technology, too often employing very small sample sizes in a laboratory setting. It is very likely that more small to medium-sized effects would have been detected if more of the studies in this review had been supplied with adequate sample sizes. Also, there are barriers in comparability grounded in different definitions of terms such as "regular use" or "heavy use". Because it is impossible to administer cannabis to volunteers for many years in a laboratory, any study of long-term cannabis effects must rely on naturalistic studies of "users" in the field that are hard to compare (Pope et al. 1995). The attempt to exclude confounders such as premorbid cognitive reserves, psychiatric functioning, other substance use, or head injuries, neuropsychological deficits such as attention deficit hyperactivity disorder, conduct disorder, antisocial behavior and family history of schizophrenia render the remaining sample even more artificial with regard to clinical relevance. Other confounders such as anxiety (Jacobus et al. 2012), alcohol hangover symptoms (Mahmood et al. 2010), concomitant alcohol abuse (Jacobus et al. 2014) or nicotine withdrawal (Jacobsen et al. 2007) may have gone undetected in many studies. In addition, different neuropsychological tests are influenced in complex ways by attention and motivation of subjects, are diverse and hard to compare and have their limits regarding everyday life relevance. Or, as in the case of memory and learning, the localization of this domain within the brain is difficult, since it is broadly distributed within different regions of the brain such as the hippocampus, temporal lobe, and hippocampal formation (Garcia-Lazaro et al. 2012), and is highly dense in CB1 receptors. Functional differences compared to non-users were detected in adult and adolescent CU when activated and at rest status. Former CU showed different activity patterns compared to NC in functional imaging studies, however, these are unspecific and inconsistent in many cases. Structural magnetic resonance cannot provide information on the microstructure of the brain. Changes in neuronal numbers (for example, atrophy) or neuronal disorders (e.g., inflammation), or structural changes in synaptic density may possibly affect signal strength, which cannot be detected by structural magnetic resonance imaging methods (Matochik et al. 2005).

Second, there is the possibility of *compensatory mechanisms*. The human brain seems to be capable of a certain degree of functional reorganization between different brain regions. For instance, Chang et al. (2006) demonstrated an altered pattern of brain activation during visual attention in

chronic CU and greater activation in a reserve brain network in active CU suggesting neuroadaptation in the attention network due to chronic marijuana exposure. The recruitment of additional regions, such as the prefrontal cortex and hippocampus differentiates users from controls during cognitive performance (Block et al. 2002; Eldreth et al. 2004; Gruber and Yurgelun-Todd 2005; Jager et al. 2007). This may indicate that increased neurocognitive resources are required to maintain memory and executive processes in this group. Moderately greater task-related activation in these areas may reflect impaired efficiency of processing following cannabis use, such that more activation is required to maintain normal performance. This is broadly consistent with the cognitive efficiency hypothesis (Vernon 1983) proposing that more direct connections between task-critical brain regions may correspond to decreases in task-related neural activity and improvements in performance (Rypma and D'Esposito 2000). Within imaging, activation patterns were not always clearly distributed. In understanding why some studies found evidence and other not, a functional compensation (Rajah and D'Esposito 2005) could be an answer: CU recruit more neural tissue in areas with high CB1 receptor density such as the frontal lobe, hippocampal/temporal regions, basal ganglia, and cingulate cortices to adequately perform the tasks. Findings suggest a change in neural recruitment throughout the course of abstinence. This could relate to "residual drug effects or withdrawal symptoms during early abstinence, less need for neural compensation, or a change in neurocognitive strategy as the brain adapts to different stages of sobriety" (Schweinsburg et al. 2008b, p. 8). Some polymorphisms from the endocannabinoid system have been repeatedly associated with drug addiction (Lopez-Moreno et al. 2012) but their exact influence on neurocognitive impairments is not well understood. However, even though the brain seems to be capable of activating brain regions in CU that are not usually engaged in NC to achieve the cognitive demand, the real impact of such alterations in daily users' lives and its possibility to induce psychiatric disorders are still controversial (Martin-Santos et al. 2010).

Third, *inter-substance interactions* may have acted as confounders for (non-)effects. Prior research suggests differential neurocognitive effects of cannabis that depend on whether the individual also uses other substances (Lundqvist 2005; van Holst and Schilt 2011). There is marked inter-individual variability in the patterns of substance use (e.g., duration, frequency, dosage, type) and, with the exception of a few studies, most researchers were not able to definitively isolate the effects of a single specific substance due to a history of polysubstance use (Yucel et al. 2007). Some studies (e.g., Ashtari et al. 2011) did not control for the amount of alcohol or other drug intake. In other studies, interaction effects with binge drinking were found (Jacobus et al. 2009b; Mahmood et al. 2010). An under-investigated issue is whether concurrent use of different substances (e.g., cannabis and alcohol or methamphetamine) may potentiate the long-term adverse effects of each drug (Winward et al. 2014; Cuzen et al. 2015; Nguyen-Louie et al. 2015). For example, Jacobus et al. (2014) demonstrated significantly worse results in CU with concomitant alcohol use in the domains of complex attention, memory, processing speed, and visuospatial functioning compared to controls with limited substance use histories. However, the study was limited by a minimum abstinence of one day before testing and the question of different inter-substance effects. While synergistic or additive effects are plausible, there is also speculation that use of some substances may mask or protect against the neurocognitive sequelae of other substances (Jacobus et al. 2009b; Mahmood et al. 2010; Medina et al. 2007b; Schweinsburg et al. 2011). This even goes for inter-substance effects within cannabis itself: some evidence indicates that cannabidiol (*CBD*) might moderate the adverse effects of cannabis on mental health (Schoeler and Bhattacharyya 2013). As reported by Hermann (2011), cannabis and CBD can exert opposing effects that could be interpreted as a protecting factor. Next to neuroadaptive processes, this might explain the better performance by CU in some studies, for instance in the "visual spatial" domain (Chang et al. 2006; Medina et al. 2007a). To date, it is unclear whether increased cannabis content has been accompanied by changes in levels of CBD.

The Role of Early Onset

Impairments in EO users—compared to users with later onset of cannabis use—were less pronounced in neuropsychological tests than in the area of functional and structural imaging (for example, Jacobus et al. 2014). One possible explanation relates to the fact that imaging may be more powerful than test performance. As Pope et al. (2001a, b, p. 509) state, "individuals may display grossly normal performance on crude paper and pencil tests, yet show obvious abnormalities on more technically sophisticated tests, such as electrophysiological or imaging assessments". Thus, while structural or functional imaging technology may detect a small but statistically significant difference between EO and later onset users on a given measure, the behavioral consequences of this difference may be subtle and undetectable in self-report and neuropsychological test. This, however, does not explain our findings as well as the idea that persons who begin consumption at early age may display stronger compensatory mechanisms that are made visible by functional and structural imaging. Their brain may have learned to balance deficits better through longer experience, but it uses more neurocognitive resources in performing the same tasks than the brain of users with later onset. Also, the neuropsychological tests chosen may have failed to tap important domains: even if an individual does not underperform on a variety of quantitative measures, he or she might display "subtle impairments of judgment or

social inappropriateness that are readily detectable to a human observer" (Pope et al. 2001a, b, p. 509).

Perhaps our criterion of "onset under age 18" led to excluding studies with very similar subjects compared with the "EO" subjects (i.e., not much older when starting consumption). We may have missed some "EO" studies in cases where the information provided did not suffice to determine the exact age of onset. Besides this, age of onset is usually based on anamnestic data. The duration of time between consumption onset and testing is different for each individual. Both points in time are heterogeneous between studies, since neither age of onset nor an optimal age for testing are clearly defined. Hence, we can merely search for tentative associations between the beginning of consumption and trends regarding performance or activation. Above and beyond this, it is likely that there is another effect with far more impact than the age of substance use onset, and that is the intensity of use over time. Several findings indicate that there may be a *threshold level*, i.e. a dose-effect relationship that separates moderate and recreational CU from high-risk, heavy CU (Crean et al. 2011). In fact, all of the studies in our review explicitly referring to "heavy cannabis users" (Herning et al. 2005; Mahmood et al. 2010; Matochik et al. 2005; Pillay et al. 2008; Pujol et al. 2014) detected effects of CU in different domains. In contrast, results from a longitudinal cohort study by Pardini et al. (2015) suggest that adolescents who engage only in low to moderate marijuana use may experience an increase in observable attention and academic problems. However, these problems appeared to be minimal and were eliminated following sustained abstinence. It remains likely that residual impairments are linked to the duration and quantity of cannabis use, maybe more so than to the sole variable "age of onset"that – at least in the studies at hand – does not consistently separate moderate from heavy users. Block and Ghoneim (1993) compared intellectual functioning before the onset of drug use and in adult CU and NC by testing mathematical skills and verbal expression. They found that impairments depended on the frequency of chronic cannabis use. Cheetham et al. (2012) found smaller orbitofrontal cortex volumes at age 12 years that predicted initiation of cannabis use by age 16 years. The volumes of other regions (amygdala, hippocampus and anterior cingulate cortex) did not predict later cannabis use. In a longitudinal study, Fried et al. (2005) assessed cognitive functioning in 9- to 12-year-olds before the initiation of cannabis use, and again when youths were ages 17 to 21. After controlling for baseline performance and demographics, they found that current heavy cannabis use showed deficits in immediate and delayed memory, processing speed and overall IQ (cave: abstinence duration of 24 h). In general, prospective longitudinal studies have provided evidence for additional cognitive and brain abnormalities following the onset of CU that are above and beyond premorbid differences in personality, cognition and brain structure (Maurage et al. 2009; White and Batty 2012; Hicks et al. 2012; Meier et al. 2012; Jacobus et al. 2014; Nguyen-Louie et al. 2015). In the Dunedin study conducted in New Zealand, Meier et al. (2012) collected neuropsychological data of individuals at age 13 and again at age 38, after a pattern of persistent cannabis use had developed (although the status of abstinence was not asserted by testing). Persistent cannabis use was associated with neurocognitive decline broadly across domains of functioning, even after controlling for confounders such as education level. Impairment was concentrated among adolescent-onset CU, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neurocognitive functioning among adolescent-onset CU.

Limitations

Regarding evidence level, studies did not exhibit much variance, so this criterion did not yield particularly meaningful differences for interpretation (studies of 2+ versus 2++ design quality according to SIGN). We tested if ES were biased depending on study quality. In neurocognitive function measures, ES was $r = .343$ (CI 95 % [.283; .400]) in 2+ studies, and $r = .202$ (CI 95 % [.082; .318]) in 2++ studies. Though studies of better design quality reveal lower ES than those of lower quality here, the difference is not significant ($Z = 0.557$; $p = .289$). In functional and structural imaging measures, ES was $r = .449$ (CI 95 % [.376; .517]) in 2+ studies, and $r = .434$ (CI 95 % [.287; .562]) in 2++ studies. Again, the difference between studies of different design quality is not significant ($Z = 0.048$; $p = .481$).

Seventeen of the included 38 empirical studies and three of the above-mentioned reviews were conducted by the same laboratory in San Diego/California (*SDCA;* research group around S.F. Tapert) which might hint at some bias in publications. However, in *neurocognitive performance,* both SDCA studies ($I^2 = 49.7$ %) and others ($I^2 = 59.3$ %) are of medium heterogeneity and their ES (SDCA $r_{mean} = .216$; others $r_{mean} = .368$) differ only with a small effect ($q = .156$; Cohen 1988). Thus, we assume the same underlying population effect could have been measured. In *functional and structural imaging* studies, SDCA studies ($r_{mean} = .673$) and others ($r_{mean} = .392$) do differ with a medium ES ($q = .402$), and SDCA studies reveal a high heterogeneity ($I^2 = 72.0$ %) whereas the others reveal zero heterogeneity ($I^2 = -4.8\ \% \approx 0\ \%$ by definition). But, inspecting Table 3, we assume that heterogeneity in SDCA imaging studies mainly reflects the variety of measures employed by this research group rather than population effects. In sum, we consider any possible bias contributed by the SDCA studies negligible.

Other factors further limit the interpretation of our results. For one thing, the methodological heterogeneity described above as well as differences in subjects, particularly with regards to amount and duration of cannabis use, make

comparisons between studies difficult. For instance, drug amount used prior to abstinence was operationalized as "joints per day" or duration of time was "6 times per week". The variability in the respondent's definition of a 'joint' was as large as was the variability in "length of use" that was defined as "the time from initial use to time of current abstinence period" in some studies and as "beginning of time with heavy consumption" in others. Though these are common kinds of limitations in literature reviews, they must be mentioned here. Also the definition and measurement of our outcome parameters is difficult. For example what exactly are executive functions? One concept of executive functions could be that they are a heterogeneous psychological construct summarizing cognitive processes such as planning, task flexibility, impulsive control or problem solving as well as decision making and execution. It is not hard to understand the difficulty of subsuming all these different aspects in order to make one clear statement. Next, the inclusion criterion of a two week abstinence may have led to exclusion of subjects with poorer executive functions who were not able to refrain from the drug in this period of time. The characteristics of a drug-using lifestyle such as higher risk-taking make head injuries during intoxication hard to control. This plays a role in measuring neurocognitive performance. The cross-sectional nature of the studies at hand limits the interpretation of cause and effect as well as the domains included here, something that must be remarked after decades of cannabis research. Of specific relevance here are questions of co-occurring psychiatric disorders, including mood, anxiety, personality and especially psychotic disorders. Finally, gender as a variable of possible influence has not yet been adequately addressed. Research on the pharmacology of alcohol shows that men and women are affected differently. Several of the reported studies use all-male samples, and frequently, males are over-represented.

Where to go from Here

There is no easy explanation for complex reality. Like others before, this systematic review encountered shortcomings in preceding research and revealed certain desiderata. It is our goal to foster the ongoing scientific discussion on potential risks and neurocognitive long-term effects in CU. In this sense, this review contributes to the body of information towards a responsible social and health policy on cannabis and its use. Results are heterogenic and until now not fully understood. In our review we found no clear and general associations between neuropsychology, neurocognition and neuromorphology. However, our findings add a neurocognitive aspect to the growing body of evidence documenting the long-term psychosocial problems associated with phases of regular cannabis consumption (Wadsworth et al. 2006; Richer and Bergeron 2009; van Ours and Williams 2009; Best et al. 2005; Flory et al. 2004). They also point out barriers to a deeper understanding of neurocognitive effects caused by cannabis use that are yet to be overcome. We need studies with larger sample sizes that possess a larger generalizability and enable researchers to identify small(er) effects, also because a statistically small ES can be of major clinical relevance. And as Hall (2015) stated "there is a need for larger, better-controlled neuroimaging studies that use standardized tasks and measures" (p. 24). Also, we need better classification of terms and more accurate assessment methods with regard to predictors, confounders, and outcomes. Twin studies like Lyons et al. (2004) would help in the area of comparability and untangling cause and effect such as the abovementioned issue of preexisting brain abnormalities. Finally, we need more longitudinal-design studies. Recently, there have been first efforts to gain longitudinal data (Squeglia et al. 2014; Nguyen-Louie et al. 2014; Pardini et al. 2015). An ideal study would obtain neuropsychological testing results from a large general population, and then obtain neuropsychological results many years later, after some of the individuals had become CU and combining functional as well as structural information of the human brain. By taking into account a broader array of variables, longitudinal studies can put neurocognitive research back into proportion by uncovering the brain's role in shaping young and heavy cannabis consumer's trajectories toward adverse psychosocial outcomes over time.

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Authors' contributions FG, SK, SB planned the design, in-/excluded eligible literature and drafted the manuscript. PMS contributed methods, consulting and critical revision. PMS, SB, FG, SK analyzed and interpreted data. Under SB's supervision, JB and LvO collected data, researched articles, and graded studies. FG, RT were involved in all parts of the review as general supervisors of the research group. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interests All authors declare that there is no conflict of interest.

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