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Cannabis and its effects on driving skills

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Highlights :

- Cannabis impairs cognitive and psychomotor performances
- An 8-hour delay after maximal effects is recommended for cannabis self-treatment
- Blood THCCOOH level > 40 µg/l suggests regular cannabis use and long-term impairment
- No correlation was found between psychomotor task performance and THC blood levels
- Acute cannabis consumption nearly doubles the risk of a collision

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Abstract :

Traffic policies show growing concerns about driving under the influence of cannabis, since cannabinoids are one of the most frequently encountered psychoactive substances in the blood of drivers who are drug-impaired and/or involved in accidents, and in the context of a legalization of medical marijuana and of recreational use. The neurobiological mechanisms underlying the effects of cannabis on safe driving remain poorly understood. In order to better understand its acute and long-term effects on psychomotor functions involved in the short term ability and long-term fitness to drive, experimental research has been conducted based on laboratory, simulator or on-road studies, as well as on structural and functional brain imaging. Results presented in this review show a cannabis-induced impairment of actual driving performance by increasing lane weaving and mean distance headway to the preceding vehicle. Acute and long-term dose-dependent impairments of specific cognitive functions and psychomotor abilities were also noted, extending beyond a few weeks after the cessation of use. Some discrepancies found between these studies could be explained by factors such as history of cannabis use, routes of administration, dose ranges, or study designs (e.g. treatment blinding). Moreover, use of both alcohol and cannabis has been shown to lead to greater odds of making an error than use of either alcohol or cannabis alone. Although the correlation between blood or oral fluid concentrations and psychoactive effects of THC needs a better understanding, blood sampling has been shown to be the most effective way to evaluate the level of impairment of drivers under the influence of cannabis. The blood tests have also shown to be useful to highlight a chronic use of cannabis that suggests an addiction and therefore a long-term unfitness to drive. Besides blood, hair and repeated urine analyses are useful to confirm abstinence.

Keywords : THC; cannabis; psychomotor effects; fitness to drive; driving.

Introduction

Growing concerns are emerging worldwide regarding cannabis policies reforms that involve the legalisation of cannabis for therapeutic and recreational uses in the context of a regulated commercial cannabis market with major consequences on the incidence on driving while intoxicated and in assessment of the fitness to drive. An example is the situation in Colorado State as reported in the World Drug Report 2015 [1]. According to the Colorado State Patrol, marijuana was related to 12.2 per cent of all citations for driving under the influence of any substance in 2014, while among road accidents involving fatalities the number of drivers who tested positive for marijuana doubled from 37 in 2006 to 78 in 2012. However, the authors indicate in their report that several years will be required before any change specifically attributable to retail marijuana sales and traffic deaths is evident. Moreover it has been shown that early onset of cannabis use, in adolescence or young adulthood, could lead to impairing effects on brain structures including the precuneus (integrated functions), the hippocampus (learning and memory), the prefrontal networks (executive function) and the subcortical networks (habits and routines) [2,3], and is associated with both cannabis dependence and driving under the influence of cannabis [4].

In this context, specific criteria must be established for assessing drivers' ability and fitness to drive. Therefore, field and/or laboratory experimental studies on the acute and long-term effects of cannabis on psychomotor skills are crucial to improve road safety. According to the recommendations provided by the guidelines for research on driving under the influence of drugs [5] (table 1), experimental studies have first assessed the acute effects of cannabis on neurocognitive functions required in normal driving tasks on the automative, control and executive planning levels of behaviour, using neuropsychological, simulator and on-road testing. Several studies have then also suggested that, in case of heavy cannabis use, a long-term impairment in neuropsychological tests performance could be observed after cannabis use [6-8], and may persist even after a period of abstinence [9-11]. In this non-systematic review,

PubMed, Google Scholar and Web of Science databases were used to identify and select publications up to year 2016 dealing with driving and cannabis.

Table 1 Recommended neuropsychological tests to assess executive functions and the related levels of behavior involved in crash risks according to the International Council on Alcohol, Drugs, and Traffic Safety (adapted from Walsh et al.) [5].

Executive functions	Tests
Attention and information processing *(executive planning)*	Choice reaction-time Selective attention task Focused attention task
Cognition and judgment *(executive planning)*	Tower of London task
Divided attention *(control behavior)*	Dual attention task
Motor performance and maneuvers *(control behavior)*	Reaction time Car following
Perception *(control behavior)*	Time-to-collision task
Risk-taking and impulsivity *(executive planning)*	Stop signal task Iowa gambling
Sustained attention *(automative behavior)*	Mackworth Clock Test
Tracking and steering *(automative behavior)*	Road tracking Critical tracking Compensatory tasks

Observational epidemiology studies

According to the project "Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID)" [12] co-funded by the European Commission, the proportion of positive cannabis drivers involved in accidents vary from 4% to 14%. In comparison, delta-9-tetrahydrocannabinol (THC) was detected in the blood of a lower 1 to 7% of drivers not involved in a traffic accident. In Switzerland, a study conducted by Senna et al. [13] estimated that cannabinoids were present in 48% of blood samples gathered from suspected drug impaired drivers, being the most frequently encountered illicit drugs. A meta-analysis based on 9 studies, including 49,411

participants, concluded that the risk of a motor vehicle collision was almost twice in drivers under the influence of a recent cannabis use compared to sober drivers [14]. Moreover, car crash injuries after an acute marijuana intake appeared strongly associated with a regular (at least once a week) use during the previous 12 months [15], although the increased risk was no longer significant in occasional users after adjustment for confounders. However, the prevalence of drivers under the influence of cannabis involved in traffic accidents, as well as in the general driving population, remains poorly estimated. Knowing not only the frequency of crashes involving and not involving cannabis use and positive THC blood tests but also the frequency of noncrashes involving and not involving cannabis use and positive THC blood tests allows for the calculation of an odds ratio as an estimate of the crash risk. Selection bias of the different groups, confounding factors such use of other drugs may result in a distortion of the true relationship between cannabis exposure and crash risk. In addition to methodological choices, limitations of such epidemiological studies are due to the low reliability of self reported data collected from sober and drug-impaired drivers, and strongly depend on subject's consent and public policies.

Acute cannabis effects on driving ability

As epidemiological data show a more frequent involvement of cannabis users in car accidents, researchers used experimental studies, including laboratory, simulator and on-road testing, to assess the influence of cannabis effects on driving ability. Since the 70's experimental studies have shown that acute cannabis inhalation alters specific psychomotor skills or cognitive functions involved in normal driving tasks [16-19], and in a dose-related manner [20-23]. Reaction time measurement [17,23-27], divided attention tasks (DAT), critical tracking tasks (CTT) [24,28], or the response to an urgent task [16] appeared as mostly affected. Results of cannabis-induced acute effects on neurocognitive functions are detailed in

table 2. Subjects were defined as occasional smokers when cannabis use occurred less than once a week.

Table 2 Acute effects of cannabis on neurocognitive function in experimental studies.

References	n (M/F)	Cannabis history	THC doses		Recall tasks	Digit span tasks	Time perception	WCST	Stroop test	Stop signal task	Go / no-go task	BART	EDT	Tower of London	Gambling task	Virtual maze	Tracking task	Divided attention task	Reaction time	Mean speed	SD speed	Mean headway	SD headway	SDLP	Collisions
Battistella et al. (2013)	31	O	42 mg	Laboratory													X[a]								
Sewell et al. (2013)	44	O; F	0.015-0.05 mg/kg (IV)				X[b]																		
Metrik et al. (2012)	136	F	2.80%						X	X		ns	ns												
Schwope et al. (2012)	9/1	F	6.80%														ns	ns							
Theunissen et al. (2012)	24	O; F	500 μg/kg 13% (≈ 250-270 mg)							X[c]								X[b,c]							
Ramaekers et al. (2011)	15/6	F	400 μg/kg (≈ 28 mg)							ns				ns			ns	X							
Ramaekers et al. (2009)	12	O; F	500 μg/kg (≈ 35 mg)							X				ns			X[b]	X[b]							
Weinstein et al. (2008)	14	F	13; 17 mg				ns	X							X	X									
Vadhan et al. (2007)	36	F	1.8%; 3.9%												X										
Ramaekers et al. (2006)	14/6	NS	250; 500 μg/kg (≈ 17.5; 35 mg)							X				X	ns		X								
Lane et al. (2005)	5/5	O; F	1.77%; 3.58%												X										
MacDonald et al. (2003)	18/19	O	7.5; 15 mg (oral)		ns	X	X			X	ns				ns										
Hart et al. (2001)	10/8	F	1.8%; 3.9%		X	ns												X[e]	X						
Sexton et al. (2000)	15	NS	1.7%; 2.67%															X	ns						
Chait & Perry (1994)	14	NS	3.60%		ns	ns	X											X							
Anderson et al. (2010)	50/35	NS	22.9 mg	Simulator														X	ns	X	ns			ns	
Lenné et al. (2010)	47	NS	19; 38 mg															X	X	X	X	X	X	X	
Ronen et al. (2010)	7/5	O	13 mg															X		X	ns			ns	X
Ronen et al. (2008)	10/4	O	13; 17 mg																X	X	X			X	X
Ménétrey et al. (2005)	8	O	16.5; 45.7 mg (oral); 20 mg														X								
Papafotiou et al. (2005)	26/14	NS	14; 52 mg														X								
Sexton et al. (2000)	15	NS	1.7%; 2.67%																X	X				X	
Rafaelsen et al. (1973)	8	O	8; 12; 16 mg (oral)																X	ns					
Ramaekers et al. (2000)	9/9	NS	100; 200 μg/kg	On-road															ns			X		X	
Robbe (1998s1)	12/12	NS	100; 200; 300 μg/kg																	ns	ns			X	
Robbe (1998s2)	8/8	NS	100; 200; 300 μg/kg																ns			X		X	
Robbe (1998s3)	8/8	NS	100 μg/kg														ns								
Robbe (1998s4)	9/9	NS	100; 200 μg/kg																ns				X	X	

BART: Balloon anlogue risk task; EDT: experiential discounting task; F: frequent; NS: not specified; ns: not significant; O: occasional; SD:standard deviation; SDLP: standard deviation of lateral position; WCST: Wisconsin card sorting test; X: impaired.

[a] fMRI.

[b] In occasional users.

[c] Event-related potentials.

[d] PET.

[e] Improved.

Cannabis consumption has shown to impair working memory in frequent and occasional smokers after a 3.9% THC inhalation [29] as well as after IV administration of 2.5 mg of synthetic THC [30]. Some studies found an increased measure of impulsivity or motor inhibition of inappropriate behaviour during acute THC intoxication [23,26,31], in a dose-related manner [32], and in occasional and heavy users [33]. Divided attention tasks have been reported as particularly impaired by the acute effects of cannabis [16,19], showing significant performance decrease after a 2.67% THC dose [22] or after a 17 mg THC cigarette inhalation [32]. These

results were replicated in occasional and regular smokers [23,30,33,34], suggesting that an increased mental load may impair the information processing and thus the performance on a central task. Interestingly, other studies using DAT observed no significant differences after acute THC intoxication in a cohort of heavy chronic cannabis smokers [35], or even an improvement of daily cannabis users performances [29], suggesting an hypothetical adaptation to long-term cannabis exposure. Findings regarding the acute effect of cannabis on time perception or decision-making are discrepant. The altered estimation of time intervals found by Chait et al. [28] and MacDonald et al. [26] was not replicated with chronic cannabis users using inhaled [32] or IV administered THC doses [36]. Ramaekers et al. [23] found that recreational smokers were less likely to make correct decisions when tested with a Tower of London task after receiving ≈ 35 mg THC. These results have not been replicated with frequent smokers [33,34]. An increased risk-taking behaviour was observed after 3.6% and 17 mg THC doses [32,37]. Conversely, several investigators [23,26] found that the subjects were not significantly impaired in their performance after cannabis use [38].

In the recent years, brain imaging appears to be an important tool to understand the effects of cannabis use on brain structures and cerebral function. The authors reported a brain metabolism increase in areas related with motor coordination and attention, while it was reduced in those associated to visual integration of motion, suggesting an acute effect of cannabis on brain networks that modulate coordinated movement and driving, and thus on cognitive–motor skills [39]. Another study using a brain blood oxygen level dependent functional magnetic resonance imaging (BOLD-fMRI) paradigm based on a tracking task [40], which depicts changes in deoxyhemoglobin concentration consequent to task-induced or spontaneous modulation of neural metabolism, reported an impaired activity of areas involving the Control Executive network that operate once saliencies are identified. Lower attention to task performance may be explained by an increased self-oriented mental activity corresponding to the more intense activation observed in the rostral anterior cingulate cortex and ventromedial

prefrontal cortices. Event-related potentials (ERPs) recordings of occasional or heavy cannabis smokers while performing DAT and SST testing after a 500 μg/kg THC suggested the occurrence of a tolerance to some of the negative behavioural effects of cannabis intoxication [41].

Driving simulator and on-road experiments allowed a better in-depth investigation of cannabis effects on specific driving performances. However discrepancies between these two approaches have been detected, that can be explained by a poor or a lack of validation of simulated driving scenario with on-the-road-driving situations. Direct within subjects comparisons between cannabis-induced effects in simulated and on-the-road driving are, indeed, sparse. Veldstra et al. [42] found that the driving simulator was sensitive enough for demonstrating THC-induced effects particularly at higher doses. Treatment effects of THC on weaving were comparable with driving on the road. Mean headway distance to the preceding vehicle, braking latency, speed and road tracking precision appeared mostly altered [21,24,27,43]. Standard deviation of lateral position (SDLP) appeared to be one of the most sensitive road-tracking measure for revealing THC induced impairment as observed by Sexton et al. [22] in participants under the influence of a ≈ 20 mg THC dose. Subsequent studies have shown similar results after a range of 13 to 38 mg smoked THC doses [24,27], or after ingestion of 16.5 or 45.7 mg THC decoction or 20 mg synthetic THC (dronabinol) [43]. Other experiments found no significant increases in SDLP after a 13 mg dose [44] or after a 22.9 mg dose [45]. Such discrepancies could be explained by a variability in subjects cannabis history as well as in the time-lapse between the end of cannabis consumption and the beginning of the task. Former findings regarding the alteration of subject's behaviour under the influence of cannabis and facing an unexpected situation, resulting in a lesser risk taking, were cited by Smiley [18] and highlighted an impairment during DATs. More recent studies confirmed a dose-related increase in headway mean and SD after smoking a range of 13 to 38 mg THC doses, as well as a decrease in mean speed [22,24,27,44,45].

A serie of on-road studies conducted in the Netherlands by Robbe [21] are known as most relevant to characterize the influence of cannabis on driving skills. According to a pilot study, which defined the THC amount (20,8 mg ≈ 308 µg/kg) necessary to achieve a psychological "high" effect, dose escalation (100, 200 and 300 µg THC/kg body weight) was used to produce a significant increase in the SDLP, whereas blood plasma THC concentrations of the subjects were not related to their degree of impairment. The road-tracking and car-following tasks, performed in normal traffic, resulted in a dose-related SDLP increase and in a lengthened mean headway. The investigator suggested that, while road-tracking is basically controlled by an automatic information processing system more vulnerable to internal factors as THC than to environmental changes, the car-following task is more accessible for compensatory mechanisms, depending more on controlled information processing. Ramaekers et al. [46] described a similar road-tracking impairment using 100 or 200 *µ*g/kg THC doses and reported highest SDLP values 75 min after inhalation. Moreover, several studies have suggested that drivers under the influence of cannabis seem to be aware of their impairment and try to compensate by driving more cautiously or by renouncing to drive [24,27,43,45,47,48], in contrast to cocaine and alcohol using drivers.

Cannabis and alcohol combination

Several studies have been carried out to measure and compare the effects of cannabis alone, of alcohol alone or of their combination (table 3). While alcohol consumption is known to induce faster driving [44], cannabis has shown to reduce driving speed. Moreover, alcohol increases self-confidence estimation [27], whereas drivers under the influence of cannabis seem to be more cautious in accordance with some experimental results. On the roads, a Swiss prevalence study [13] pointed out that, among a population of drivers suspected of Driving Under the Influence of Drugs (DUID), cannabinoids were the most frequently encountered drugs (in 48% of total cases) and a combination with alcohol was detected in nearly 20% of the whole

blood samples that exceeded the 2.2 ng/ml THC Swiss legal technical limit (1.5 ng/ml with a 30% measurement uncertainty). Furthermore, a case-crossover self-report study [49] demonstrated a significant odds ratio (OR) increase for a driving-related injury after a cannabis and alcohol combined exposure relative to cannabis alone (OR of 10.9 and 5.8 respectively).

Table 3 Interaction of acute effect of combined cannabis and alcohol on neurocognitive function.

References	n (M/F)	Cannabis history	THC doses	BAC (g/l)		Recall tasks	Time perception	Stop signal task	Tower of London	DSST	Tracking task	Divided attention task	CTI	Body sway	Reaction time	Mean speed	SD speed	Mean headway	SD headway	Time out of lane	SDLP	Collisions	Driving impairment score
Ramaekers et al. (2011)	15/6	F	400 µg/kg (≈ 28 mg)	0.5; 0.7	Laboratory		ni	ni		ni	X												
Bramness et al. (2010)	5042												X										
Ronen et al. (2010)	7/5	O	13 mg	0.5							X												
Liguori et al. (2002)	8/4	NS	1.75%; 3.33% (≈ 16; 30 mg)	0.25; 0.5									ni										
Chait & Perry (1994)	14	NS	3.60%			ni	X			ni													
Hartman et al. (2015)	13/6	NS	2.9%; 6.7%	0.65	Simulator																X		
Downey et al. (2013)	25/15	24 F / 16 O	1.8%; 3%	0.3; 0.5																			X
Lenné et al. (2010)	47	NS	19; 38 mg	0.4; 0.6								ni			ni	ni	ni	ni	ni		ni		
Ronen et al. (2010)	7/5	O	13 mg	0.5												X	ni				X	X	
Liguori et al. (2002)	8/4	NS	1.75%; 3.33% (≈ 16; 30 mg)	0.25; 0.5																			
Ramaekers et al. (2000)	9/9	NS	100; 200 µg/kg	0.4	Road										X			X		X	X		
Robbe (1998s4)	9/9	NS	100; 200 µg/kg	0.4											X				X		X		

CTI: clinical test for impairment; DSST: digit symbol substitution test; F: frequent; ni: no interaction; NS: not specified; O: occasional; SD: standard deviation; SDLP: standard deviation to lateral position; X: interaction.

Several studies included laboratory experimental results on alcohol and cannabis combination effects. Although some studies reported additive cannabis–alcohol impairments, other reported no interactions. In occasional smokers, a time-estimation task showed that, in combination, the effects of a 3.6% THC dose and an alcohol consumption of 0.6 g/l for men or 0.5 g/l for women cancelled each other [28]. Although a 3.3% THC (≈ 30 mg) marijuana cigarette decreased the standing steadiness, and 0.5 g/l alcohol increased brake latency, no interaction was observed with their combination [50]. The authors speculated that the discrepancies observed were likely due to the method of investigation or an awareness of the participant's impairment. DATs have been shown to be a sensitive measure of the effects of cannabis on driving performance. Ronen et al. [44] found that both 13 mg THC and 0.5 g/l alcohol increase false-alarm responses and that combination of both substances lead to a strongest impairment. Ramaekers et al. [34] confirmed these results in a group of heavy

smokers after inhalation of 400 μg/kg (≈ 28 mg) THC and ingestion of 0.5 g/l or 0.7 g/l alcohol. This combination significantly impaired neurocognitive tasks performances, whereas THC affected only measures of divided attention and was potentiated by the impairing effects of alcohol. A retrospective cross-sectional forensic database study conducted by Bramness et al. [51] using a clinical test for impairment (CTI) concluded that most of the CTI items were not correlated to blood THC concentration, however the risk of being judged as an impaired driver increased in a blood THC concentration-related manner and was strongly associated with alcohol combination. For example, no alcohol or low (0.01-0.5 g/l) and high (> 0.5 g/l) BACs in combination with THC concentrations between 0.3 and 1.6 ng/ml were associated with 45%, 91% or 97% impairment, respectively.

Former results from simulator studies were unclear concerning cannabis and alcohol interaction. While one study showed a slight increase of the mean speed and the number of collisions with a 0.5 g/l BAC and 13 mg smoked THC relative to THC alone and no SDLP difference [44], another reported no interaction between all possible combinations of 0, 19 or 38 mg THC and 0, 0.2 or 0.5 g/l BAC in SDLP or in the mean speed [24]. Another experiment [52] involving the smoking of marijuana containing 0%, 1.8% or 3% THC together with a 0, 0.3 or 0.5 g/l BAC concluded that the driving performances were more impaired in the THC and alcohol combined conditions and that regular cannabis users displayed more driving errors than occasional users. More recently, a study confirmed that SDLP is a sensitive cannabis-impairment measure on which cannabis-alcohol effects are additive [53].

Impairing effects of cannabis and alcohol interaction were obvious in an on-road study that administered combinations of 100 or 200 μg/kg (≈ 7 or 14 mg) THC doses with a 0.4 g/l BAC. Cannabis alone increased SDLP in a dose-related manner and slightly altered other measures of the actual driving. However, when these low or moderate THC doses were taken in combination with a low dose of alcohol, the observed impairment was equivalent to that

resulting from a 0.9 or 1.4 g/l BAC, respectively. SDLP, time out of lane and reaction time were strongly increased [21,46].

A review by Sewell et al. [48] suggested that even a low dose of cannabis (6.25 mg) appears to impair driving skills requiring automatic functions such as tracking, although the more complex driving skills involving a conscious control are not impaired up to higher doses. Alcohol seems to cause impairment in the opposite way, and drivers under the additive effects of cannabis and alcohol taken together tend to compensate less effectively for their deficits and to have increased difficulties to cope with unexpected events. More recently, Dubois et al. [54] concluded that drivers positive for both alcohol and cannabis presented greater odds of making an error than those positive for either alcohol or cannabis only, and proposed that public health education should highlight the association between low levels of alcohol, cannabis and crash risk. Hartman et al. [55] suggested that cannabis could mitigate drivers' tendency to drive faster with alcohol.

Medical marijuana and driving

The relation of medical use of marijuana to driving performance remains unclear. As reviewed by Neavyn et al. [56], many experimental studies that examined psychomotor performance after cannabis smoking evaluated subjects over 2-3 hours or for at least 24 hours, but they did not measure driving skills directly. According to the results described earlier, it has been shown that the majority of psychomotor impairments occurs in the first 2 hours and disappears within 3 to 6 hours after smoking. Moreover, neither serum THC concentration nor cannabinoid tests were related to the degree of impairment and patients using marijuana as a self-treatment for medical purposes commonly achieve a subjective "high" leading to a very variable blood level. Therefore, Neavyn et al. [56] recommend that such patients abstain from driving for 8 hours after a subjective "high" and that healthcare providers should deliver information regarding the potential additive effects of alcohol and other psychoactive drugs.

Nevertheless, a positive trend in the proportion of marijuana positive drivers who were involved in a fatal crash was reported in Colorado since mid-2009 when legal medical marijuana became commercially available, although no similar change was observed in states where no medical marijuana was available [57].

Long term consequences of chronic cannabis use

The long-term effects of cannabis use on executive functions that are required for safe driving appeared to be related to the duration of use [58] even after several weeks of abstinence in former chronic heavy cannabis users, allowing the elimination of residual effects of acute cannabis intoxication. Some findings suggest that the cognitive deficits improve after cannabis is discontinued [59], but other show enduring impairments [60] mostly seen in decision-making, concept formation and planning (table 4).

Table 4 Long term effects of cannabis on neurocognitive function.

References	n (M/F)	Cannabis history	Abstinence	Tracking task	Divided attention task	FrSBe	Gambling task	PET	Digit span tasks	Stroop test	Inspection time	WAIS	WCST	Symbol digit	RAVLT	BSRT	BVRT	WMS	Time perception	ROCF	CVLT	Selective attention task
Bosker et al. (2013)	49 or 50	19 F; 30 or 31 ctrl	1; 2; 3 weeks	X	X																	
Verdejo-Garcia et al. (2006)	26/6	NS	> 2 weeks			X																
Bolla et al. (2005)	22	11 F; 11 ctrl	25 days				X	X														
Verdejo-Garcia et al. (2005)	32/6	NS	> 2 weeks						ns	ns												
Kelleher et al. (2004)	44	22 F; 22 ctrl	subacute								X[c]											
Lyons et al. (2004)	[redacted][b]	54 fF; 54 ctrl	> 1 year									X										
Whitlow et al. (2004)	16/4	10 O; 10 F	12 hours				X[d]															
Bolla et al. (2002)	19/3	F	28 days							X			X	X	X							
Pope et al. (2002)	116/48	NS	1; 7; 28 days							ns			ns			X	ns	ns				
Solowij et al. (2002)	97/38	102 F; 33 ctrl	17 hours							X[e]			ns		X				X			
Pope et al. (2001)	146/34	63 F; 45 fF; 72 O	28 days							ns			ns			X[d]	ns	ns				
Pope & Yurgelun-Todd (1996)	69/60	65 F; 64 O	19 hours							X[f]			X					ns		ns	X	
Solowij (1995)	22/6	fF	> 6 weeks[a]																			X

BSRT: Buschke's selective reminding test; BVRT: Benton visual retention test; CVLT: California verbal learning test; F: frequent; fF: former frequent; FrSBe: Frontal systems behavior scale; NS: not specified; ns: not significant; O: occasional; PET: positron emission tomography imaging; RAVLT: Rey auditory verbal learning test; ROCF: Rey-Osterreith complex figure test; WAIS: Wechsler adult intelligence scale; WCST: Wisconsin card sorting test; WMS: Wechsler memory scale; X: impaired.

[a]: mean 2 years.
[b]: twin pairs.
[c]: in subacute users.
[d]: in frequent users.
[e]: with additional interference condition.
[f]: in male.

A few studies have examined the long-term effects of cannabis use on working memory and found no differences between heavy and light cannabis smokers performances after a 19-hours abstinence [6] or in abstinent cannabis users compared to polysubstance users [61]. In

contrast, Solowij et al. [7] concluded that long-term heavy cannabis users perform less well than short-term and control users on memory after a 12-hours abstinence. This effect was still present beyond the period of intoxication and worsened with increasing years of regular cannabis use. As discussed by Crean et al. [62], the results of studies assessing the long-term effects of cannabis on inhibition and impulsivity appear to be mainly related to investigation strategies. The Wisconsin card sorting test (WCST) resulted in significant differences between cannabis users and control groups [9,10,59], whereas the Stroop test produced no significant differences [10,59,61,63], suggesting an impairment in the process of concept formation, planning or sequencing which are required to perform well in the WCST. In contrast, Solowij et al. [7] found an inverse relationship between duration of cannabis use and performance on a Stroop test with additional interference condition suggesting a vulnerability to task complexity with increasing demand. Verdejo-Garcia et al. [64] also evaluated the performance on decision-making and risk-taking tasks in a group of polysubstance abusers and found a slight impairment in the cannabis subgroup after a 25-days abstinence, in accordance with former findings suggesting that long-term heavy marijuana smokers make more costly decisions on a gambling task [65]. Several studies found no significant differences on attention or concentration abilities between heavy cannabis users who had remained abstinent from 28 days to one year and control subjects [10,59,61,63]. Conversely, Solowij et al. [66] examined cannabis users abstinent from 6 weeks to 2 years and found significant impairment of attention and concentration. These results were replicated by Bolla et al. [9] who reported long-term deficits in attention and concentration in a group of heavy, chronic cannabis users with a duration of abstinence of approximately 28 days. Bosker et al. [67] found that sustained cannabis abstinence moderately improved CTTs and DATs performance in chronic daily cannabis smokers, although impairment was still observable compared to controls after 3 weeks of abstinence. According to these findings, it has been suggested that some discrepancies in the results could be attributable to impairment in basic information processing abilities rather than in

attention. A study by Kelleher et al. [68] highlighted that heavy chronic cannabis users in the abstinent state showed slower information processing speed compared to non-cannabis users, which normalized after acute intoxication. They could then be at risk to resume cannabis smoking to avoid adverse effects of abstinence following chronic cannabis use.

Brain imaging sheds new light on the health consequences of chronic cannabis use. Firstly, Positron Emission Tomography imaging (PET) using a novel CB1 high affinity inverse agonist radioligand showed decreased CB1 receptor binding in living human cortical brain regions in chronic daily cannabis smokers [69]. This downregulation was found to be reversible after about 4 weeks of continuously monitored abstinence. Downregulation may underlie tolerance to effects of cannabis. Interestingly, CB1 downregulation did not occur in basal ganglia, midbrain and cerebellum, regions where CB1 receptors may drive the feeling of high and motor impairment. This observation may explain why tolerance develops for memory impairment, but not for the feeling of high or motor impairment. Secondly, Battistella et al. [70] using MRI and Voxel Based Morphometry provided evidence that regular cannabis use is associated with structural changes in specific brain regions. They observed in chronic cannabis smokers gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex; these regions are rich in CB1 receptors and functionally associated with motivational, emotional, and affective processing. Alteration in these brain areas may influence driving habits and skills.

Detection of drivers under the influence of cannabis

Although THC blood concentrations are not directly correlated with those in the brain that are responsible for adverse cognitive and behavioural effects [71], blood sampling has been shown to be the most effective way to detect a recent use of cannabis. In order to determine the level of impairment of drivers under the influence of cannabis, two broad approaches were proposed to screen cannabinoids in body fluids. First, several authors proposed to associate the

influence of acute effect of cannabis on driving with specific THC blood levels. Indeed, THC blood level is known to reach a peak of concentrations within 10 minutes, before dropping rapidly, remaining detectable for about 4-8 hours. However, the correlation between THC blood levels and the cannabis effects responsible for driver's impairment appeared to be non-linear, according to the complex pharmacokinetics and metabolism of THC. Second, according to the duration of impairment due to cannabis smoking observed in some pharmacodynamical studies, the calculation of the time-lapse between cannabis exposure and blood sampling, using a THC single concentration in blood or the THCCOOH / THC concentrations ratio (as suggested by Huestis et al. [72]), may indicate whether the adverse effect occurred during the time-period of THC influence or not. Nevertheless, according to Hartman et al. [73], a back-extrapolation of THC concentrations in blood during driving is difficult due to an unknown time after intake and interindividual variability in rates of decrease, and the authors recommend that blood sample is collected by trained officers at the start of impairment evaluation. Furthermore, among the broad range of psychoactive (e.g. 11-OH-THC, 8β-OH-THC) and non-psychoactive metabolites into which THC is metabolized, inactive THCCOOH may be still detectable in blood up to several hours or even days after consumption, as observed by Bergamaschi et al. [74]. Other cannabinoids found in lower concentrations in blood, such as THC-glucuronide, THC-A, cannabidiol or cannabinol, have also been advocated as possible markers of recent cannabis use [75,76].

Oral fluid, urine and hair are other biological matrices known to be useful for cannabis screening and interpretation of circumstances and frequency of use. The glucuronidated THC-COOH is notably excreted into urine where it can be easily detected from 30 minutes after ingestion to several weeks by a panel of physico-chemical methods. Although its detection demonstrates cannabis exposure, it provides no evidence of any impairment at the time of detection. Between 2003 and 2005, oral fluid drug testing devices have been evaluated by the European Rosita projects. None met the criteria for accurate and reliable tests. Moreover, no

reliable correlation between oral fluid and blood THC concentrations was found [77]. Conversely, oral fluid was supported as an interesting matrix for clinical and forensic cannabinoids screening in recent use, while a strong correlation with blood concentrations was observed (as reviewed by Lee and Huestis [78]). Nevertheless, the authors noted a need for a better understanding of the relationship between oral fluid THC cut-off concentration and impairment. More recently, Desrosiers et al. [79] proposed the Draeger DrugTest 5000 test cassette as a highly sensitive, specific and efficient on-site device for oral fluid cannabinoid detection. Although hair analysis is informative in the context of evidence of abstinence or demonstration of chronic use, a significant correlation with urine THCCOOH concentration or self-reported frequency has not been established and passive cannabis smoke contamination may occur (as discussed by Fabritius et al. [80]). Considering the large variations that exist between individuals with respect to the subjective and objective effects of cannabis, the standardized field sobriety tests (SFSTs) were proposed as a direct assessment of Driving Under the Influence of Cannabis (DUIC). If THC smoking significantly increased subjective effects of high and heart rate, with concentration-effect relationship, it demonstrated non-linear correlation with counter-clockwise hysteresis. The loop induced by the dynamic lag between THC effects and blood levels means that for a given concentration of THC, the subjective effect may be low or high depending on when the blood sample was taken, either during the upward or the downward phase of THC blood levels [35].

Limited evidence support the validity of using the SFSTs to establish impairment due to the adverse effects of cannabis. Papatofiou et al. [81] assessed the sensitivity of the SFSTs to measure an impaired driving behaviour after THC smoking on 40 participants exposed to either placebo, 1.74% or 2.93% THC and found results corresponding to those of a simulator testing in 65.8% to 76.3% after low and high THC doses consumption, respectively. These authors then considered the SFSTs as a moderate predictor of driving impairment following the consumption of THC. Two studies conducted by Bosker et al. [82,83] compared the percentage of impaired

cannabis users on the SFST to the sensitivity of oral fluid devices after receiving a combination of 400 µg/kg THC and 0.5 or 0.7 g/l BAC, or to the actual driving performance in occasional or heavy users who received 10 and 20 mg medicinal dronabinol. Excepting the one leg stand test, SFST components have not been shown to be consistent predictors of cannabis effects on behavioural performance and are insensitive measure to discriminate between occasional or heavy users. Another trial of 80 participants [84] highlighted the limited reliability of the SFST to identify subjects who have recently used cannabis in the absence of any evidence of driving impairment. Finally, findings reported by Porath-Waller et al. [85] confirmed that cannabis is associated with adversely affected performances on the one leg stand test and support its use to identify DUID.

Driving under influence of cannabis: policies

As noted earlier, the relationship between cannabinoids levels in blood and behavioural or cognitive impairments is not obvious. In order to identify DUID which need to be prosecuted, the DRUID project defined three approaches, so called: the "impairment approach if the driver shows clear symptoms of impairment whether in his personal behaviour or its driving style", the "*per se* limits if a drug is found in a driver's body fluid above a defined cut-off concentration", and the " two-tier system" that combined *per se* limits with an impairment approach (table 5). Per se threshold estimations were based on risk analysis taking cannabis effects on driving ability into account. According to meta-analyses of laboratory studies, Ramaekers et al. [86] suggested that THC whole blood levels greater than 7 ng/ml were associated with maximal performance impairment. In a subsequent paper, a THC whole blood level from 1 ng/ml was proposed as a suitable numerical limit [87]. As a criterion to assess the frequency of cannabis use and to objectively distinguish heavy from occasional users, Fabritius et al. [80] measured THCCOOH levels of whole blood samples collected in two groups of smokers in order to propose a THCCOOH threshold concentration. According to previously published experimental

data, heavy use has shown to be associated with concentrations higher than 40 µg/l, suggesting this threshold as a cut-off for DUIC disqualification. Furthermore, THCCOOH concentrations below 3 µg/l would not require medical assessment.

Table 5 Cannabis cut-off values applied in some European countries in whole blood (upper part of the table) or plasma/serum (middle part of the table), and in United States, Canada and Australia (lower part of the table) (adapted from Verstraete et al., Armentano, Wong et al.) [77,88,89].

Countries	Policies	THC (ng/ml)	THCCOOH (ng/ml)
Switzerland	Zero tolerance	1.5 + 30%	
Denmark	Impairment	1	
Finland	Two-tier	1	5
France	Two-tier	1	
Great Britain	Impairment	2	10
Greece	Impairment	1	
Ireland	Impairment	2	5
Italy	Zero tolerance	0.5	0.5
Norway	Impairment	1.3	
Poland	Zero tolerance	2	50
Portugal	Zero tolerance	3	5
Belgium	Two-tier	1[a]	
Germany	Two-tier	1[a]	
Luxembourg	Impairment	2[a]	
Slovenia	Zero tolerance	0.3[a]	5[a]
Australia	Impairment	-	-
Canada	Impairment	-	-
United States	Impairment or zero tolerance[b]	1 - 5[b]	1 - 35[b]

[a] According to Giroud et al. [90], the thresholds determined for whole blood may be recalculated for serum by multiplying by a 1.7 factor.

[b] Arizona, Delaware, Georgia, Illinois, Indiana, Iowa, Michigan, Rhode Island, Utah and Wisconsin impose zero tolerance per se thresholds. Nevada, Ohio, Pennsylvania and Washington enforce per se levels for THC and/or its metabolites.

Conclusions

In Western countries, cannabinoids are the most frequently encountered illicit drugs detected in the blood of impaired or injured drivers, leading to awareness that these substances

are detrimental to safe driving. To take account of this particular situation, road traffic laws have been adapted accordingly during the last 20 years. The new implementation in a few countries of a regulated cannabis market, the recent changes in legislative regulations that ease the availability of cannabis for medical and/or recreational use pose a new challenge to road safety experts. In this context, on-the-road and/or laboratory experimental studies have shown dose-dependent alteration of several cognitive and psychomotor functions, particularly in road tracking by increasing lane position variability and also by slightly impairing the ability to maintain a constant headway while following another car. These results are consistent with brain imaging investigations that highlighted changes in activations of brain areas and networks potentially involved in drivers' skills adversely affected by cannabis smoking. Moreover consumption of both alcohol and cannabis leads to greater odds of making an error than use of either alcohol or cannabis alone, suggesting that public health education should highlight the association between low levels of alcohol, cannabis and crash risk. Nevertheless, the correlation between blood levels and psychoactive effects of THC is challenged by a non-linear time relationship, making the detection of DUIC and the interpretation of single blood THC levels difficult. Three approaches to identifying DUIDs have been proposed: per se laws specify that drivers have committed an offence if their THC blood level exceeds a specified value. This value indicates impairment or corresponds to an increased risk of accident. Zero tolerance regulation relies on performances of analytical methods and of their limits of quantification. Combination of both approaches has been also implemented. The demonstration of regular cannabis use is based on other strategies. In this respect, a driver's whole blood THCCOOH concentration higher than 40 µg/l was proposed as a strong suggestion of heavy use, requiring further medical assessment of the fitness to drive.

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Table 1 Recommended neuropsychological tests to assess executive functions and the related levels of behavior involved in crash risks according to the International Council on Alcohol, Drugs, and Traffic Safety (adapted from Walsh et al.) [5].

Executive functions	**Tests**
Attention and information processing *(executive planning)*	Choice reaction-time Selective attention task Focused attention task
Cognition and judgment *(executive planning)*	Tower of London task
Divided attention *(control behavior)*	Dual attention task
Motor performance and maneuvers *(control behavior)*	Reaction time Car following
Perception *(control behavior)*	Time-to-collision task
Risk-taking and impulsivity *(executive planning)*	Stop signal task Iowa gambling
Sustained attention *(automative behavior)*	Mackworth Clock Test
Tracking and steering *(automative behavior)*	Road tracking Critical tracking Compensatory tasks

Table 2 Acute effects of cannabis on neurocognitive function in experimental studies.

References	n (M/F)	Cannabis history	THC doses		Recall tasks	Digit span tasks	Time perception	WCST	Stroop test	Stop signal task	Go/no-go task	BART	EDT	Tower of London	Gambling task	Virtual maze	Tracking task	Divided attention task	Reaction time	Mean speed	SD speed	Mean headway	SD headway	SDLP	Collisions
Battistella et al. (2013)	31	O	42 mg	Laboratory													X[a]								
Sewell et al. (2013)	44	O; F	0.015-0.05 mg/kg (IV)				X[b]																		
Metrik et al. (2012)	136	F	2.80%						X	X		ns	ns												
Schwope et al. (2012)	9/1	F	6.80%														ns	ns							
Theunissen et al. (2012)	24	O; F	500 μg/kg 13% (≈ 250-270							X[c]								X[b,c]							

			mg)																
Ramaekers et al. (2011)	15/6	F	400 μg/kg (≈ 28 mg)							ns			ns				ns	X	
Ramaekers et al. (2009)	12	O; F	500 μg/kg (≈ 35 mg)							X			ns				X[b]	X[b]	
Weinstein et al. (2008)	14	F	13; 17 mg				ns	X						X	X				
Vadhan et al. (2007)	36	F	1.8%; 3.9%											X					
Ramaekers et al. (2006)	14/6	NS	250; 500 μg/kg (≈ 17.5; 35 mg)							X			X	ns			X		
Lane et al. (2005)	5/5	O; F	1.77%; 3.58%											X					
MacDonald et al. (2003)	18/19	O	7.5; 15 mg (oral)		ns	X	X			X	ns			ns					
Hart et al. (2001)	10/8	F	1.8%; 3.9%		X	ns												X[e]	X
Sexton et al. (2000)	15	NS	1.7%; 2.67%															X	ns
Chait & Perry	14	NS	3.60%		ns	ns	X											X	

(1994)													
Anderson et al. (2010)	50/35	NS	22.9 mg	Simulator		X	ns	X	ns			ns	
Lenné et al. (2010)	47	NS	19; 38 mg			X	X	X	X	X	X	X	
Ronen et al. (2010)	7/5	O	13 mg			X		X	ns			ns	X
Ronen et al. (2008)	10/4	O	13; 17 mg				X	X	X			X	X
Ménétrey et al. (2005)	8	O	16.5; 45.7 mg (oral); 20 mg dronabinol		X								
Papafotiou et al. (2005)	26/14	NS	14; 52 mg		X								
Sexton et al. (2000)	15	NS	1.7%; 2.67%				X	X				X	
Rafaelsen et al. (1973)	8	O	8; 12; 16 mg (oral)				X	ns					
Ramaekers et al. (2000)	9/9	NS	100; 200 μg/kg	On-road			ns			X		X	
Robbe (1998s1)	12/12	NS	100; 200; 300					ns	ns			X	

			μg/kg									
Robbe (1998s 2)	8/ 8	NS	100; 200; 300 μg/kg					ns		X		X
Robbe (1998s 3)	8/ 8	NS	100 μg/kg				ns					
Robbe (1998s 4)	9/ 9	NS	100; 200 μg/kg					ns			X	X

BART: Balloon anlogue risk task; EDT: experiential discounting task; F: frequent; NS: not specified; ns: not significant; O: occasional; SD:standard deviation; SDLP: standard deviation of lateral position; WCST: Wisconsin card sorting test; X: impaired.

[a] fMRI.

[b] Inoccasional users.

[c] Event-related potentials.

[d] PET.

[e] Improved.

Table 3 Interaction of acute effect of combined cannabis and alcohol on neurocognitive function.

References	n (M/F)	Cannabis history	THC doses	BAC (g/l)		Recall tasks	Time perception	Stop signal task	Tower of London	DSST	Tracking task	Divided attention task	CTI	Body sway	Reaction time	Mean speed	SD speed	Mean headway	SD headway	Time out of lane	SDLP	Collisions	Driving impairment score
Ramaekers et al. (2011)	15/6	F	400 μg/kg (≈ 28 mg)	0.5; 0.7	Laboratory			ni	ni		ni	X											
Bramness et al. (2010)	50 42												X										
Ronen et al. (2010)	7/5	O	13 mg	0.5								X											
Liguori et al. (2002)	8/4	NS	1.75%; 3.33% (≈ 16; 30 mg)	0.25; 0.5										ni									
Chait & Perry (1994)	14	NS	3.60%			ni	X			ni													
Hartman et al. (2015)	13/6	NS	2.9%; 6.7%	0.65	Simulator																X		
Downey et al. (2013)	25/15	24 F / 16 O	1.8%; 3%	0.3; 0.5																			X
Lenné et al. (2010)	47	NS	19; 38 mg	0.4; 0.6								ni			ni	ni	ni	ni	ni		ni		
Ronen et al. (2010)	7/5	O	13 mg	0.5												X	ni				X	X	
Liguori et al. (2002)	8/4	NS	1.75%; 3.33% (≈ 16; 30 mg)	0.25; 0.5																			
Ramaekers et al. (2000)	9/9	NS	100; 200 μg/kg	0.4	Road										X			X		X	X		
Robbe (1998s4)	9/9	NS	100; 200 μg/kg	0.4											X				X		X		

CTI: clinical test for impairment; DSST: digit symbol substitution test; F: frequent; ni: no interaction; NS: not specified; O: occasional; SD: standard deviation; SDLP: standard deviation to lateral position; X: interaction.

Table 4 Long term effects of cannabis on neurocognitive function.

References	n (M/F)	Cannabis history	Abstinence	Tracking task	Divided attention task	FrSBe	Gambling task	PET	Digit span tasks	Stroop test	Inspection time	WAIS	WCST	Symbol digit	RAVLT	BSRT	BVRT	WMS	Time perception	ROCF	CVLT	Selective attention task
Bosker et al. (2013)	49 or 50	19 F; 30 or 31 ctrl	1; 2; 3 weeks	X	X																	
Verdejo-Garcia et al. (2006)	26/6	NS	> 2 weeks			X																
Bolla et al. (2005)	22	11 F; 11 ctrl	25 days				X	X														
Verdejo-Garcia et al. (2005)	32/6	NS	> 2 weeks						ns	ns												
Kelleher et al. (2004)	44	22 F; 22 ctrl	subacute								X[c]											
Lyons et al. (2004)	54[b]	54 fF; 54 ctrl	> 1 year									X										
Whitlow et al. (2004)	16/4	10 O; 10 F	12 hours				X[d]															
Bolla et al. (2002)	19/3	F	28 days							X			X	X	X							
Pope et al. (2002)	116/48	NS	1; 7; 28 days							ns			ns			X	ns	ns				
Solowij et al. (2002)	97/38	102 F; 33 ctrl	17 hours							X[e]			ns		X				X			
Pope et al.	146	63 F;	28							ns			ns			X[d]	ns	ns				

(2001)	/34	45 fF; 72 O	days							
Pope & Yurgelun-Todd (1996)	69/ 60	65 F; 64 O	19 hours		X[f]		X		ns	ns	X	
Solowij (1995)	22/ 6	fF	> 6 weeks[a]									X

BSRT: Buschke's selective reminding test; BVRT: Benton visual retention test; CVLT: California verbal learning test; F: frequent; fF: former frequent; FrSBe: Frontal systems behavior scale; NS: not specified; ns: not significant; O: occasional; PET: positron emission tomography imaging; RAVLT: Rey auditory verbal learning test; ROCF: Rey-Osterreith complex figure test; WAIS: Wechsler adult intelligence scale; WCST: Wisconsin card sorting test; WMS: Wechsler memory scale; X: impaired.

[a]: mean 2 years.

[b]: twin pairs.

[c]: in subacute users.

[d]: in frequent users.

[e]: with additional interference condition.

[f]: in male.

Table 5 Cannabis cut-off values applied in some European countries in whole blood (upper part of the table) or plasma/serum (middle part of the table), and in United States, Canada and Australia (lower part of the table) (adapted from Verstraete et al., Armentano, Wong et al.) [77,88,89].

Countries	Policies	THC (ng/ml)	THCCOOH (ng/ml)
Switzerland	Zero tolerance	1.5 + 30%	
Denmark	Impairment	1	
Finland	Two-tier	1	5
France	Two-tier	1	
Great Britain	Impairment	2	10
Greece	Impairment	1	
Ireland	Impairment	2	5
Italy	Zero tolerance	0.5	0.5
Norway	Impairment	1.3	
Poland	Zero tolerance	2	50
Portugal	Zero tolerance	3	5
Belgium	Two-tier	1[a]	
Germany	Two-tier	1[a]	
Luxembourg	Impairment	2[a]	
Slovenia	Zero tolerance	0.3[a]	5[a]
Australia	Impairment	-	-
Canada	Impairment	-	-
United States	Impairment or zero tolerance[b]	1 - 5[b]	1 - 35[b]

[a] According to Giroud et al. [90], the thresholds determined for whole blood may be recalculated for serum by multiplying by a 1.7 factor.

[b] Arizona, Delaware, Georgia, Illinois, Indiana, Iowa, Michigan, Rhode Island, Utah and Wisconsin impose zero tolerance per se thresholds. Nevada, Ohio, Pennsylvania and Washington enforce per se levels for THC and/or its metabolites.