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REVIEW

The acute effects of cannabinoids on memory in humans: a review

Mohini Ranganathan · Deepak Cyril D'Souza

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Abstract
Rationale Cannabis is one of the most frequently used substances. Cannabis and its constituent cannabinoids are known to impair several aspects of cognitive function, with the most robust effects on short-term episodic and working memory in humans. A large body of the work in this area occurred in the 1970s before the discovery of cannabinoid receptors. Recent advances in the knowledge of cannabinoid receptors' function have rekindled interest in examining effects of exogenous cannabinoids on memory and in understanding the mechanism of these effects.
Objective The literature about the acute effects of cannabinoids on memory tasks in humans is reviewed. The limitations of the human literature including issues of dose, route of administration, small sample sizes, sample selection, effects of other drug use, tolerance and dependence to cannabinoids, and the timing and sensitivity of psychological tests are discussed. Finally, the human literature is discussed against the backdrop of preclinical findings.
Results Acute administration of Δ-9-THC transiently impairs immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner. In particular, cannabinoids increase intrusion errors. These effects are more robust with the inhaled and intravenous route and correspond to peak drug levels.
Conclusions This profile of effects suggests that cannabinoids impair all stages of memory including encoding, consolidation, and retrieval. Several mechanisms, including effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter (GABA, glutamate, acetyl choline, dopamine) release, have been implicated in the amnestic effects of cannabinoids. Future research in humans is necessary to characterize the neuroanatomical and neurochemical basis of the memory impairing effects of cannabinoids, to dissect out their effects on the various stages of memory and to bridge the expanding gap between the humans and preclinical literature.

Keywords Cannabinoids · Cannabis · Marijuana · Δ-9-THC · Memory · Learning · Cognition

Abbreviations

CB	cannabinoid
CB1	cannabinoid 1 receptor
Δ-9-THC	delta-9-tetrahydrocannabinol
CBD	cannabidiol

M. Ranganathan · D. C. D'Souza
Schizophrenia Biological Research Center,
VA Connecticut Healthcare System,
West-Haven, CT, USA

M. Ranganathan · D. C. D'Souza
Abraham Ribicoff Research Facilities,
Connecticut Mental Health Center,
New Haven, CT, USA

M. Ranganathan · D. C. D'Souza
Department of Psychiatry, Yale University School of Medicine,
New Haven, CT, USA

D. C. D'Souza (✉)
Psychiatry Service, 116A, VA Connecticut Healthcare System,
950 Campbell Avenue,
West Haven, CT 06516, USA
e-mail: deepak.dsouza@yale.edu

Introduction

Cannabis or marijuana is the most widely used illicit drug in the Western hemisphere, and among its many effects it is known to produce cognitive effects. The most robust cognitive effects of cannabis are on memory. However, the mechanism of action of these compounds has long remained an enigma. Recent advances in the understanding of cannabinoid receptor function have renewed interest in the effects of cannabis and other cannabinoids on cognition.

Reviewing the effects of cannabinoids on memory is relevant to both normal physiology and pathological states. Cannabis use disorders are not uncommon; therefore, understanding the effects of cannabinoids on memory is important. More recently, there is growing interest in the association between cannabis use and schizophrenia, a disorder characterized by memory impairments that are considered to be core manifestations of the illness. In fact, laboratory studies with cannabinoids are receiving increasing scrutiny as possible "models" of schizophrenia. Preclinical findings suggest a role for the endocannabinoid system in memory processes. Finally, with an explosion in preclinical research on the endocannabinoid system, it seems timely to revisit and review the literature on the effects of cannabinoids on memory in humans.

The objective of this paper is to review the acute effects of cannabinoids on short-term memory in humans and to examine their effects on the various stages of memory. One other objective of this paper is to draw attention to the possible role of the endocannabinoid system in the physiology of memory by briefly discussing the preclinical literature. While there is considerable debate about the long-term effects of cannabinoids, this paper only reviews the acute effects of cannabinoids. Similarly, while there is evidence that cannabinoids impair other cognitive function, e.g., attention and time perception, this paper only reviews the effects of cannabinoids on short-term memory. The literature on the cognitive effects of cannabinoids is divided into roughly two eras; one predominantly in the 1970s and one after the discovery and characterization of a brain endocannabinoid system in the 1990s. These two phases, while valuable and informative, are challenging to compare because of widely differing methodologies including differences in tasks, controls, etc., which will be discussed later. Furthermore, relative to other drugs known to impair memory, e.g., benzodiazepines and ketamine, the cannabinoid literature presents some unique challenges. The cannabinoid literature includes studies using herbal cannabis, unassayed amounts of delta-9-tetrahydrocannabinol (Δ-9-THC) and varying routes of administration, which as discussed later, make the interpretation of the literature difficult. In this paper, the clinical literature will first be reviewed, followed by a review of the more recent preclinical literature with the goal of providing potential mechanistic explanations and stimulating further research in the field.

As a prelude to reviewing the studies about the effects of cannabinoids on memory, we first review the constituents of cannabis, issues related to the dose and route of administration of cannabinoids, and cannabinoid receptor function. The large majority of pharmacological studies were conducted with herbal cannabis and its principal active ingredient Δ-9-THC. Herbal cannabis contains more than 600 compounds, more than 70 of which are cannabinoids. Of these, Δ-9-THC is thought to be the ingredient responsible for most of the cognitive and behavioral effects of cannabis.

In addition to the classic natural cannabinoids found in herbal cannabis, there are a number of synthetic cannabinoids that have been studied in man. These include dronabinol, nabilone, and levonantradol. Dronabinol is synthetic Δ-9-THC. The 9-trans keto-cannabinoid nabilone is a synthetic analog of Δ-9-THC that was developed as an antiemetic and is available in Europe as Cesamet. Levonantradol was developed as an analgesic agent, but was abandoned because of a high incidence of intolerable behavioral side effects.

Δ-9-THC has a long half-life of approximately 4 days (Johansson et al. 1988). Its principal active metabolite, 11-hydroxy-THC, is more potent than Δ-9-THC. The time course of 11-hydroxy-THC blood levels correlates well with the psychological effects of inhaled and oral Δ-9-THC (reviewed in Agurell et al. 1986). Therefore, in relating cognitive or behavioral data with blood levels, both Δ-9-THC and 11-hydroxy-THC blood levels need to be considered.

Route of administration

The pharmacokinetics and effects of Δ-9-THC vary as a function of its route of administration. In attempting to quantify the dose of Δ-9-THC extracted from a typical cannabis cigarette, several factors need to be considered including, but not limited to, the weight of a cannabis cigarette, the potency of Δ-9-THC in the herbal cannabis preparation, and the presence of other cannabinoids (Karniol and Carlini 1973; Karniol et al. 1974, 1975; Turner et al. 1980). Furthermore, the amount of Δ-9-THC delivered is influenced by several factors including the rate of inhalation, depth of puffs, duration of puffs, volume inhaled, extent of breath-holding after inhalation, the amount lost by smoke escaping into the air or respiratory dead space, vital capacity, the length of cigarette smoked, the adeptness of smoking, and the subject's overall experience in titrating the dose. A typical cannabis cigarette contains varying doses of Δ-9-THC (0.3% to as much as 10% in hashish). Standard NIDA cigarettes, which have been used in many of the studies to be

discussed, weigh about 0.35 g and contain various concentrations of Δ-9-THC. Only 10–25% of the Δ-9-THC content of a cannabis cigarette enters the circulation when smoked (Adams and Martin 1996). With smoking, peak plasma concentrations of Δ-9-THC are reached within 3–10 min. Psychotropic effects start within seconds to a few minutes, reaching a peak after 15–30 min and then tapering off within 2–3 h. With oral consumption, the absorption of Δ-9-THC is slower and its bioavailability is lower (about 4–12%). An extensive first pass metabolism further reduces bioavailability after oral administration (McGilveray 2005). Peak plasma concentrations occur after 1–2 h and multiple peaks may be seen (Agurell et al. 1986; Grotenhermen 2003). With oral ingestion, psychotropic effects set in with a delay of 30–90 min, reach their maximum after 2–3 h, and last for about 4–12 h (Agurell et al. 1986; Hollister et al. 1981; Ohlsson et al. 1980, 1981). Intravenous dosing follows the pharmacokinetics and pharmacodynamics (Fig. 1) of the inhaled route, though blood levels tend to be higher. While Δ-9-THC is consumed by the oral or inhaled route, nabilone is administered by oral route, and levonantradol is administered by intramuscular route.

Given that cannabinoids have been studied using the oral, sublingual, inhaled, intramuscular, and intravenous routes, the literature on the effects of cannabinoids on memory is a little more challenging to interpret than studies with other drugs known to impair memory. For example in most studies with ketamine, the drug is administered by the intravenous route; therefore, these studies are easier to compare. Thus, the intensity, onset. and duration of cannabinoid effects on memory should be interpreted in the context of the route of drug administration.

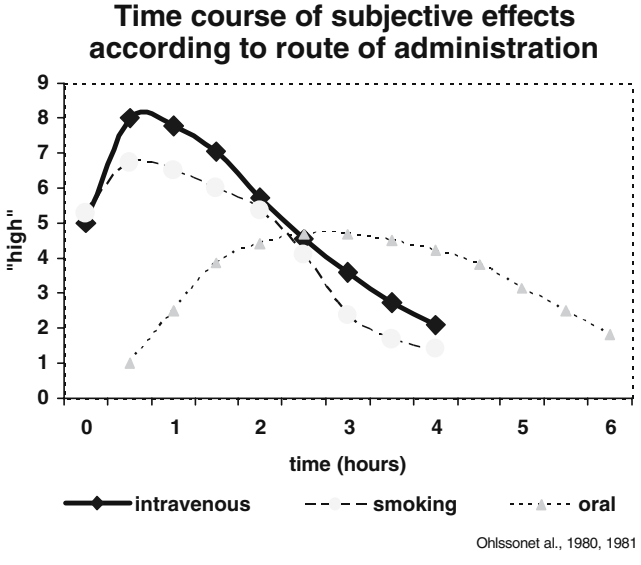

Fig. 1 Figure shows the time course of the acute behavioral effects of Δ-9-THC (feeling high) as a function of route of administration (intravenous, inhaled and oral)

Withdrawal, tolerance, and dependence

There is evidence of a withdrawal syndrome, albeit mild, with the cessation of cannabis use (Budney et al. 2003, 2004), as well as tolerance to the effects of cannabinoids (reviewed in Howlett 2004; Iversen 2003, 2005; Tanda and Goldberg 2003). In fact, tolerance to the memory disruptive effects of cannabinoids has been shown in animals to involve adaptation by specific hippocampal neurons (Hampson et al. 2003). The large majority of studies reviewed here included subjects who were using cannabis regularly and were therefore likely to be tolerant to some of the effects of cannabis. Furthermore, variability in defining subject samples with regard to extent of cannabis exposure and interval from last use may complicate comparison across studies. None of the studies that we are aware of included cannabis-naïve individuals. Therefore, in reviewing pharmacological studies involving cannabis users, it is important to consider whether withdrawal, tolerance, and residual carryover effects confound the results.

Cannabinoid receptors

Thus far, two cannabinoid receptors have been identified and cloned, and a third has been recently described. The CB1 receptor (Matsuda 1997; Matsuda et al. 1990) is a G-protein coupled receptor and is distributed extensively in the forebrain and the cerebellum (molecular layer), with the highest density in the basal ganglia, substantia nigra (pars reticulata), and hippocampus and peripherally in the spleen, tonsils and other viscera (Herkenham et al. 1990; Mailleux et al. 1992; Mailleux and Vanderhaeghen 1992; Tsou et al. 1998; Fig. 2). The behavioral, cognitive, and physiological effects of cannabis are believed to be primarily mediated via this receptor.

The hippocampus includes the CA1–CA3 regions and the dentate gyrus. Information entering the hippocampus flows through the dentate gyrus proceeding through the CA3 and CA1 regions to the subiculum. The CA1–CA3 regions have pyramidal cells as their main neurons. Both the dentate gyrus and the CA1–CA3 regions (with CA3 being more dense than CA1) have higher densities of CB1 (Heyser et al. 1993), correlating well with the known effects of cannabinoids on learning and memory.

Anandamide and 2-arachidonoyl glycerol (2-AG) are the main endogenous agonists of CB1 receptors. Note that Δ-9-THC is a partial agonist with modest affinity (K_i=35–80 nmol) and low intrinsic activity (Compton et al. 1992; Gerard et al. 1991; Howlett et al. 2002; Matsuda et al. 1990; Mechoulam et al. 1995), while levonantradol is a full agonist (Fig. 3) and SR141716A (Rimonabant) is a potent antagonist.

The second cannabinoid receptor CB2 (Munro et al. 1993), distributed mainly peripherally (reviewed in Demuth

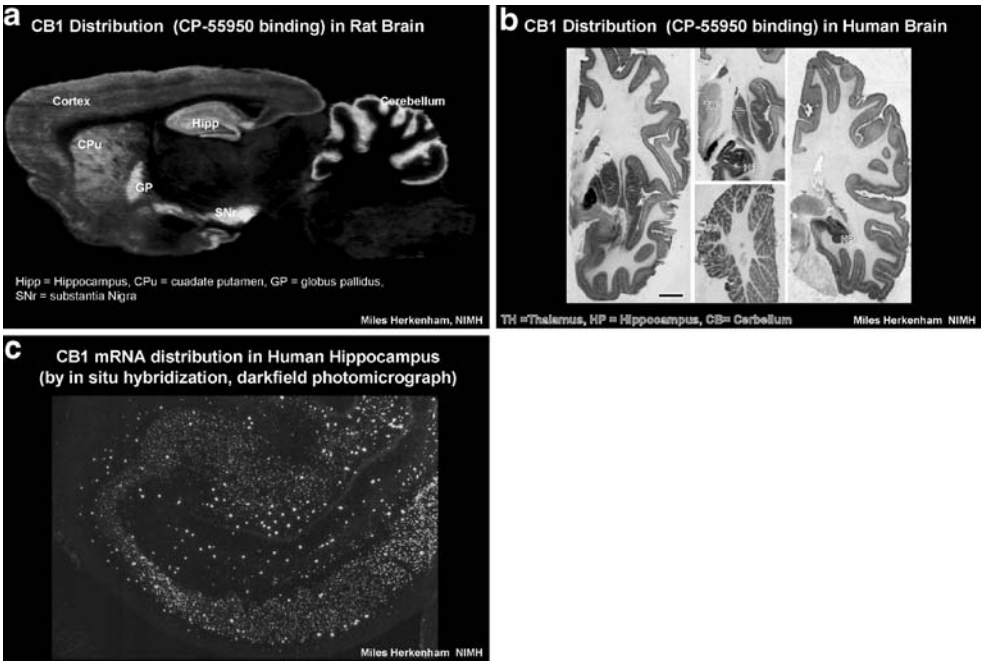

Fig. 2 The figures show the distribution of cannabinoids receptors in specific brain areas. **a** Distribution of CB1 receptor in the rat brain. **b** Distribution of CB1 receptor in the human brain. **c** Distribution of CB1 receptor mRNA in the human brain (Miles Herkenham, personal communication)

and Molleman 2005), is not relevant to the cognitive effects of cannabinoids. There are a number of putative novel non-CB1/CB2 receptors that have been identified, some of which may be relevant to the cognitive effects of cannabinoids (Baker et al. 2006).

Memory subtypes and processes

Since there is considerable variability in the terminology relating to memory in the published literature, we now briefly define some basic concepts related to memory subtypes and processes (reviewed in Atkinson and Shiffrin 1968; Baddeley 1999; Stout and Murray 2001). While there are several classifications of memory, for the purpose of this review we have classified memory into short term, long term, and working memory.

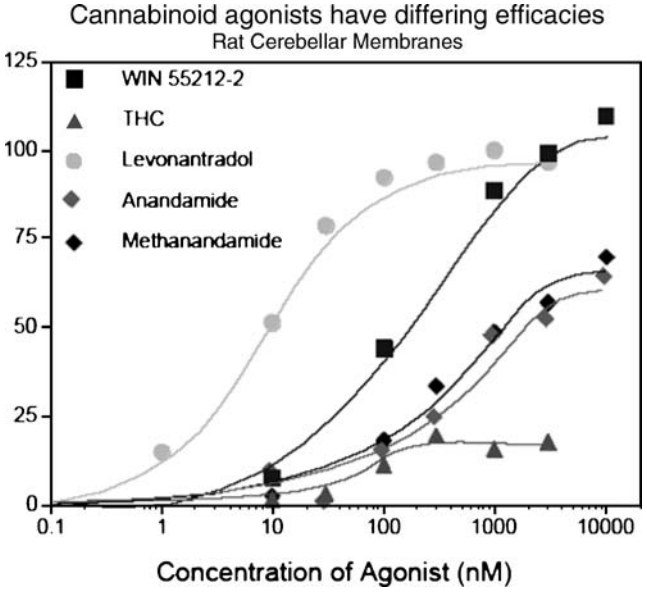

Fig. 3 Figures show varying efficacies of cannabinoid agonists at the CB1 receptor. Note that Δ-9-THC is a partial agonist

Short-term memory (STM) refers to that process or processes involved in the storage of a limited amount of information for a limited amount of time, usually considered less than a minute. To facilitate longer retention, information must be periodically rehearsed so that it will reenter the short-term store and be retained for longer periods of time. Furthermore, STM appears to have a limited capacity, which is estimated to be about seven "chunks" of information; the latter is roughly equivalent to about seven digits or about five to six words. In contrast, *long-term memory* (LTM) refers to the process or processes by which unlimited amount of information is stored indefinitely. However, the existence of a genuine distinction between STM and LTM remains controversial. One line of evidence supporting the existence of a short-term store is that anterograde amnesia affects LTM while leaving STM intact. Long-term memory can be divided into explicit and implicit memory. Explicit or declarative memory involves the conscious recollection of past events or experiences and is typically measured through recall or recognition. It includes semantic and episodic memory (Tulving 1972). Semantic memory refers to the memory of the meaning of words, facts, rules, or abstract concepts. Episodic memory or autobiographical memory is the memory of temporally dated events or episodes (Tulving and Markowitsch 1998). It includes time, place and

associated emotions. In contrast, implicit memory or procedural memory involves demonstrations of learning or facilitation of performance in the absence of conscious recollection.

Working memory (WM) in this review refers to processes that subserve a very limited capacity system to store and manipulate information for short durations. WM is distinct from STM in that it places emphasis on the manipulation of the stored information (Baddeley 1999; Baddeley et al. 2001). It is central to cognitive function and its disruption can result in impaired processing across many other cognitive domains. It is believed that there are distinct circuits underlying the manipulation and maintenance components of working memory with manipulation corresponding with dorsolateral prefrontal cortex activity and maintenance corresponding with ventral prefrontal activity (reviewed in Fletcher and Henson 2001).

The cannabinoid literature is dominated by studies examining cannabinoid effects on short-term, episodic and verbal memory. A small number of studies examined cannabinoid effects on short-term spatial episodic memory, working memory, and long-term semantic memory. There is a paucity of data on whether cannabinoids impair procedural or implicit memory. While a multitude of tests were used to study the effects of cannabinoids on memory, making comparisons across studies somewhat difficult, verbal memory is most commonly tested using a number of word list tasks. Typically, subjects learn a supraspan list of words presented over multiple trials. Capacity for learning is assessed with immediate free recall, delayed free recall, cued and recognition recall (reviewed in Stout and Murray 2001). In verbal recall tasks, word lists are sometimes semantically organized into categories. On immediate recall tasks, subjects are presented with information, which they are asked to recall immediately. Sometimes the information is presented across trials to aid learning, and in such cases, the sum of information recalled across trials (total immediate recall) is used as an index of learning. During this task, recall of information not previously presented in the list to be learned is referred to as intrusions. Typically, after a variable delay (1–30 min), subjects are asked to recall the information previously presented without cues (delayed free recall) and then with the help of cues (delayed cued recall). Finally, in the recognition recall task, subjects are presented with a list of items that includes some of the items initially presented for learning; erroneously recognized information on this task is referred to as false positive. Immediate recall yields items from short-term memory, while delayed recall yields items from long-term memory. A minority of studies of cannabinoid effects have employed nonverbal memory tasks such as reproduction of previously learned geometric designs, e.g., the Rey Osterrieth complex figure tests.

The processes involved in learning and memory include encoding, storage or consolidation and retrieval, and relevant to long-term memory, reconsolidation. These processes may not be entirely dissociable, but are important constructs in understanding memory. Encoding refers to the stage of processing during which information is initially learned, followed by a series of changes that consolidate the new information against disruption and decay. Retrieval refers to the access of previously encoded memories. Dissociating these effects can be accomplished to some extent with a variety of manipulations. Various cognitive manipulations have been used in an attempt to locate episodic memory deficits with respect to encoding and retrieval stages. However, identification of stage-specific deficits is problematic because a performance deficit could reflect impaired encoding, consolidation, or retrieval (or all). Usually, deficits in immediate recall after learning trials on memory tasks are attributed to encoding deficits. Thus, administering a drug during encoding but terminating its effects before consolidation and retrieval would isolate encoding deficits. However, given the long half-life of Δ-9-THC, this would be difficult to do. The preservation of immediate free recall combined with impairments in delayed free recall implicates consolidation/storage deficits. Impairment on free recall combined with intact recognition memory implicates retrieval deficits. Impaired recall of information encoded before drug administration would suggest storage or retrieval deficits.

With this background, we now review the effects of cannabinoids on memory. Results from studies on the effects of cannabinoids on short-term, episodic memory and working memory are discussed below.

Short-term, episodic memory

These results of studies have been organized according to the task: word, prose, digit recall. In addition, Table 1 provides a list of studies reviewed with route and dose of Δ-9-THC, test administered and results.

Word recall

In the early 1970s, Abel (1971) tested the effect of unassayed doses of cannabis on recall of word lists learned before (n=49) and after ad lib smoking (n=10) in cannabis users. Relative to placebo, cannabis had no effect on the accuracy of delayed recall (both free and recognition) of word lists that had been presented before smoking. In the subsequent placebo-controlled study, the author tested the effect of cannabis on encoding. Both free and recognition recall of word lists presented after Δ-9-THC administration were significantly impaired by cannabis. The lack of effects

Table 1 List of studies reviewed with route and dose of Δ-9-THC, test administered, and results

Year	Author	Subjects	Estimated Δ-9-THC dose	Route	Tests	Results (only THC effects)			
						IFR	DFR	Recognition recall	Miscellaneous
1970	Tinklenberg et al.	Eight infrequent users	0, 20, 40, 60 mg	O	Digit span	↓ Forward and backward span at all doses			
1971	Abel et al.	49 users and nonusers	unassayed	I	Word lists (10 per list)		Trend ↓	↔ DRR	↑ False positive in DRR
		10 users			Word lists (12 per list)	↓	↓		
1972	Tinklenberg et al.	15 users	0, ~26 mg; ETOH	O	GDSA, RMS	↔ GDSA errors, ↔ digit (RMS) span			
1973	Darley et al.	12 regular users	0, 20 mg	O	Word lists	↔ Accuracy, ↑ RT			
1974	Darley et al.	48 occasional users	0, 20 mg	O	Word lists (20 per list), fixed vs. free rehearsal	↓	↔	↔	Recency effect maintained; fixed rehearsal did not reduce THC effects
1974	Vachon et al.	8 occasional users	0, 25 mg	I	CPT	↔CPT			
					DSST	↓ Learning curve, ↓ accuracy and speed on DSST			
1976	Miller et al.	40 moderate users	0, 9.4 mg	I	Word lists: cued (first letter) vs uncued	↓ IFR in cued and uncued condition. Cues did not significantly improve the impaired recall in the THC condition; ↑ intrusions			
1977	Pfefferbaum et al.	16 users	0, 0.3 mg/kg	O	Word lists—with overt and associative rehearsal	↓			↑ Intrusions
1977	Miller et al.	28 moderate users	0, 14 mg	I	40 words, 40 pictures, 5 trials	↓ (both pictures & words)			Learning was better for words than pictures over trials.
1977	Miller et al.	34 heavy and regular users	0, 14 mg	I	Word lists (15 words per list), first list repeated 4 times at intervals	↓	↓	↔	No practice effect on repeated list, ↔ shape of serial position curve, ↑ external intrusions in IFR, ↑ intrusions in DR, ↑ false positive in recognition recall
1978	Miller and Cornett	16 regular users	0, 5, 10, 15 mg	I	Word lists (40 words)	↓	↓	↔	↑ Intrusions
1977	Darley et al.	16 occasional users	0, 0.3 mg/kg	O	Common facts recall test	↔ Recall of facts, ↔ ability to assess memory			
1977	Sulkowski et al.	6 occasional users	0, 10 mg and propranolol, 120 mg (PO)	I	DSST (with and without memory), CPT, digit matching	↓ Learning in DSST, ↔ CPT, ↔ matching task (no effect of propranolol on THC-induced impairment)			
1977	Miller et al.	40 moderate and regular users	0, 10.2 mg, days 1 and 2	I	Prose recall	↓	↓		↑ Intrusions; cues did not improve recall in the THC condition
1978	Miller et al.	22 moderate and regular users	0, 14 mg	I	2-D design recall with 10 trials	↓			↑ Intrusion errors in first 5 trials, ↑ errors in field dependent group
1979	Miller et al.	12 Moderate and regular users	0, 10 mg	I	Word lists (15 words per list)	↓	↓	↔	↑ Intrusion errors
1980	Belmore and Miller	16 Moderate and regular users	0, 14 mg	I	Word lists (16 words per list)—processing questions for each word	↓	↓		Better recall of later lists semantic processing more impaired by THC
1982	Wetzel et al.	41 Moderate–heavy regular users	0, 6 mg	I	Word list (14 words per list) Long-term recall	↓			↔ Shape of serial position curve, ↔ long-term recall
1987	Hooker and Jones	12 Infrequent Users	0, 10.7 mg	I	PASAT	↔			
					SCWT	↓ Rate of reading, ↑ interference effect			

					Randt memory battery	↔	↔	↑ Intrusions in word recall, ↑ intrusions and omissions in prose DFR
					COWAT	↔		
1990	Kelly et al.	15 Regular users	0, 1.3, 2.3, 2.7%	I	DSST, vigilance, sorting task	DSST: ↑ errors, ↔ vigilance and sorting		
1990	Heishman et al.	3 Moderate and regular users	0, 25.7 mg—1, 2, 4 cigs	I	PAB—two-letter search, digit recall, SAS, logical reasoning	↓ Accuracy on serial addition subtraction and digit recall, ↔ all other tests		
1992	Block et al.	48 Moderate and regular users	0, 19 mg	I	Buschke selective reminding task	↓	↓	Consistent long-term retrieval, no effect of breath-holding on THC effects
					Text learning	↓	↓	
					PAL	↓ Learning of associations		
1994	Wilson et al.	10 users	0, 1.75%, 3.55% ad lib	I	DSST	↓ Performance on DSST with memory;↑ RT		
					CPT	↔		
					Tracking task	Dose-dependent impairment		
					Keyboard RT	Dose-related ↑ RT		
1994	Chait et al.	14 Occasional and heavy users	0, 36 mg (4 puffs) + ETOH	I	Free recall	↔ On recall		
					DSST	↓ Percentage of correct responses		
					Backward digit span	↔		
					Divided attention	↔ RT, ↑ false positives		
					Logical reasoning	↔		
1997	Heishman et al.	5 Regular users (variable)	0, 35.5 mg THC—4, 8, 16 puffs + ETOH	I	Word recall	↓		
					DSST	↓ Speed and accuracy on DSST		
					RT task	↔		
					Number recognition	↔ Number recognition		
1998	Fant et al.	10 Social users	0, 15.6 mg and 25.1 mg	I	Walter Reed PAB- rapid arithmetic skill, digit recall, logical reasoning	↔ All tests		
2000	Greenwald and Stitzer	5 Moderate users	0, ~35 mg	I	Digit span	↔		
					DSST	↑ RT, ↔ Accuracy		
					Divided attention	↑ RT		
2001	Hart et al.	18 Infrequent and heavy users	0, 18 and 39 mg	I	Digit recall	↓ Digit recall only with 39 mg		
					Micro Cog battery	↑ Premature responses and ↑ time to complete microcog battery		
					DSST	↔		
					Reasoning and flexibility task	↔		
2002	Curran et al.	15 Infrequent users	0, 7.5 and 15 mg	O	Buschke selective reminding task	↔	↓	↓ Learning (15 mg)
					Prose recall	↓	↓	Persisting up to 6 h
					Baddeley logical reasoning task	↑ RT logical reasoning		
					Serial sevens	↔		
					RVIP	↔		
					Choice RT	↔		
					Single/double digit cancellation task	↔		

Table 1 (continued)

Year	Author	Subjects	Estimated Δ-9-THC dose	Route	Tests	Results (only THC effects)			
						IFR	DFR	Recognition recall	Miscellaneous
2004	D'Souza et al.	22 Infrequent users	0, 2.5, 5 mg	IV	HVLT	↓	↓		↓ DCR, ↑ false positives; ↑ intrusions
					CPT	↔			
					DMTS	↓ Accuracy in easy WM task, ↔ RT; ↔ hard subtask			
2004	Ilan et al.	10 Casual users <1/week	0, 3.45%	I	Word recognition (20 words per list)	↔ Learning;↑ false alarms			
					Spatial N-back	↑ RT,↓ accuracy in high load task			
					EEG	Altered θ and α power, ↓ N100			
2005	Ilan et al.	24 Chronic regular users	THC 0, 1.8/3.6%; CBC: <0.2/0.5%; CBD:<0.4/>1%	I	EM: WP/WR—24 per list	WP, ↓ ERP amplitudes; WR, ↓ accuracy to new words, ↔ RT; WR, Slow wave ↓, N400 to new words ↓			
					WM: spatial, N-back	↓ Accuracy, ↑ RT; WM:↓ P300			
2005	Lane et al.	5 occasional users	0, ~11 mg, ~38.9%	I	DMTS	↓ Percentage of correct responses as a function of delay interval			
2005	D'Souza et al.	13 Schizophrenia patients with previous exposure but no abuse	0, 2.5, 5 mg	IV	CPT	↑ Omission errors, ↔ commission			
					HVLT	↓	↓	↓ DRR	↓ DCR, ↓ learning, ↑ intrusions and false positives
2006	Makela et al.	19 Occasional regular users	0, 5 mg: as 8.5 mg/ml sublingual spray	S/L	CANTAB-spatial WM task	↑ accuracy- in women			
					Spatial span task	↔ Span, ↓ errors in men, ↑ errors in women			

↑ = Increase, ↓ = decrease, ↔ = no change

CANTAB Cambridge Neuroscience test battery, *COWAT* controlled oral word assessment test, *CPT* continuous performance test, *DSST* digit symbol substitution test, *DFR* delayed free recall, *EM* episodic memory, *DRR* delayed recognition recall, *FR* free recall, *HVLT* Hopkins verbal learning test, *GDSA* goal-directed serial alternation, *I* inhaled, *IFR* immediate free recall, *IM* intramuscular, *IRR* immediate recognition recall, *IV* intravenous, *MicroCogBattery* a computer administered cognitive battery testing attention, *RT* reasoning, spatial ability and memory (the tests for memory include digit span, California verbal learning task and story recall), *O* oral, *PAB* performance assessment battery, *PAL* paired associate learning, *PASAT* paced auditory serial addition test, *RMS* running memory span, *RT* reaction time, *DMTS* delayed match to sample task, *RVIP* rapid visual information processing task from CANTAB, *SCWT* Stroop color word test, *SL* sublingual, *WM* working memory, *WP* word presentation, *WR* word recognition

on retrieval of information learned under normal conditions and the impairment in recall of information learned under the influence of Δ-9-THC was interpreted as an effect on encoding rather than retrieval. The use of unassayed cannabis, the differences in the composition of the placebo and Δ-9-THC groups, and the selective inclusion of only those subjects who reported feeling "high" in the analysis confound the interpretation of the results. In addition, the author used the serial position curves to investigate the effects of cannabis. While the recency effect of lists remained unaffected, recall of earlier lists (primacy effect) was significantly decreased by cannabis. The author interpreted this effect on the serial position of word lists as evidence that cannabis did not impair recall from short-term memory, but did impair recall of information that should have been transferred into long-term memory.

Darley et al. (1973) used the Sternberg (1966) task in an attempt to evaluate which stage of short-term memory was impaired by cannabis. The Sternberg task, a short-term recognition memory paradigm, has periods of encoding, retention, and recognition that are all separated in time. In this task, subjects are asked to memorize a set of items that are presented on a computer screen. After this, a series of items appear one at a time, and the subject has to tap a "Yes" or "No" button to indicate whether the item was from the memorized set. Response times and numbers of errors are recorded. Two measures are derived from a plot of reaction time (RT) against size of memory set: (1) the slope representing the time taken to compare the test item with memorized set, and (2) the intercept on the *Y*-axis, i.e., time taken to encode test stimulus and respond. Darley et al. (1973) utilized memory sets comprised of word lists. The effects of both single and daily (for 5 days) doses of Δ-9-THC were studied. Subjects were tested first on day 1 both before and after they all received 20 mg of Δ-9-THC. After this, half the subjects received 20 mg Δ-9-THC daily on days 2–5 and the other half received placebo. On day 5, subjects underwent the same test as on day 1 before and after they received the same study drug (Δ-9-THC or placebo) that they had been randomized to. Accuracy of response on the Sternberg task was unaffected by Δ-9-THC by both single and repeated daily dosing with Δ-9-THC. There were no other significant effects of Δ-9-THC except that on day 5, i.e., cumulative dosing (5 days × 20 mg/day) Δ-9-THC appeared to increase the time to encode and respond.

The work of Miller and colleagues (Miller et al. 1977a,c,d, 1979; Miller and Cornett 1978) has been a major contribution to the literature on the effects of cannabinoids on memory. Using word lists, they found that relative to placebo, Δ-9-THC at varying doses decreased immediate free recall of word lists without affecting recognition recall and increased the number of intrusions (Miller and Cornett 1978; Miller et al. 1977c, 1979). Although lower than placebo at all time points, the shape of the serial position curve was unaltered by Δ-9-THC (Miller et al. 1977c). The authors speculated that the observed effects on recall might be a consequence of Δ-9-THC's effects on processing the information to be learned. To test this hypothesis, Δ-9-THC (14 mg) or placebo was administered to 16 moderate to heavy users in 2 sessions separated by 1 week. Word lists, where presentation of each word was followed by four kinds of strategies to facilitate meaningful processing, were used (Belmore and Miller 1980). The strategies were yes/no answers to questions about the number of letters making up the word, rhyming with other words, syntax and semantics. Δ-9-THC significantly decreased both immediate and delayed free recall as in previous studies. Furthermore, more meaningful processing (i.e., semantic and syntactic processing) improved immediate free recall regardless of drug condition. However, subjects under the influence of Δ-9-THC were especially impaired on delayed free recall of more meaningfully processed words from the lists presented later. Block et al. (1992) also examined the acute effects of Δ-9-THC on verbal memory, associative learning, text learning, and RT. In addition, they examined the effect of different durations of breath-holding on the effects of smoked cannabis. While Δ-9-THC (19 mg) significantly affected performance in most domains tested relative to placebo, breath-holding did not seem to affect this impairment.

Rehearsal is necessary for information to reenter the short-term store and to be retained for longer periods. The effect of Δ-9-THC on recall was proposed to be mediated by deficient rehearsal during the encoding process. Thus, fixed rehearsal was expected to reduce or eliminate Δ-9-THC-induced recall impairments. Darley et al. (1974) studied the effects of rehearsal and state on learning. Fixed rehearsal did not improve Δ-9-THC-induced recall deficits on a verbal learning task. In two separate sessions spaced 3 days apart, occasional cannabis users were presented with a total of 20 word lists. On the first day (day 1), subjects were instructed to learn the lists alternately by free or fixed rehearsal. After being presented with each list, subjects were asked to recall the list. At the end of the tenth list, subjects were asked to recall all ten previously presented lists. Subjects were then administered a single dose of 20-mg Δ-9-THC, followed 90 min later by another ten lists. Δ-9-THC significantly decreased immediate free recall, an effect that was not improved by the fixed rehearsal procedure. However, fixed rehearsal altered the serial position effect reducing the primacy effect, a phenomenon that is described in further detail later. Subjects returned 3 days later (day 4) and half of them received Δ-9-THC (20 mg) and the other half placebo. This was followed by delayed free and recognition recall of all 20 word lists: the

first ten lists that had been presented before Δ-9-THC on day 1, and the second ten lists that had been presented after Δ-9-THC administration on day 1. To determine if recall was state-dependent, day 4 delayed free recall and delayed recognition recall were analyzed separately for lists 1–10 (day 1, pre-Δ-9-THC lists) and 11–20 (day 1, post Δ-9-THC list). Δ-9-THC administered on day 4 did not impair delayed free or recognition recall of lists learned on day 1 in the pre-Δ-9-THC condition. Similarly, the type of rehearsal procedure (free or fixed) did not impair delayed free or recognition recall of lists learned on day 1 in the pre-Δ-9-THC condition. However, relative to placebo, Δ-9-THC on day 4 was associated with better free recall of lists learned under the influence of Δ-9-THC on day 1. These data support a state-dependent learning hypothesis according to which information learned under the influence of Δ-9-THC is also recalled better under the influence of Δ-9-THC. One limitation of this study was a floor effect on delayed recall, which may have masked the detection of other effects. Of note, the delay period in this study far exceeds the delay period in other studies of cannabinoid effects and the lack of an effect on recognition recall is consistent with the vast majority of studies.

More recently, Curran et al. (2002) studied the effects of oral 7.5 and 15 mg of Δ-9-THC on measures of working memory, attention, executive functioning, reaction time, learning, and recall in infrequent cannabis users in a double-blind, placebo-controlled study. Only the higher dose of Δ-9-THC significantly impaired learning across trials on Buschke's selective reminding task (Buschke and Fuld 1974). These effects peaked at 2 h coinciding with peak plasma Δ-9-THC levels, before returning to baseline at 6 h. In this task, subjects are read a list of 16 words and then asked to recall as many words as possible. The experimenter then reads out only those words not recalled, and the subject has to again recall the entire list. This procedure is repeated three times. Measures of recall from short- and long-term memory, as well as forgetting from long-term memory, are obtained. Δ-9-THC also altered the standard learning curve, i.e., the recall on the third trial was not greater than that on the first, demonstrating that ability to learn new material was impaired by Δ-9-THC.

D'Souza et al. (2004, 2005) studied the effect of IV Δ-9-THC (2.5 and 5 mg) in healthy subjects and schizophrenia patients in two separate studies. Unlike most of the published studies, in this study subjects with a lifetime history of any cannabis use disorder were excluded. Therefore, tolerance, withdrawal, or residual effects did not confound the acute Δ-9-THC effects. Learning and recall measured by the Hopkins verbal learning task, vigilance and distractibility (continuous performance task), verbal fluency and working memory (DMST) were assessed in the subjects who rarely used cannabis. Δ-9-THC significantly impaired immediate recall in a dose-dependent manner across all three trials of immediate recall in healthy individuals (Fig. 4). However, its effects on learning were not statistically significant. Δ-9-THC also impaired delayed (+30 min) free and cued delayed recall and cued recall in a significant, dose-dependent manner. However, its effect on delayed recognition recall showed a trend toward significance. Finally, Δ-9-THC increased the number of false positives and intrusions with a trend toward significance. Similar effects on immediate, delayed free, and delayed cued recall were seen in schizophrenic patients. However, learning over trials and delayed recognition recall were significantly impaired by Δ-9-THC only in the schizophrenia group. In fact on the 5-mg Δ-9-THC dose condition, there was no learning across trials.

Prose recall

While most studies have examined the effects of Δ-9-THC on word lists, a few have also studied its effects on prose recall. Miller et al. (1977b) demonstrated that Δ-9-THC (10.2 mg) significantly decreased both immediate and delayed prose recall in a group of 40 moderate users as compared to placebo. The second day, one half of the group received the same drug as they received on the first day, while the other half received the other drug condition. Thus, subjects who received Δ-9-THC on the second day consisted of subjects who received Δ-9-THC on both days and those who received placebo the first day and Δ-9-THC on the second. Δ-9-THC significantly impaired delayed prose recall of the story presented on day 1 in this group. Subjects who received Δ-9-THC on day 1 and placebo on day 2 also showed delayed recall impairments that persisted to day 2. These data suggest lasting effects of Δ-9-THC on prose recall. Similar to this, Curran et al. (2002) demonstrated that prose recall (story recall), which is more indicative of day-to-day memory continued to show Δ-9-THC-induced impairments even at 6 h, lasting longer than the other impairments. However, other studies of prose recall have had mixed results (Block et al. 1992; Hart et al. 2001).

Δ-9-THC is associated with an increase in both external and internal intrusion errors in the recall of word and prose recall and with false positives in recognition recall (Abel 1971; Hooker and Jones 1987; Miller and Cornett 1978; Pfefferbaum et al. 1977). This increase in intrusion errors appears to be a robust and relatively unique effect of cannabinoids.

Digit recall

In a randomized study of infrequent cannabis users, Tinklenberg reported that relative to placebo, oral Δ-9-

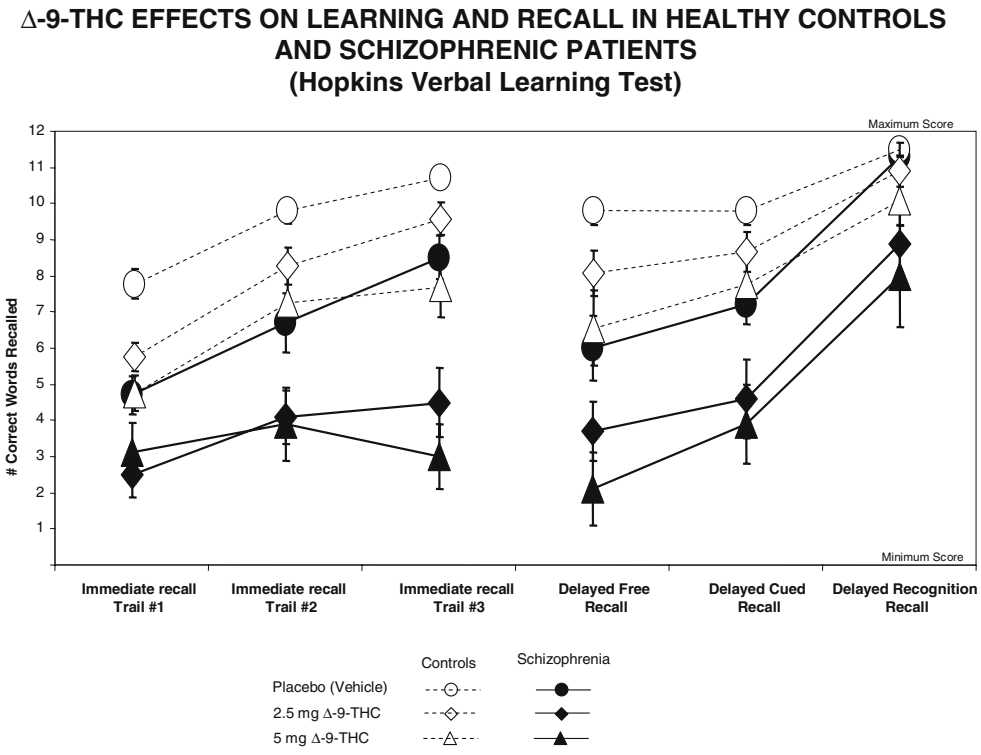

Fig. 4 Learning and recall with placebo and two doses of intravenous Δ-9-THC in health controls and schizophrenic patients (D'Souza et al. 2005)

THC significantly decreased both digit forward and backward recall at all doses (20, 40, and 60 mg) in a manner that is not dose-dependent (Tinklenberg et al. 1970). While the impairment of forward delayed free digit recall peaked at 1.5 h and returned to near baseline at 3.5 h, the impairment in backward recall persisted beyond 3.5 h.

Tinklenberg et al. (1972) did not find any significant 406 effects of oral Δ-9-THC (0.35 mg/kg body weight equivalent to 24.05 mg in a 70-kg individual) on a digit span task in cannabis users. Their observation that lowest recall corresponded with peak drug effects suggested impairments induced by Δ-9-THC. However, the effects did not reach significance and were attributed to a possible floor effect.

Heishman et al. (1990), in their small sample of infrequent users, reported that inhaled Δ-9-THC significantly impaired performance on a serial addition/subtraction task. The task difficulty i.e., the chunks of information that need to be learned and recalled, and the route of administration might account for the differences in results. On the contrary, Chait and Perry (1994) failed to find any effect of Δ-9-THC on backward digit recall.

Visual recall

In light of the notion that cannabis may facilitate mental and visual imagery, Miller et al. (1977d) tested the hypothesis that Δ-9-THC impaired picture recall to a lesser extent than verbal recall. Moderate users completed two test days (Δ-9-THC 14 mg or placebo) 1 week apart. Relative to placebo, Δ-9-THC impaired both verbal and picture recalls; however, while practice improved verbal recall in the Δ-9-THC condition, picture recall remained impaired. Subjective organization of information correlated with recall, but was not influenced by Δ-9-THC. The same group examined whether learning strategy, i.e., field dependent vs independent, influenced Δ-9-THC effects on figure recall (Miller et al. 1978). They hypothesized that the significant variability in recall deficits produced by Δ-9-THC might be explained by differences in cognitive style. Field independence is defined as the ability to overcome embedding contexts in perceptual function and is measured by the Witkin's embedded figures test (Witkin and Oltman 1967). In general, individuals who adopt a field-independent cognitive style perform better on free recall tasks. Consistent with their previous study, Δ-9-THC impaired immediate recall on figure recall, which improved with practice. However, field-dependent individuals made more recall errors on the Δ-9-THC condition, suggesting that learning strategy may influence response to Δ-9-THC.

Working memory

Of several cognitive measures, Wilson found the Digit Symbol Substitution Test (DSST) to be the most sensitive

to Δ-9-THC effects in occasional cannabis users (Wilson et al. 1994). In the DSST, subjects are presented a code of letters substituting for digits. Subjects are then presented the letters prompting them to respond by indicating the appropriate digit. In the easy version, the code is available for reference through task performance. Others have reported that Δ-9-THC increased error rates (Kelly et al. 1990) and decreased both speed and accuracy on the DSST (Heishman et al. 1997). In chronic cannabis users, Δ-9-THC was shown to decrease the number of attempts and correct responses on the DSST without changing overall accuracy (Greenwald and Stitzer 2000).

Lane et al. (2005) showed dose-dependent effects of Δ-9-THC in performance on a pattern recognition delayed match to sample task (DMTS). Occasional users of cannabis received placebo and two doses of Δ-9-THC via a paced smoking procedure. In the delayed match to sample task, two or more comparison stimuli are presented after the presentation of a sample stimulus. The subjects are required to correctly choose the stimulus that matches the previously shown sample. The sample and choice stimuli are separated by a delay period, which can be manipulated. Δ-9-THC disrupted DMTS performance in a dose- and delay-dependent manner. However, Heishman et al. (1997) found that in moderate to heavy cannabis users (one to six joints per week), inhaled Δ-9-THC administered by three paced smoking procedures did not impair performance on a DMTS task that used numbers instead of figures. Perhaps the differences in doses, degree of tolerance in the sample and task parameters account for the disparate results. Similarly, Curran et al. (2002) found that Δ-9-THC did not impair performance on the serial sevens task and a continuous performance task even though it impaired verbal recall. Finally, D'Souza et al. (2004) found that intravenous Δ-9-THC reduced the number of correct responses, but not response time, on a working memory task for figures in healthy subjects.

The continuous performance task (CPT), which is often used to test attention or vigilance, requires subjects to pay attention to sequentially presented items. Subjects are required to constantly utilize a "rule" (e.g., respond when a "9" is preceded by a "1") and also to keep the preceding item in mind while responding. Thus, it may be considered to have a small working memory component. Δ-9-THC does not appear to impair performance on CPT (D'Souza et al. 2004; Vachon et al. 1974; Wilson et al. 1994).

Finally, Ilan et al. (2004) studied the effects of Δ-9-THC on electrophysiological correlates of working and verbal memory. Occasional users of cannabis (n=10) performed the easy and hard versions of a spatial N-back task and word recognition task before and after smoking Δ-9-THC (3.45%) or placebo. The N-Back task, often used to test working memory, is one task where subjects are presented with a series of items (verbal or nonverbal). They are then required to attend to a particular aspect of these items such as description, color, or position, and to respond when the current item is similar to an item presented "n," i.e., 0, 1 or 2 trials before (Owen et al. 2005). Relative to placebo, Δ-9-THC decreased accuracy in performance on both the word recognition task and the high load version of the N-back task. Furthermore, Δ-9-THC also increased reaction times on both versions of the N-back task. Δ-9-THC attenuated several time-locked, event-related potentials (ERPs) under both task conditions. Δ-9-THC specifically decreased the N100, P300 amplitude associated with spatial N-back task performance. Δ-9-THC also attenuated the slow waves associated with the working memory and word recognition task. The attenuation of slow wave patterns associated with the working memory and word recognition task, as well as the P300 associated with the WM paradigm, is thought to reflect encoding processes and suggests that Δ-9-THC disrupts encoding. Recognition of old words relative to new words is associated with a broad positive shift of the ERP, referred to as the "memory-evoked shift." Δ-9-THC attenuated this memory evoked shift. Finally, Δ-9-THC attenuated the N400 to new words, which may reflect a diminished sense of novelty.

While most studies demonstrate that smoking Δ-9-THC cigarettes produces significant impairments in learning and recall (Heishman et al. 1990, 1997; Miller et al. 1977b,c), a few studies discussed below failed to find such effects (Chait and Perry 1994; Fant et al. 1998; Hart et al. 2001). Hart studied the effects of Δ-9-THC in heavy cannabis users (n=18) averaging 24 cannabis cigarettes per week, in a double-blind, randomized, balanced-order study. During the three sessions, each of which were separated by at least 72 h, participants smoked cannabis cigarettes containing 0, 1.8, or 3.9% Δ-9-THC in a paced smoking procedure. Subjects completed baseline computerized cognitive tasks, smoked a single cannabis cigarette, and completed additional cognitive tasks. The cognitive battery (microcog) consisted of tests for reaction time, attention, immediate digit recall, immediate prose recognition recall, delayed prose recognition recall, delayed recognition recall of names and addresses, visuospatial processing, reasoning, flexibility, and mental calculation. In addition, a standard computerized battery was used, which consisted of a digit recall task, a digit–symbol substitution task, a divided attention task, and a repeated acquisition task. Although Δ-9-THC significantly increased the number of premature responses and the time participants required to complete several tasks, it had no effect on accuracy on measures of cognitive flexibility, mental calculation, and reasoning. The absence of acute Δ-9-THC effects was most likely related to significant tolerance to cannabinoids in this sample of heavy users and or the limited sensitivity of the battery. Chait and

Perry (1994) also found no effect of Δ-9-THC on their measures. They studied subjects who varied in their usual Δ-9-THC use (1–16/month) and tested them more than an hour after smoking. Previous studies have demonstrated that the peak effects of inhaled Δ-9-THC occur within 30 min of smoking (Chait and Zacny 1992), and this may account for the lack of any effect seen.

Fant et al. (1998) compared Δ-9-THC and placebo administered by a paced smoking procedure in occasional cannabis users. Subjects received active Δ-9-THC in a fixed order design (15.6 mg followed by 25.1 mg) and were tested using the Walter Reed performance assessment battery, which includes a rapid arithmetic task, a digit recall task, logical reasoning, and a spatial perception task. Although Δ-9-THC produced behavioral and physiological effects, no effects were detected on the cognitive battery. The authors acknowledged that practice effects related to the fixed order of drug administration may have prevented the detection of Δ-9-THC effects.

Discussion

In summary, Δ-9-THC transiently impairs the learning and recall of both verbal and nonverbal information in a manner that is dependent on dose and task difficulty. These memory impairments cannot be accounted for by cannabinoid disruption of attentional processes (Chait and Perry 1994; Curran et al. 2002; D'Souza et al. 2004; Hart et al. 2001), though the latter could certainly contribute to the former.

Some, but not all, studies suggest that cannabinoids impair verbal learning across trials. Δ-9-THC clearly impairs free recall of information learned under the influence of the drug, and most studies demonstrate that Δ-9-THC does not appear to impair recognition recall. One interpretation of this profile of effects is that cannabinoids interfere with the retrieval of information without disrupting encoding. Furthermore, retrieval cues appear to facilitate recall of information learned under the influence of the drug but do not completely restore recall (Miller et al. 1976). The facilitatory effects of retrieval cues on recall suggest that cannabinoids may be disrupting access to memory traces or the organization of information. In contrast to information learned under the influence of Δ-9-THC, the recall of information learned under normal conditions is not impaired by Δ-9-THC. One interpretation of this profile of effects is that cannabinoids do not impair the retrieval of information once it is encoded. Cannabinoids preferentially impair primacy effects but not recency effects, suggesting that these compounds interfere with the process by which information is transferred into longer-term memory. Furthermore, one of the most consistent and unique effects of cannabinoids is an increase in intrusion errors during recall of both word list and prose recall. The increase in intrusion errors may reflect increased mental activity and subsequent irrelevant associations induced by cannabinoids, spilling over into the retrieval processes; a possible mechanism for these effects is discussed later. Taken collectively, the literature suggests that cannabinoids impair both encoding and retrieval. Finally, cannabinoids may also impair the process of consolidation, whereby immediate memory is stored for later retrieval. This process of consolidation is possibly strengthened by the rehearsal of information.

One issue that has received little attention is the role of motivation in test performance in these studies. Some have suggested that recall impairments under the influence of cannabinoids may reflect a reduced motivation state (Miller et al. 1977a). Alternatively, others have speculated that subjects under the influence of cannabinoids may compensate for perceived impairments by working harder, resulting in an underestimation of the extent of drug-induced impairments (Curran et al. 2002). Since their subjects reported an awareness of the drug-induced impairments, the authors went on to speculate that they actively compensated for these impairments resulting in the lack of observable Δ-9-THC effects on some measures. None of the studies reviewed used any procedures to control for effort on cognitive test performance. Recent brain imaging studies raise the intriguing possibility that despite similar cognitive test performance, groups may differ on the extent and degree of brain activation. Kanayama et al. (2004) studied brain activation during performance of a spatial working memory task in heavy cannabis users after recent (6 h) cannabis exposure using functional MRI (fMRI). While there were no significant differences in performance on the working memory task between cannabis users and controls, cannabis users had more prominent and widespread activation in response to the working memory task, including regions not usually used in working memory. The authors suggested that cannabis users recruit more regions in a more pronounced manner so as to meet the demands of the tasks as compared to controls.

The mechanisms underlying the memory impairing effects of cannabinoids

Studies with cannabinoids in animals provide a backdrop to understand the memory impairing effects of cannabinoids in humans. Natural and synthetic exogenous cannabinoids impair learning and memory processes in rodents and nonhuman primates (Aigner 1988; Brodkin and Moerschbaecher 1997; Castellano et al. 2003; Collins et al. 1994; Lichtman et al. 2002). These impairments occur

at doses lower than those required to elicit other well-characterized effects of cannabinoids including motor effects, analgesia, hypothermia and, therefore, suggest that cannabinoids have selective effects on memory. The most robust effects are on working memory and short-term memory, both of which require intact hippocampus and prefrontal cortex and both of these regions have high densities of CB1 receptors (Fig. 2).

Maze tasks specifically measure spatial learning and memory, both of which appear to be hippocampal-dependent tasks. Acute administration of Δ-9-THC and a number of synthetic cannabinoids impair performance on a number of maze tasks (Carlini et al. 1970a,b). Chronic administration of Δ-9-THC can result in the development of tolerance in rats. Finally, the fact that intrahippocampal administration of cannabinoids impairs maze performance in rats implicates the centrality of the hippocampus in some of the effects of cannabinoids (Fig. 5; Aigner 1988; Ferraro 1980; Ferraro and Grilly 1974; Winsauer et al. 1999; Zimmerberg et al. 1971).

Acute administration of Δ-9-THC and synthetic cannabinoids also impairs performance on the delayed match-to-sample (DMTS) and delayed nonmatch-to-sample tasks in rodents (Heyser et al. 1993) and nonhuman primates (Aigner 1988; Ferraro 1980; Ferraro and Grilly 1974; Winsauer et al. 1999; Zimmerberg et al. 1971). These impairments induced by Δ-9-THC on DMTS task performance are evident when the delay is long (Heyser et al. 1993). The absence of an effect at short delay times indicates that cannabinoids do not impair the ability to perform the basic task, but instead produce a selective learning and memory deficit. The lack of an effect of Δ-9-THC on DMTS task performance, after very brief delays between sample and match phases and increasing impairment of performance with increasing delay, is akin to the pattern of deficits produced by lesions of the hippocampus and related structures (Freedland et al. 2002; Margulies and Hammer 1991). Recordings from hippocampal complex spike cells indicated that DMTS deficit induced by Δ-9-THC is associated with a specific decrease in hippocampal cell discharge during the sample (but not match) phase of the task (Lichtman 2000; Terranova et al. 1996; Wolff and Leander 2003). These and other data support a central role for CB1 receptors located in the hippocampus and neighboring structures in the memory-impairing effects of cannabinoids. It is notable that people diagnosed with schizophrenia, an illness in which hippocampal dysfunction has been reported, are more sensitive to the learning and memory impairments induced by Δ-9-THC (D'Souza et al. 2005), suggesting that the hippocampus is the locus of the learning and memory impairments induced by cannabinoids. Exogenous administration of Δ-9-THC and other cannabinoid ligands produced widespread, dose-dependent alterations in brain function in the hippocampus, basal ganglia, cerebellum, amygdala, and striatum (Da Silva and Takahashi 2002; Davies et al. 2002). These changes parallel closely both the dose-dependent nature of the effects on cannabinoid-induced behaviors and the time course of the onset of these behaviors, indicating that these alterations in functional activity are the substrates of these behaviors. As discussed later, other areas, particularly the prefrontal cortex, are also likely to be involved.

Many of the effects of Δ-9-THC and other synthetic cannabinoids can be reversed or blocked by CB1 antagonists, supporting the view that the effects of cannabinoids on memory are indeed mediated via actions at CB1 receptors (Marsicano et al. 2002). Furthermore, some studies (Lichtman et al. 2002; Terranova et al. 1996; Wolff and Leander 2003), but not others (Da Silva and Takahashi 2002; Davies et al. 2002), suggest that the CB1R antagonist/inverse agonist, when administered on their own, may enhance memory on tasks that recruit memory processes that span minutes to hours. Systemic SR141716A has been shown to disrupt the extinction of aversive memories in mice (Bohme et al. 2000). More recently, SR141716A has been shown to improve spatial memory

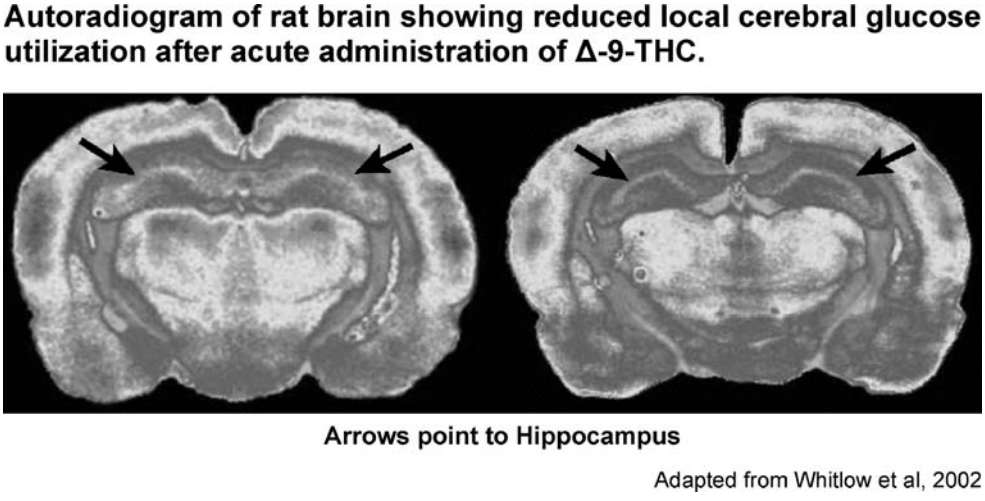

Fig. 5 Effect of acute administration of Δ-9-THC 0.0 mg/kg (*left*) and 2.5 mg/kg (*right*) on rates of glucose utilization in the hippocampi of rats 15 min after administration. Note that the rate of glucose utilization decreases with active Δ-9-THC administration. Panel on the *right* shows the range of rates of cerebral glucose utilization

when administered before or immediately after the training, but not when administered before the test (Maccarrone et al. 2002; Reibaud et al. 1999). The profile of effects of SR141716A suggests that it facilitates the acquisition and consolidation of memory without affecting retrieval (Varvel and Lichtman 2002).

CB1 receptor knockout mice were reported to show enhanced long-term potentiation (LTP), a basic process that is discussed in further detail later. CB1 knockout mice showed enhancement of hippocampal LTP (de Oliveira Alvares et al. 2005) and improved performance on memory tasks that rely on hippocampal function test (Marsicano et al. 2002). In contrast Varvel and Lichtman (2002) showed that in the reversal test of the water maze task, another test that relies on hippocampal function, knockout mice spent significantly more time returning to the position where the platform was formerly located and showed impairments in locating the new platform position (Lichtman et al. 2002; Marsicano et al. 2002). Similarly, intrahippocampal administration of the highly selective cannabinoid antagonist AM251 was shown to disrupt induction of LTP in rodents (Dudai 2004; Dudai and Eisenberg 2004; Moscovitch 1995; Squire and Alvarez 1995). CB1 knockout mice showed impairments in both short- and long-term extinction of aversive memories (Hajos et al. 2000; Hoffman and Lupica 2000). These data from CB1 knockouts suggest that the endocannabinoid system may facilitate the extinction of learned behaviors and play a key role in the forgetting of information stored in the long-term memory, in addition to their role in encoding of memory (Wilson and Nicoll 2002). As discussed later forgetting irrelevant information is an important aspect of memory.

Memory consolidation begins when information, registered initially in the neocortex, is integrated by the hippocampal complex/medial temporal lobes and related structures to form a memory trace that consists of an ensemble of bound hippocampal complex-neocortical neurons (Spencer et al. 2003). This initial binding into a memory trace involves short-term processes, the first of which may be completed within seconds and the last of which may be completed within minutes or, at most, days. If every encoded internal representation is instantly stabilized and consolidated, then it is possible that the brain's computational space will be quickly consumed by useless/irrelevant information leading to rapid saturation of processing and storage capacity. Perhaps the endocannabinoid system, as studies with knockout mice have shown, contributes to the mechanisms that prevent the automatic and instantaneous consolidation of memory. Perhaps, similar to endocannabinoids, exogenous cannabinoids prevent or attenuate the consolidation of newly learned memory.

Behavioral studies in animals support the clinical literature and suggest, with respect to the hippocampus, that exogenous cannabinoid treatment selectively affects encoding processes. However, this may be different in other brain areas, for instance the amygdala, where a predominant involvement in memory consolidation and forgetting of information or the extinction of learned behaviors has been established. Extinction is believed to involve active suppression of previously learned associations and seems to involve molecular mechanisms distinct from those associated with normal learning (Abel and Lattal 2001). This possible mechanism may underlie the intrusion errors observed on recall tasks in humans under the influence of cannabinoids. All memories are susceptible to decay over time. If endocannabinoids modulate tonic forgetting, then a partial cannabinoid agonist such as Δ-9-THC may lower this tone. In doing so, this agonist permits "forgotten" information to "intrude" on the learning and recall of new information. This mechanism may underlie the robust increase in intrusion errors seen in studies with Δ-9-THC. If the endocannabinoid system were involved in forgetting and/or extinction processes, then disrupting it via pharmacological or genetic deletion of CB1 receptors may seem in some models to improve memory (Lichtman 2000; Reibaud et al. 1999; Terranova et al. 1996). This is because disruption of endocannabinoid signaling prolonged retention compared with control animals. Conversely, in tasks that require the suppression of previously learned responses, endocannabinoid inhibition may actually interfere with learning, as in the reversal test of this study. CB1 (−/−) mice demonstrated increased perseverance of an acquired spatial memory at the expense of learning a new one (Varvel and Lichtman 2002). Several other reports have demonstrated that disruption of CB1 receptor signaling impairs memory in fear-conditioning procedures. Previously, SR 141716-treated mice and CB1 (−/−) mice exhibited impaired extinction of conditioned freezing to a tone that had been paired with foot shock (Marsicano et al. 2002). Interestingly, presentation of the conditioned stimulus (CS) tone during extinction was sufficient to increase endogenous levels of anandamide and 2-AG in the amygdala. A subsequent study found that SR 141716 also impaired conditioned freezing to the test chamber in which the mice had received the shock (Suzuki et al. 2004). Given the extent to which the endocannabinoid system appears to modulate short-term and long-term forms of synaptic plasticity, it should not be surprising that this system plays a tonic role in mnemonic processes.

Neurochemical mechanisms contributing to the memory-impairing effects of cannabinoids

In the hippocampus, CB1R are located primarily on cholecystokinin containing GABAergic interneurons (Hajos et al. 2001; Katona et al. 2000, 2001). These GABAergic interneurons are believed to orchestrate fast synchronous

oscillations in the gamma range, a critical process in synchronizing pyramidal cell activity (Wilson and Nicoll 2002). Gamma oscillations are synchronized over long distances in the brain and are hypothesized to "bind" together sensory perceptions and to play a role in cognition reviewed in (Shen et al. 1996; Shen and Thayer 1999; Sullivan 1999, 2000). Abnormalities in gamma band synchronization have been reported in schizophrenia (Hajos et al. 2001). Activation of these presynaptic CB1Rs reduces GABA release by interneurons (Martin and Shapiro 2000), which in turn would disrupt the synchronization of pyramidal cell activity (Misner and Sullivan 1999), thereby interfering with associative functions.

Glutamate

Cannabinoids might produce their effects on learning and memory via modulation of glutamate release. The observation that CB1 agonists decrease evoked excitatory postsynaptic current in hippocampal neurons suggests that cannabinoids decrease the release of glutamate through a presynaptic mechanism (Pistis et al. 2001). Recent data also raise the presence of a novel cannabinoid receptor that may be involved in the modulation of glutamate release (Hajos et al. 2000, 2001; Katona et al. 2000).

Memories are believed to be formed by a process involving a rapidly formed and relatively long-lasting increase in the probability that postsynaptic neurons in the hippocampus will fire in response to neurotransmitters released from presynaptic neurons. The leading candidate neural substrates for this mechanism are long-term potentiation (LTP) and long-term depression (LTD) of CA3–CA1 synaptic transmission. LTP is a long-lasting enhancement of synaptic transmission in response to brief, high-frequency stimulation of presynaptic neurons. LTP is readily induced in hippocampal neurons (Martin and Shapiro 2000). LTD is a weakening of a synaptic transmission that lasts from hours to days. It results from either strong synaptic stimulation (cerebellum) or persistent weak synaptic stimulation (as in the hippocampus). Hippocampal LTD may be important for the clearing of old memory traces. Cannabinoid receptor activation inhibits both LTP and LTD induction in the hippocampus (Collins et al. 1994; Misner and Sullivan 1999; Nowicky et al. 1987; Stella et al. 1997; Sullivan 2000; Terranova et al. 1995; Van Sickle et al. 2005). In particular, activation of CB1 receptors blocks LTP of field potentials in the CA1 region and was found recently to inhibit hippocampal LTD of CA1 field potentials as well (Misner and Sullivan 1999).

Acetylcholine

CB1R activation also effects acetylcholine release in an inverted "U" dose response fashion (Acquas et al. 2000, 2001; Gessa et al. 1997, 1998; Nava et al. 2001; Rodriguez de Fonseca et al. 2005). Inhibition of acetylcholine release from cholinergic hippocampal neurons located in the septohippocampal pathway may provide another mechanism for the amnestic effects of cannabinoids.

Dopamine

CB1R receptor activation stimulates mesoprefrontal dopamine (DA) transmission (Chen et al. 1990; Diana et al. 1998; Jentsch et al. 1998; Pistis et al. 2001). Considering that supranormal stimulation of DA D1 receptors in the PFC was shown to impair working memory, the negative effects of cannabinoids on working memory and other cognitive processes might be related to the activation of DA transmission in the PFC. Alternatively, cannabinoids, by inhibiting GABA release from GABAergic interneurons, may also suppress one mechanism by which DA controls PFC neuronal excitability. This might lead to nonspecific activation of the PFC, which in turn may disrupt normal signal processing and result in poor integration of transcortical inputs (Pistis et al. 2001).

Future directions

There is a need to replicate much of the existing data in larger samples. Almost all the data on the effects of cannabinoids on memory in humans is from studies using Δ-9-THC or Δ-9-THC containing herbal cannabis. As discussed earlier, Δ-9-THC is a partial CB1 agonist. Future studies need to investigate the effects of full CB1 agonists and CB1antagonists. Furthermore, studies with putative selective agonists and antagonists of the novel non-CB1/CB2 receptors that are relevant to the cognitive effects of cannabinoids will be important in clarifying the contributions of CB receptor subtypes in the memory impairing effects of cannabinoids. Most studies have included frequent users or heavy users. Future studies should include nonusers, users, and abusers of cannabis to further clarify the effects of tolerance, dependence, and residual Δ-9-THC effects on memory. Most of the literature on cannabinoids is from studies employing verbal memory tasks. However, other forms of memory may be affected by cannabinoids. CB1 receptor transmission was shown to be involved in emotional learning phenomena (Marsicano et al. 2002; Varvel et al. 2005; Varvel and Lichtman 2002). Do cannabinoids impair emotional memory in humans? Related to this, preclinical findings showing the critical role of cannabinoids in forgetting needs to be investigated in humans.

Similarly, there is a need to characterize the neural circuitry of the memory-impairing effects of cannabinoids in humans using brain imaging techniques with good spatial (fMRI or PET) and temporal (EEG) resolution. For

example, do verbal recall impairments induced by cannabinoids correlate with reduced medial temporal blood oxygen level dependent (BOLD) response during encoding of word lists? The development of CB1 receptor imaging radioligands, which has been challenging until now (Dhawan et al. 2006), may provide the tools to establish the relationship between the memory-impairing effects of cannabinoids and changes in CB1 receptor occupancy. Such approaches may permit the translation of preclinical data in humans. In this regard, using assessments of memory that can be used in animals and humans would bridge the gap between the preclinical and clinical literature.

It will also be important to establish the contributions of other neurotransmitters, e.g., dopamine, glutamate, and GABA to the memory-impairing effects of cannabinoids in humans. This could be accomplished, with some limitations, by studying the interactive effects of cannabinoids and drugs acting at other neurotransmitter systems on memory. In this regard, there are distinct differences between the amnestic effects of cannabinoids and other amnestic drugs, e.g., alcohol, benzodiazepines, and NMDA receptor antagonists. For example, the latter three are associated with the phenomenon of retrograde facilitation, which has not been observed with cannabinoids. Thus, comparing cannabinoid effects with the memory impairing effects of better-studied drugs, e.g., scopolamine or ketamine, would help in determining the specificity of cannabinoid effects. Finally, further work is also necessary to determine the differential effects of cannabinoids on encoding, consolidation, and retrieval.

Conclusions

Data from the 1970s and more recent data have shown that exogenous cannabinoids impair several aspects of memory and endocannabinoids may be involved in modulating memory. While progress in the understanding of cannabinoid receptor function has renewed interest and stimulated significant clinical and preclinical research on the cognitive effects of cannabinoids, there is a need to bridge the gap between the preclinical and clinical data.

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References

Abel EL (1971) Marihuana and memory: acquisition or retrieval? Science 173:1038–1040

Abel T, Lattal KM (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. Curr Opin Neurobiol 11:180–187

Acquas E, Pisanu A, Marrocu P, Di Chiara G (2000) Cannabinoid CB (1) receptor agonists increase rat cortical and hippocampal acetylcholine release in vivo. Eur J Pharmacol 401:179–185

Acquas E, Pisanu A, Marrocu P, Goldberg SR, Di Chiara G (2001) Delta9-tetrahydrocannabinol enhances cortical and hippocampal acetylcholine release in vivo: a microdialysis study. Eur J Pharmacol 419:155–161

Adams IB, Martin BR (1996) Cannabis: pharmacology and toxicology in animals and humans. Addiction 91:1585–1614

Agurell S, Halldin M, Lindgren JE, Ohlsson A, Widman M, Gillespie H, Hollister L (1986) Pharmacokinetics and metabolism of delta 9-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev 38:21–43

Aigner TG (1988) Delta-9-tetrahydrocannabinol impairs visual recognition memory but not discrimination learning in rhesus monkeys. Psychopharmacology (Berl) 95:507–511

Atkinson R, Shiffrin RM (1968) Human memory: a proposed system and its control processes. New York Academic Press, New York

Baddeley A (1999) Essentials of human memory. Psychology Press

Baddeley A, Chincotta D, Adlam A (2001) Working memory and the control of action: evidence from task switching. J Exp Psychol Gen 130:641–657

Baker D, Pryce G, Davies WL, Hiley CR (2006) In silico patent searching reveals a new cannabinoid receptor. Trends Pharmacol Sci 27:1–4

Belmore SM, Miller LL (1980) Levels of processing and acute effects of marijuana on memory. Pharmacol Biochem Behav 13:199–203

Block RI, Farinpour R, Braverman K (1992) Acute effects of marijuana on cognition: relationships to chronic effects and smoking techniques. Pharmacol Biochem Behav 43:907–917

Bohme GA, Laville M, Ledent C, Parmentier M, Imperato A (2000) Enhanced long-term potentiation in mice lacking cannabinoid CB1 receptors. Neuroscience 95:5–7

Brodkin J, Moerschbaecher JM (1997) SR141716A antagonizes the disruptive effects of cannabinoid ligands on learning in rats. J Pharmacol Exp Ther 282:1526–1532

Budney AJ, Moore BA, Vandrey RG, Hughes JR (2003) The time course and significance of cannabis withdrawal. J Abnorm Psychology 112:393–402

Budney AJ, Hughes JR, Moore BA, Vandrey R (2004) Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 161:1967–1977

Buschke H, Fuld PA (1974) Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 24:1019–1025

Carlini EA, Hamaoui A, Bieniek D, Korte F (1970a) Effects of (−) delta-9-trans-tetrahydrocannabinol and a synthetic derivative on maze performance of rats. Pharmacology 4:359–368

Carlini EA, Santos M, Claussen U, Bieniek D, Korte F (1970b) Structure activity relationship of four tetrahydrocannabinols and the pharmacological activity of five semi-purified extracts of Cannabis sativa. Psychopharmacologia 18:82–93

Castellano C, Rossi-Arnaud C, Cestari V, Costanzi M (2003) Cannabinoids and memory: animal studies. Curr Drug Targets CNS Neurol Disord 2:389–402

Chait LD, Perry JL (1994) Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. Psychopharmacology (Berl) 115:340–349

Chait LD, Zacny JP (1992) Reinforcing and subjective effects of oral delta 9-THC and smoked marijuana in humans. Psychopharmacology 107:255–262

Chen J, Paredes W, Lowinson JH, Gardner EL (1990) Delta 9-tetrahydrocannabinol enhances presynaptic dopamine efflux in medial prefrontal cortex. Eur J Pharmacol 190:259–262

Collins DR, Pertwee RG, Davies SN (1994) The action of synthetic cannabinoids on the induction of long-term potentiation in the rat hippocampal slice. Eur J Pharmacol 259:R7–R8

Compton DR, Johnson MR, Melvin LS, Martin BR (1992) Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents. J Pharmacol Exp Ther 260:201–209

Curran HV, Brignell C, Fletcher S, Middleton P, Henry J (2002) Cognitive and subjective dose–response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology (Berl) 164:61–70

Da Silva GE, Takahashi RN (2002) SR 141716A prevents delta 9-tetrahydrocannabinol-induced spatial learning deficit in a Morris-type water maze in mice. Prog neuropsychopharmacol Biol Psychiatry 26:321–325

Darley CF, Tinklenberg JR, Hollister TE, Atkinson RC (1973) Marihuana and retrieval from short-term memory. Psychopharmacologia 29:231–238

Darley CF, Tinklenberg JR, Roth WT, Atkinson RC (1974) The nature of storage deficits and state-dependent retrieval under marihuana. Psychopharmacologia 37:139–149

Davies SN, Pertwee RG, Riedel G (2002) Functions of cannabinoid receptors in the hippocampus. Neuropharmacology 42:993–1007

de Oliveira Alvares L, de Oliveira LF, Camboim C, Diehl F, Genro BP, Lanziotti VB, Quillfeldt JA (2005) Amnestic effect of intrahippocampal AM251, a CB1-selective blocker, in the inhibitory avoidance, but not in the open field habituation task, in rats. Neurobiol Learn Mem 83:119–124

Demuth DG, Molleman A (2005) Cannabinoid signalling. Life Sci 78:549–563

Dhawan J, Deng H, Gatley SJ, Makriyannis A, Akinfeleye T, Bruneus M, Dimaio AA, Gifford AN (2006) Evaluation of the in vivo receptor occupancy for the behavioral effects of cannabinoids using a radiolabeled cannabinoid receptor agonist, R-[(125/131)I] AM2233. Synapse 60:93–101

Diana M, Melis M, Gessa GL (1998) Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur J Neurosci 10:2825–2830

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29:1558–1572

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry 57:594–608

Dudai Y (2004) The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 55:51–86

Dudai Y, Eisenberg M (2004) Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. Neuron 44:93–100

Fant RV, Heishman SJ, Bunker EB, Pickworth WB (1998) Acute and residual effects of marijuana in humans. Pharmacol Biochem Behav 60:777–784

Ferraro DP (1980) Acute effects of marijuana on human memory and cognition. NIDA Res Monogr 31:98–119

Ferraro DP, Grilly DM (1974) Effects of chronic exposure to delta9-tetrahydrocannabinol on delayed matching-to-sample in chimpanzees. Psychopharmacologia 37:127–138

Fletcher PC, Henson RN (2001) Frontal lobes and human memory: insights from functional neuroimaging. Brain 124:849–881

Freedland CS, Whitlow CT, Miller MD, Porrino LJ (2002) Dose-dependent effects of Delta9-tetrahydrocannabinol on rates of local cerebral glucose utilization in rat. Synapse 45:134–142

Gerard CM, Mollereau C, Vassart G, Parmentier M (1991) Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem J 279:129–134

Gessa GL, Mascia MS, Casu MA, Carta G (1997) Inhibition of hippocampal acetylcholine release by cannabinoids: reversal by SR 141716A. Eur J Pharmacol 327:R1–R2

Gessa GL, Casu MA, Carta G, Mascia MS (1998) Cannabinoids decrease acetylcholine release in the medial-prefrontal cortex and hippocampus, reversal by SR 141716A. Eur J Pharmacol 355:119–124

Greenwald MK, Stitzer ML (2000) Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. Drug Alcohol Depend 59:261–275

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327–360

Hajos N, Katona I, Naiem SS, MacKie K, Ledent C, Mody I, Freund TF (2000) Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci 12:3239–3249

Hajos N, Ledent C, Freund TF (2001) Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. Neuroscience 106:1–4

Hampson RE, Simeral JD, Kelly EJ, Deadwyler SA (2003) Tolerance to the memory disruptive effects of cannabinoids involves adaptation by hippocampal neurons. Hippocampus 13:543–556

Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW (2001) Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacology 25:757–765

Heishman SJ, Huestis MA, Henningfield JE, Cone EJ (1990) Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. Pharmacol Biochem Behav 37:561–565

Heishman SJ, Arasteh K, Stitzer ML (1997) Comparative effects of alcohol and marijuana on mood, memory, and performance. Pharmacol Biochem Behav 58:93–101

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC (1990) Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 87:1932–1936

Heyser CJ, Hampson RE, Deadwyler SA (1993) Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. J Pharmacol Exp Ther 264:294–307

Hoffman AF, Lupica CR (2000) Mechanisms of cannabinoid inhibition of GABA(A) synaptic transmission in the hippocampus. J Neurosci 20:2470–2479

Hollister LE, Gillespie HK, Ohlsson A, Lindgren JE, Wahlen A, Agurell S (1981) Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? J Clin Pharmacol 21:171S–177S

Hooker WD, Jones RT (1987) Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. Psychopharmacology (Berl) 91:20–24

Howlett AC (2004) Efficacy in CB1 receptor-mediated signal transduction. Br J Pharmacol 142:1209–1218

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 54:161–202

Ilan AB, Smith ME, Gevins A (2004) Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology (Berl) 176:214–222

Iversen L (2003) Comparing cannabis with tobacco: arithmetic does not add up (comment). BMJ 327:165

Iversen L (2005) Long-term effects of exposure to cannabis. Curr Opin Pharmacol 5:69–72

Jentsch JD, Verrico CD, Le D, Roth RH (1998) Repeated exposure to delta 9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. Neurosci Lett 246:169–172

Johansson E, Agurell S, Hollister LE, Halldin MM (1988) Prolonged apparent half-life of delta 1-tetrahydrocannabinol in plasma of chronic marijuana users. J Pharm Pharmacol 40:374–375

Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA (2004) Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology (Berl) 176:239–247

Karniol IG, Carlini EA (1973) Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. Psychopharmacologia 33:53–70

Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA (1974) Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. Eur J Pharmacol 28:172–177

Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE (1975) Effects of delta9-tetrahydrocannabinol and cannabinol in man. Pharmacology 13:502–512

Katona I, Sperlagh B, Magloczky Z, Santha E, Kofalvi A, Czirjak S, Mackie K, Vizi ES, Freund TF (2000) GABAergic interneurons are the targets of cannabinoid actions in the human hippocampus. Neuroscience 100:797–804

Katona I, Rancz EA, Acsady L, Ledent C, Mackie K, Hajos N, Freund TF (2001) Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. J Neurosci 21:9506–9518

Kelly TH, Foltin RW, Rose AJ, Fischman MW, Brady JV (1990) Smoked marijuana effects on tobacco cigarette smoking behavior. J Pharmacol Exp Ther 252:934–944

Lane SD, Cherek DR, Lieving LM, Tcheremissine OV (2005) Marijuana effects on human forgetting functions. J Exp Anal Behav 83:67–83

Lichtman AH (2000) SR 141716A enhances spatial memory as assessed in a radial-arm maze task in rats. Eur J Pharmacol 404:175–179

Lichtman AH, Varvel SA, Martin BR (2002) Endocannabinoids in cognition and dependence. Prostaglandins Leukot Essent Fatty Acids 66:269–285

Maccarrone M, Valverde O, Barbaccia ML, Castane A, Maldonado R, Ledent C, Parmentier M, Finazzi-Agro A (2002) Age-related changes of anandamide metabolism in CB1 cannabinoid receptor knockout mice: correlation with behaviour. Eur J Neurosci 15:1178–1186

Mailleux P, Vanderhaeghen JJ (1992) Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. Neuroscience 48:655–668

Mailleux P, Parmentier M, Vanderhaeghen JJ (1992) Distribution of cannabinoid receptor messenger RNA in the human brain: an in situ hybridization histochemistry with oligonucleotides. Neurosci Lett 143:200–204

Margulies JE, Hammer RP Jr (1991) Delta 9-tetrahydrocannabinol alters cerebral metabolism in a biphasic, dose-dependent manner in rat brain. Eur J Pharmacol 202:373–378

Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgansberger W, Di Marzo V, Lutz B (2002) The endogenous cannabinoid system controls extinction of aversive memories (see comment). Nature 418:530–534

Martin PD, Shapiro ML (2000) Disparate effects of long-term potentiation on evoked potentials and single CA1 neurons in the hippocampus of anesthetized rats. Hippocampus 10:207–212

Matsuda LA (1997) Molecular aspects of cannabinoid receptors. Crit Rev Neurobiol 11:143–166

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346:561–564

McGilveray IJ (2005) Pharmacokinetics of cannabinoids. Pain Res Manag 10:15A–22A

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR (1995) Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 50:83–90

Miller LL, Cornett TL (1978) Marijuana: dose effects on pulse rate, subjective estimates of intoxication, free recall and recognition memory. Pharmacol Biochem Behav 9:573–577

Miller LL, Cornett T, Brightwell D, McFarland D, Drew WG, Wikler A (1976) Marijuana and memory impairment: the effect of retrieval cues on free recall. Pharmacol Biochem Behav 5:639–643

Miller LL, Cornett T, Drew W, McFarland D, Brightwell D, Wikler A (1977a) Marijuana: dose–response effects on pulse rate, subjective estimates of potency, pleasantness, and recognition memory. Pharmacology 15:268–275

Miller LL, Cornett TL, Brightwell DR, McFarland DJ, Drew WG, Wikler A (1977b) Marijuana: effects on storage and retrieval of prose material. Psychopharmacology (Berl) 51:311–316

Miller LL, McFarland D, Cornett TL, Brightwell D (1977c) Marijuana and memory impairment: effect on free recall and recognition memory. Pharmacol Biochem Behav 7:99–103

Miller LL, McFarland DJ, Cornett TL, Brightwell DR, Wikler A (1977d) Marijuana: effects on free recall and subjective organization of pictures and words. Psychopharmacology (Berl) 55:257–262

Miller LL, Cornett T, Nallan G (1978) Marijuana: effect on nonverbal free recall as a function of field dependence. Psychopharmacology (Berl) 58:297–301

Miller LL, Cornett TL, Wikler A (1979) Marijuana: effects on pulse rate, subjective estimates of intoxication and multiple measures of memory. Life Sci 25:1325–1330

Misner DL, Sullivan JM (1999) Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA1 neurons. J Neurosci 19:6795–6805

Moscovitch M (1995) Recovered consciousness: a hypothesis concerning modularity and episodic memory. J Clin Exp Neuropsychol 17:276–290

Munro S, Thomas KL, Abu-Shaar M (1993) Molecular characterization of a peripheral receptor for cannabinoids. Nature 365: 61–65

Nava F, Carta G, Colombo G, Gessa GL (2001) Effects of chronic Delta(9)-tetrahydrocannabinol treatment on hippocampal extracellular acetylcholine concentration and alternation performance in the T-maze. Neuropharmacology 41:392–399

Nowicky AV, Teyler TJ, Vardaris RM (1987) The modulation of long-term potentiation by delta-9-tetrahydrocannabinol in the rat hippocampus, in vitro. Brain Res Bull 19:663–672

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK (1980) Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 28:409–416

Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK (1981) Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. NIDA Res Monogr 34:250–256

Owen AM, McMillan KM, Laird AR, Bullmore E (2005) N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25:46–59

Pfefferbaum A, Darley CF, Tinklenberg JR, Roth WT, Kopell BS (1977) Marijuana and memory intrusions. J Nerv Ment Dis 165:381–386

Pistis M, Porcu G, Melis M, Diana M, Gessa GL (2001) Effects of cannabinoids on prefrontal neuronal responses to ventral tegmental area stimulation. Eur J Neurosci 14:96–102

Reibaud M, Obinu MC, Ledent C, Parmentier M, Bohme GA, Imperato A (1999) Enhancement of memory in cannabinoid CB1 receptor knock-out mice. Eur J Pharmacol 379:R1–R2

Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M (2005) The endocannabinoid system: physiology and pharmacology. Alcohol 40:2–14

Shen M, Thayer SA (1999) Delta9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. Mol Pharmacol 55:8–13

Shen M, Piser TM, Seybold VS, Thayer SA (1996) Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci 16:4322–4334

Spencer KM, Nestor PG, Niznikiewicz MA, Salisbury DF, Shenton ME, McCarley RW (2003) Abnormal neural synchrony in schizophrenia. J Neurosci 23:7407–7411

Squire LR, Alvarez P (1995) Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 5:169–177

Stella N, Schweitzer P, Piomelli D (1997) A second endogenous cannabinoid that modulates long-term potentiation. Nature 388:773–778

Sternberg S (1966) High-speed scanning in human memory. Science 153:652–654

Stout JC, Murray LL (2001) Assessment of memory in neurogenic communication disorders. Semin Speech Lang 22:137–145

Sullivan JM (1999) Mechanisms of cannabinoid-receptor-mediated inhibition of synaptic transmission in cultured hippocampal pyramidal neurons. J Neurophysiol 82:1286–1294

Sullivan JM (2000) Cellular and molecular mechanisms underlying learning and memory impairments produced by cannabinoids. Learn Mem 7:132–139

Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 24:4787–4795

Tanda G, Goldberg SR (2003) Cannabinoids: reward, dependence, and underlying neurochemical mechanisms—a review of recent preclinical data. Psychopharmacology (Berl) 169:115–134

Terranova JP, Michaud JC, Le Fur G, Soubrie P (1995) Inhibition of long-term potentiation in rat hippocampal slices by anandamide and WIN55212-2: reversal by SR141716 A, a selective antagonist of CB1 cannabinoid receptors. Naunyn Schmiedebergs Arch Pharmacol 352:576–579

Terranova JP, Storme JJ, Lafon N, Perio A, Rinaldi-Carmona M, Le Fur G, Soubrie P (1996) Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR 141716. Psychopharmacology 126:165–172

Tinklenberg JR, Melges FT, Hollister LE, Gillespie HK (1970) Marijuana and immediate memory. Nature 226:1171–1172

Tinklenberg JR, Kopell BS, Melges FT, Hollister LE (1972) Marihuana and alcohol, Time production and memory functions. Arch Gen Psychiatry 27:812–815

Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM (1998) Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83:393–411

Tulving E (1972) Episodic and semantic memory. Academic Press, New York

Tulving E, Markowitsch HJ (1998) Episodic and declarative memory: role of the hippocampus. Hippocampus 8:198–204

Turner CE, Elsohly MA, Boeren EG (1980) Constituents of Cannabis sativa L. XVII. A review of the natural constituents. J Nat Prod 43:169–234

Vachon L, Sulkowski A, Rich E (1974) Marihuana effects on learning, attention and time estimation. Psychopharmacologia 39:1–11

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310:329–332

Varvel SA, Lichtman AH (2002) Evaluation of CB1 receptor knockout mice in the Morris water maze. J Pharmacol Exp Ther 301:915–924

Varvel SA, Anum EA, Lichtman AH (2005) Disruption of CB(1) receptor signaling impairs extinction of spatial memory in mice. Psychopharmacology (Berl) 179:863–872

Wilson RI, Nicoll RA (2002) Endocannabinoid signaling in the brain. Science 296:678–682

Wilson WH, Ellinwood EH, Mathew RJ, Johnson K (1994) Effects of marijuana on performance of a computerized cognitive–neuromotor test battery. Psychiatry Res 51:115–125

Winsauer PJ, Lambert P, Moerschbaecher JM (1999) Cannabinoid ligands and their effects on learning and performance in rhesus monkeys. Behav Pharmacol 10:497–511

Witkin HA, Oltman PK (1967) Cognitive style. Int J Neurol 6:119–137

Wolff MC, Leander JD (2003) SR141716A, a cannabinoid CB1 receptor antagonist, improves memory in a delayed radial maze task. Eur J Pharmacol 477:213–217

Zimmerberg B, Glick SD, Jarvik ME (1971) Impairment of recent memory by marihuana and THC in rhesus monkeys. Nature 233:343–345