

The effect of cannabis use on memory function: an update

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Abstract: Investigating the effects of cannabis use on memory function appears challenging. While early observational investigations aimed to elucidate the longer-term effects of cannabis use on memory function in humans, findings remained equivocal and pointed to a pattern of interacting factors impacting on the relationship between cannabis use and memory function, rather than a simple direct effect of cannabis. Only recently, a clearer picture of the chronic and acute effects of cannabis use on memory function has emerged once studies have controlled for potential confounding factors and started to investigate the acute effects of delta-9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol (CBD), the main ingredients in the extract of the cannabis plant in pharmacological challenge experiments. Relatively consistent findings have been reported regarding the acute impairments induced by a single dose of Δ 9-THC on verbal and working memory. It is unclear whether they may persist beyond the intoxication state. In the long-term, these impairments seem particularly likely to manifest and may also persist following abstinence if regular and heavy use of cannabis strains high in Δ 9-THC is started at an early age. Although still at an early stage, studies that employed advanced neuroimaging techniques have started to model the neural underpinnings of the effects of cannabis use and implicate a network of functional and morphological alterations that may moderate the effects of cannabis on memory function. Future experimental and epidemiological studies that take into consideration individual differences, particularly previous cannabis history and demographic characteristics, but also the precise mixture of the ingredients of the consumed cannabis are necessary to clarify the magnitude and the mechanisms by which cannabis-induced memory impairments occur and to elucidate underlying neurobiological mechanisms.

Keywords: cannabis, THC, CBD, memory, neuroimaging, fMRI

Introduction

Marijuana or Cannabis sativa (*C. sativa*) is the most widely used illicit drug,^{1,2} and its use often starts during teenage years.³ Cannabis contains more than 600 ingredients, including over 60 different cannabinoids,⁴ which are now recognized for both their toxic and potential therapeutic effects,⁵ and that are mediated through their effects on the endogenous cannabinoid system.⁶ Delta-9-tetrahydrocannabinol (commonly known as Δ 9-THC) is thought to be the principal psychoactive ingredient present in cannabis that is responsible for the acute and adverse effects of cannabis on various cognitive functions including memory and the induction of psychotic symptoms.⁷⁻¹⁵ In contrast, the other major cannabinoid that has attracted attention in recent years, cannabidiol (CBD), does not impair cognition,¹⁶ and may have anxiolytic and antipsychotic effects.¹⁷⁻²⁰ The potency of cannabis that is available on the street can vary and

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seems to have changed over time in many countries,^{21–23} with strains that are high in $\Delta 9$ -THC and low in CBD currently dominating the market.^{24,25} Hence, the acute effects as well as the effects of long-term use of cannabis on neurocognitive processes and psychological state are likely to vary depending on the precise mix of different cannabinoids present in the cannabis used.

Cannabis has historically been considered as a relatively harmless drug. However, the age of onset of cannabis use is decreasing and young people start to use cannabis at an earlier age,^{26,27} a time when they are likely to be more vulnerable to its impairing effects.^{28,29} Additionally, considering that the effects of $\Delta 9$ -THC on memory appear to be dose-dependent,^{9,12,30,31} and increasingly potent forms of cannabis with higher $\Delta 9$ -THC content are available on the street than before,²⁵ the modern cannabis user may be at a particular risk for its adverse cognitive effects. Several factors are likely to influence the impact of cannabis on memory, particularly the duration and frequency of previous cannabis use,^{31–33} as well as the strain of cannabis used,²⁰ which complicate the interpretation of early observational studies investigating memory function in cannabis users. Only recently have the effects of cannabis been studied, employing controlled experimental designs in conjunction with neuroimaging techniques that allow one to draw conclusions regarding the acute effects of cannabis and the neurobiological mechanisms that may underlie the effects of cannabis on memory function. This update is organized into sections addressing the acute and chronic effects of cannabis on memory function at a behavioral level, but also provides an overview regarding the potential neural mechanisms underlying these processes, reflecting the focus of the recent literature.

Acute effects of cannabis on memory

When studying the effects of cannabis on memory function, it is important to be mindful that human memory is not a unitary measurable concept. Rather, it is a construct that considers multiple subsystems with different specializations and processes being involved – all of which are localized in overlapping but different brain regions.^{34–36} In one approach, the stage model of memory refers to a temporal categorization that distinguishes between sensory memory, short-term memory, and long-term memory, and includes the processes of encoding (receiving and processing of information), followed by storage (creation of a permanent record of the encoded information), and recall (retrieval or recollection of information). As an alternative approach, the memory system

is subdivided depending on its content, which refers to the discrimination between declarative and procedural memory systems. Procedural (implicit) memory is the storage of elements which are inaccessible to the consciousness (eg, the memory of skills such as playing a guitar). Most of the memory tests that have been employed when investigating the acute effects of cannabis assessed the declarative (explicit) memory system, which requires the conscious recollection of events and facts and is further divided into episodic (facts about the world) and semantic memory (storage of elements that have an autobiographical context),³⁷ while working memory is defined as the temporary storage and manipulation of episodic information.³⁸ The challenge to measure this complex construct is reflected in the variety of different memory tests that are proposed in the literature to measure similar domains (see Table 1). Therefore, it remains a matter of debate whether test performance is comparable across the different tests being employed, a point that needs to be considered when evaluating the studies that investigated the effects of cannabis on memory function.

The acute effects of the different cannabinoids on memory function have been studied by directly administering cannabis or its different ingredients in order to examine its potential adverse or therapeutic effects.³⁹ Several pharmacological challenge studies have consistently reported that the administration of $\Delta 9$ -THC disrupted working and episodic memory in humans and animals.^{13,40–48} However, when examining the literature regarding the acute effects of $\Delta 9$ -THC, several factors that limit the direct comparability of the findings need to be considered. For instance, chronic exposure of cannabinoid drugs may result in the development of tolerance to the adverse effects of $\Delta 9$ -THC or WIN 55,212-2 (a cannabinoid receptor agonist) on memory and executive functioning in humans and animals.^{45,49–53} To illustrate, while 500 μg of $\Delta 9$ -THC per kg body weight acutely decreased performance in the Tower of London Task (executive functioning) in occasional users,⁵⁴ no such performance deficits were reported in heavy smokers following administration of the same dose.⁴⁵ In accordance, acute $\Delta 9$ -THC exposure has been associated with fewer impairments in working memory in heavy cannabis users than in occasional users,⁵⁵ which is consistent with studies that reported no acute effects of $\Delta 9$ -THC on memory function in frequent users.^{49,56}

As summarized in Table 2, the majority of memory domains tested in heavy cannabis smokers were not affected by the acute administration of $\Delta 9$ -THC or were only affected if the dose was high (eg, more than 3.9% $\Delta 9$ -THC concentration in the smoked cigarette). In contrast, occasional users

Table 1 Memory tests

Neurocognitive test	Acronym	Memory domain
Alphabet task	AT	Executive function
Benton visual retention test	BVRT	Visuospatial memory
Boston naming test	BNT	Verbal fluency (semantic memory)
Buschke selective reminding test	BSRT	Verbal learning and verbal memory
California verbal learning test	CVLT	Verbal learning and memory
Cambridge neuropsychological test automated battery	CANTAB	Verbal and visual memory, learning, working memory, executive function
– ST: paired associate learning test	– CANTAB-PAL	– Visual associative memory and learning
– ST: rapid visual information processing task	– CANTAB-RVIPT	– Working memory
– ST: spatial span	– CANTAB-SS	– Spatial memory span
– ST: spatial working memory	– CANTAB-SWM	– Spatial working memory
– ST: one-touch stockings of cambridge	– CANTAB-OTSC	– Working memory
Controlled oral word association test	COWAT	Verbal fluency (semantic memory)
Delayed matching to sample	DMTS	Visual memory and working memory
Delayed recall	DR	Long-term episodic memory
Digit recall task	DRT	Visual memory
Digit span task	DSP	Working memory
Digit symbol substitution task	DSST	Visual memory
Face–name pair learning	FNPL	Verbal learning
Hopkins verbal learning test	HVLT	Verbal learning and memory
MicroCog: assessment of cognitive functioning	MicroCog	Logical memory and working memory
N-back task	N-BACK	Working memory
Omitted numbers	ON	Working memory
Paced auditory serial addition test	PASAT	Working memory
Repeated acquisition task	RAT	Learning
Perceptual priming task	PPT	Implicit memory
Pictorial memory task	PMT	Associative memory and retrieval
Prose recall	PR	Verbal memory
Rey Auditory Verbal Learning Test	RAVLT	Verbal learning and memory
Rey-Osterrieth complex figure test	CFT	Visuospatial memory
Short-delay response task	SDRT	Working memory
Spatial working memory task	SWMT	Spatial working memory
Subtracting serial sevens	SS7	Working memory
Sternberg memory task	SMT	Working memory
Tower of London	TOL	Executive function
Verbal fluency task	VFT	Semantic memory
Verbal memory task	VMT	Verbal memory
Wechsler memory scale	WMS	Memory function
Wechsler adult intelligence scale (processing speed index)	WAIS-PS	Working memory
Wechsler adult intelligence scale (working memory index)	WAIS-WM	Working memory
Wechsler adult intelligence scale (verbal comprehension index)	WAIS-VC	Verbal memory
Wisconsin card sorting test	WCST	Executive function, working memory
Word recognition task	WRT	Verbal memory

Abbreviation: ST, substest.

and regular users seem to show memory impairments after both high doses and low doses of $\Delta 9$ -THC, with $\Delta 9$ -THC impacting on memory function in a dose-dependent manner.^{8,9,12,40,49,54,57} For instance, increases in $\Delta 9$ -THC concentration were associated with a linear decrease in performance in short-term memory tasks.⁹ Therefore, infrequent users may be more susceptible than heavy users to the acute effects of $\Delta 9$ -THC on behavior,⁵⁸ and hence it is

important to take into account the history of previous cannabis use when investigating the acute effects of $\Delta 9$ -THC on memory functioning.⁵⁹ Encouragingly, despite the acute impairments caused by $\Delta 9$ -THC, especially at high doses, a single dose of $\Delta 9$ -THC is unlikely to have persistent effects on memory function. For instance, Curran et al⁸ found that $\Delta 9$ -THC significantly impaired episodic memory and verbal recall 2 hours after the oral administration of $\Delta 9$ -THC,

Table 2 Acute effects of $\Delta 9$ -THC on memory

Author	Subjects (gender ratio)	Age in years (M)	Previous cannabis exposure	Dose of $\Delta 9$ -THC (route)	Memory test*
Low-dose $\Delta 9$-THC					
Heavy users (\geq joint/day)					
Hart et al ⁴⁹	n = 18 (10 m/8 f)	25	6.1 (M) days cannabis use/week (± 1.3); 4 joints per occasion (M)	1.8% (l)	MicroCog ^o DRT ^o DSST ^o RAT ^o N-BACK ^o WRT ^o TOL ^o
Hart et al ⁵⁶ (EEG)	n = 24 (13 m/11 f)	26	6.3 (M) days cannabis use/week (± 1.0); 4 joints per occasion (M)	1.8% (l)	
Ramaekers et al ⁴⁵	n = 21 (15 m/6 f)	23	373.7 (M) times cannabis use/year, 5 (M) joints per occasion	400 μ g/kg (l)	
Regular users (cannabis use > 1/month)					
Henquet et al ⁴²	n = 74 (56 m/18 f)	27	Cannabis use in past 12 months; 51% of the subjects had > 1 time cannabis use/day $\geq 10 \times$ lifetime cannabis use;	300 μ g/kg (l)	DMTS* RAVLT* N-BACK* WRT*
Ilan et al ⁴³ (EEG)	n = 11 (6 m/5 f)	26	15 joints (M)/month	1.8% (l)	
Occasional users (no or minimal previous exposure to cannabis)					
Bhattacharyya et al ¹⁶ (fMRI)	n = 15 (m only)	27	Lifetime cannabis use episodes ≤ 15	10 mg (O)	WMS ^o PMT ^o
Bossong et al ⁴³ (fMRI)	n = 13 (m only)	22	$\geq 4 \times$ cannabis use/lifetime; < 1/week	6 mg (l)	
Bossong et al ⁴⁴ (fMRI)	n = 17 (m only)	21	$\geq 4 \times$ cannabis use/lifetime; < 1/week	6 mg (l)	SMT*
Curran et al ⁸	n = 15 (m only)	24	Prior experience; ≤ 1 cannabis exposure/week	7.5 mg (O)	BSRT* VFT*
D'Souza et al ¹²	n = 22 (14 m/8 f)	29	Prior experience; 6 subjects used cannabis > 100 times/lifetime	5 mg (IV)	DMTS* HVL* DSP*
Englund et al ⁶¹	n = 26 (14 m/12 f)	26	Previous cannabis use ≥ 1	1.5 mg (IV)	HVL* N-BACK*
Morrison et al ⁴⁴ (EEG)	n = 16 (7 m/6 f)	26	Previous cannabis use ≥ 1	1.25 mg (IV)	
High-dose $\Delta 9$-THC					
Heavy users (\geq joint/day)					
Hart et al ⁵⁶ (EEG)	n = 24 (13 m/11 f)	26	6.3 (M) days cannabis use/week (± 1.0); 4 joints per occasion (M)	3.9% (l)	N-BACK ^o WRT ^o RAT ^o DSST ^o TOL ^o
Hart et al ⁴⁹	n = 18 (10 m/8 f)	25	6.1 (M) days cannabis use/week (± 1.3); 4 cigarettes per occasion (M)	3.9% (l)	
Ramaekers et al ⁴⁵	n = 12 (9 m/3 f)	23	340 (M) joints/year, 2.3 (M) joints per occasion, 6.2 (M) years cannabis use ≥ 1 joint/day in the last 5 years	500 μ g/kg (l)	MicroCog*
Weinstein et al ⁴¹	n = 14 (10 m/4 f)	27	$\geq 10 \times$ lifetime cannabis use; 13 joints (M)	17 mg (l)	WCST*
Regular users (cannabis use > 1/month)					
Ilan et al ⁴³ (EEG)	n = 12 (6 m/6 f)	26	$\geq 10 \times$ lifetime cannabis use; 13 joints (M)	3.6% (l)	N-BACK* WRT*

Author	n	Age (M)	Exposure	Task	Results	Measures
Ilan et al ¹⁴² (EEG)	n = 10 (NR)	27	Occasional users (no or minimal previous exposure to cannabis)	Cannabis use in past 12 months; cannabis use episodes \geq 1/month, \leq 1/week	3.45% (I)	N-BACK* WRT* SMT*
Hunault et al ⁹	n = 24 (m only)	24		7.7 (standard deviation 3.7) joints/month	69.4 mg (I)	
Ramaekers et al ⁵⁴	n = 12 (8 m/4 f)	23		55 (M) times cannabis use/year, 1.2 (M) joints per occasion, 7.4 (M) years of cannabis use	500 μ g/kg (I)	TOL**
Böcker et al ⁵⁷ (EEG)	n = 16 (m only)	18-45		>2 and <9 cigarettes/month	69.4 mg (I)	SMT*
Curran et al ⁸	n = 15 (m only)	24		Prior experience; \leq 1 cannabis exposure/week	15 mg (O)	PR* BSRT* VFT* RVIPT** SS7**
Lane et al ⁴⁰	n = 5 (3 m/2 f)	21 to 34		Cannabis use 2 to 10 times/month	2.20% (I)	DR*
Lane et al ⁴⁰	n = 5 (3 m/2 f)	21 to 34		Cannabis use 2 to 10 times/month	3.89% (I)	DMTS*
Morrison et al ¹³	n = 22 (m only)	28		2-1000 prior cannabis use episodes, negative urine test	2.5 mg (IV)	DSP* RAVLT* TOL*
Ramaekers et al ⁵⁴	n = 20 (14 m/6 f)	19-29		\geq 5 times cannabis use in past year, not daily users	500 μ g/kg (I)	
Weinstein et al ⁴¹	n = 14 (10 m/4 f)	27		\geq 1 joint/day in the last 5 years	13 mg (I)	WCST*

Notes: * Δ 9-THC induced deficits in performance; ** Δ 9-THC did not induce deficits in performance; see Table 1.
Abbreviations: Δ 9-THC, delta-9-tetrahydrocannabinol; M, mean; n, number; m, male; f, female; I, inhalation (smoking); MicroCog, MicroCog Assessment of Cognitive Functioning; DRT, digit recall task; DSST, digit symbol substitution task; RAT, repeated acquisition task; N-BACK, N-back task; WRT, word recognition task; TOL, Tower of London; RAVLT, Rey Auditory Verbal Learning Test; EEG, electroencephalography study; fMRI, functional magnetic resonance imaging study; O, oral; WMS, Wechsler Memory Scale; PMT, pictorial memory task; SMT, Sternberg memory task; IV, intravenous; HVL, Hopkins Verbal Learning Test; WCST, Wisconsin Card Sorting Test; PR, prose recall; BSRT, Buschke Selective Reminding Test; VFT, verbal fluency task; DR, delayed recall; PPT, perceptual priming task; RVIPT, rapid visual information processing task; SS7, subtracting serial sevens; DSP, digit-span task

with no residual effects being present 24 or 48 hours after administration.

The other major component in the cannabis extract is CBD, a cannabinoid that has received less attention in pharmacological challenge studies investigating the effect of cannabis on memory function – probably due to its known nonharmful effects on cognition.^{43,60} However, considering that CBD may be protective for some aspects of memory function by inhibiting the Δ 9-THC-induced impairments in episodic memory in humans and spatial memory in animals,^{20,61,62} but not in working memory,^{60,61} CBD may have therapeutic potential in reversing certain cognitive impairments induced by cannabis. Therefore, further experimental studies will be useful to understand the effects of the two main ingredients on memory function separately and in combination.

Studies have also investigated whether genetic variations may moderate variable sensitivity to the effects of Δ 9-THC. For instance, a polymorphism in the catechol-O-methyltransferase (*COMT*) gene has been shown to moderate the effect of Δ 9-THC on verbal memory.⁴² Genetic variations may thus underlie some of the inconsistencies in results across studies depending on the genetic makeup of study participants. As indicated in Table 2, the overrepresentation of mainly adult male subjects in some of these study samples may also limit the generalizability of the results, especially because there are some suggestions that gender may be an important factor in mediating variability in the response to cannabinoids in animals and humans,⁶³⁻⁶⁸ preliminary evidence also suggests an effect of gender on Δ 9-THC-induced impairments in working memory and learning in humans and animals.⁶⁹⁻⁷¹

In summary, based on the recent literature, a relatively robust picture regarding the acute effects of cannabis emerged (ie, there is convincing evidence that the acute administration Δ 9-THC impairs memory function), with several factors potentially moderating its effects, including previous exposure to cannabis, the dose of Δ 9-THC administered, the precise Δ 9-THC:CBD ratio, a genetic vulnerability to its effects, and the particular assessment of the multifactorial nature of memory function.

Long-term effects of cannabis on memory

In contrast to the acute effects, less consistency exists regarding the long-term effects of cannabis use on neurocognitive functioning. A major difficulty that appears when interpreting studies that compared cannabis users with control subjects regarding their memory performance

is the heterogeneity of the selected samples. For instance, studies used different criteria to categorize their subjects (ie, allocated them to distinct but at times overlapping categories such as former cannabis users, current regular cannabis users, or heavy cannabis users, long-term and short-term cannabis users, or early-onset and late-onset cannabis users). Based on the methodological approaches in the literature, Table 3 summarizes the studies in terms of the subject selection criteria employed and the confounding factors that have been considered.

One crucial factor that has been suggested to interfere with the accuracy and interpretability of the results is the abstinence period. For instance, a previous meta-analysis implicated that regular cannabis users present with selective long-term memory impairments, including the domains of learning and retrieval,⁷² although the magnitude of the pooled effect sizes were modest, and uncertainty exists as to whether these deficits persist beyond the acute intoxication state. The question regarding the irreversibility of the effects of cannabis has specifically been addressed by Pope et al,⁷³ who compared adult heavy and long-term cannabis users (smoked at least 5000 times in their lives and were daily smokers at study entry) and controls (who had smoked no more than 50 times in their lives) regarding their performance on neurocognitive measures at three different time-points after the first assessment. On days 0, 1, and 7, cannabis users significantly differed in terms of task performance compared to controls, and the learning and recall deficits across time points were related to $\Delta 9$ -THC-creatinine ratios at first assessment. However, by day 28, the two groups did not differ any longer, and initial $\Delta 9$ -THC concentrations were not related to task performance, suggesting that memory impairments in long-term cannabis users may not persist beyond the impact of $\Delta 9$ -THC-induced “residual effects.” This is in line with more recent studies implicating that the severity of deficits in memory and immediate recall associated with cannabis use decreased over time following abstinence;^{58,74–76} moreover, studies reported that normal memory functioning was observed in regular cannabis users when they were abstinent for between 48 hours up to a month.^{77–80}

In contrast, a more recent systematic review concluded that long-term cannabis use impairs memory, particularly verbal and working memory,⁸¹ reflecting the evidence from another set of studies that reported impairments in working memory and learning that persisted beyond the acute intoxication state in heavy cannabis users.^{30,82–84} This body of evidence points to the idea that some individuals may recover from their memory impairments after a period of abstinence,

while others continue exhibiting the memory impairments after the use of cannabis, implicating that additional factors (other than intoxication state) need to be identified in order to explain the memory deficits associated with cannabis use. To illustrate, it was reported that heavy smokers (who smoked on average 94 joints per week) that were abstinent for 28 days showed persistent impairments in a range of memory functions.³⁰ In addition, a recent study suggested that neuropsychological deficits did not recover completely even 1 year after the cessation of cannabis use in those who started using it regularly before the age of 18 years,²⁹ indicating that age of onset and frequency of cannabis use may be important moderators that need to be considered.

In fact, accumulating evidence suggests that deficits in memory performance in abstinent adolescent and adult cannabis users depend on the weekly dose of cannabis used,³⁰ as well as on the frequency, duration, and age of onset of cannabis use.^{29,31–33,81,83,85} For instance, in a group of adolescent cannabis users, the frequency of use explained 24.2% of the variance in word recall and a combined predictive model that included quantity and age of onset of cannabis use accounted for 31.5% of the variance in memory performance.³¹ In accordance, Meier et al²⁹ showed that the decline in memory performance in cannabis users who began smoking in adolescence was independent of the frequency of cannabis use, whereas the decline in adult-onset users was dependent on the frequency of use.

Finally, at a neurobiological level, long-term and early-onset cannabis use appear to cause greater morphological and functional alterations in the still developing brain rather than in the mature human and animal brain.^{71,86–91} Therefore, as summarized in Table 3, it appears that impairments in memory are unlikely to persist above and beyond the intoxication state in late-onset users and short-term users,^{74,79,80, 82,85,92} and if used only in an occasional manner.⁷⁴ In contrast, early-onset and heavy cannabis use over the long-term seem to have a particularly adverse effect on memory function and may lead to persistent impairments in a range of memory domains beyond the acute intoxication state. This is also consistent with evidence from animal studies where it has been possible to investigate this issue under controlled experimental conditions with greater methodological rigor; it was found that the adverse effects of $\Delta 9$ -THC on learning are more severe in adolescents than in adults.^{71,91} Similarly, chronic treatment with the cannabinoid receptor agonist, WIN55,212-2 (WIN), was associated with long-lasting impairments in object recognition memory in pubertal but not in adult rats.^{93,94}

However, not all studies have reported memory impairments in heavy and early-onset cannabis users.^{86,95–97} As indicated by pharmacological challenge studies, an important determinant of the long-term effects of cannabis use may be the precise mixture of the ingredients of the consumed cannabis. Although a naturalistic study reported that cannabis users who smoked cannabis high in CBD and low in $\Delta 9$ -THC were protected from the memory-impairing effects associated with cannabis strains high in $\Delta 9$ -THC,²⁰ most of the observational studies to date did not include the $\Delta 9$ -THC/CBD ratio (eg, by employing hair analysis as a proxy estimate of the amount of $\Delta 9$ -THC or CBD in the cannabis used) as a potential confounder in statistical reporting (see Table 3). Given the impact of the $\Delta 9$ -THC/CBD ratio on brain structures implicated in memory function and executive functions in cannabis users (while taking into account the variability of this ratio in street cannabis²⁵),^{98,99} consideration of this factor in the design and analysis of studies may improve the replicability and interpretability of the results, particularly because simple and valid methods are now applicable for the quantitative detection of $\Delta 9$ -THC and CBD.^{100,101}

In light of the complexities in the assessment of memory function, some of the inconsistencies in results across studies may be related to the different memory paradigms that have been used in these studies, which may have investigated related but not completely overlapping aspects of memory and employed tasks with differing levels of complexity. For instance, studies that have employed functional neuroimaging techniques to investigate the neural substrates underlying memory impairments related to cannabis use have often used tasks that are fairly simple and specific to a memory-domain rather than more complex paradigms that can assess multiple domains. While this strategy has generally been employed to avoid potential confounding effects associated with differences in task performance, which can cloud the interpretation of brain activation patterns related to specific task demands, this restricts a direct comparison of the results of these studies with those employing more complex paradigms. Interestingly, neuroimaging studies have consistently reported similar performance levels in memory tasks (eg, throughout short delay response tasks, face-name cued recall tasks, and pictorial memory tasks) in heavy cannabis users when compared to controls,^{77,78,80,86,95,97,102–104} suggesting perhaps that more challenging and multidimensional memory tasks may be required to discriminate chronic cannabis users from occasional users or nonusers. This is consistent with recent evidence from animal literature, which suggests that persistence of the adverse effects of chronic

cannabinoid exposure [eg, the agonist WIN55,212-2 (WIN)] beyond the immediate withdrawal period may depend on the specific memory domain being tested, with some forms of hippocampal-dependent short-term memory (such as that measured by the object location task) being particularly sensitive, while deficits in other measures of short-term memory (such as the object recognition and water maze tasks) recover following a short period of abstinence.¹⁰⁵

As shown in Table 1, a commonly employed and well-validated task is the Rey Auditory Verbal Learning Test (RAVLT),^{106–108} a test that assesses a range of memory domains, including immediate and delayed recall, learning rate, recognition, proactive and retroactive interference, and primacy and recency effects. There is a greater degree of consistency with regard to poorer performance using the RAVLT in adolescent and adult heavy cannabis users when compared to controls,^{29–31,33,73} unlike some of the other paradigms such as omitted numbers test, short-delay response task, or paced auditory serial addition test – all of which were tasks that were employed to measure working memory – with inconclusive results (see Table 3).^{8,33,96} Similarly, current long-term and heavy cannabis users, but not former or short-term cannabis users, performed poorer in the Buschke Selective Reminding Test (BSRT),^{73,85,109} a test that assesses multiple cognitive processes including learning and verbal memory, sensitivity to interference, recognition, and retrieval.^{106,110}

In sum, early observational studies pointed to the idea of cannabis-induced impairments in memory and learning,⁷² although the extent of the irreversible neurotoxic effects of cannabis on working memory, verbal learning, and memory functions remained a matter of contention due to a number of potential confounders that have variably been considered. Although some subsequent studies are still of limited interpretability due to a lack of consideration of crucial confounding factors,^{96,111–113} the majority of recent studies have generally attempted to address these methodological issues by considering factors such as the acute intoxication state, interindividual variability in past and current cannabis use, as well as the psychiatric and medical status of study participants (see Table 3), leading to a clearer picture of the long-term effects. There is now a growing body of evidence that tends to suggest that persistent memory deficits in a range of domains are more likely to occur in frequent and long-term cannabis users who start using cannabis early in life and consume cannabis strains high in $\Delta 9$ -THC, while impairments become particularly salient when memory is measured as a complex multifactorial construct. These findings may be particularly worrying, given the increasing prevalence of

Table 3 Effects of cannabis use on memory performance

Author	Subjects	Age in years (M)	Age of onset of use (M)	Cannabis use in years (M)	Joints [episodes]/lifetime (M)
Former cannabis users (history of cannabis use, ≤12 joints in the last 3 months)					
Pope ⁷³	n = 45	41	NR	15 (median)	11,000 (median)
Fried et al ⁷⁴	n = 16	18	14	2.2	2203
Current regular cannabis users (<30 joints/month or <20 days/month or <2000 joints/lifetime)					
Jager et al ⁷⁷ (fMRI)	n = 10	23	NR	7.1	1300 (median)
Jager et al ⁷⁸ (fMRI)	n = 20	25	NR	NR	1900 (median)
Grant et al ¹¹¹	n = 16	22	NR	NR	NR
Harvey et al ¹¹³	n = 34	16	NR	NR	NR
Current heavy cannabis users (≥30 joints/month or ≥20 days/month or ≥2000 joints/lifetime)					
Kanayama et al ⁹⁶ (fMRI)	n = 12	38	NR	NR	19,200
Smith et al ¹¹² (fMRI)	n = 10	20	NR	4.6	2697
Messinis et al ⁸³	n = 20	24	NR	7	NR
Solowij et al ³³	n = 51	29	NR	10.2	NR
Fontes et al ⁸²	n = 55	30	19	10.9	6790
Bolla et al ³⁰	n = 7	21	NR	5.3	NR
Short-term cannabis users (<4 years of cannabis use)					
Schweinsburg et al ⁷⁹ (fMRI)	n = 15	17	NR	3.4	310
Schweinsburg et al ⁸⁰ (fMRI)	n = 13	17	NR	2.3	342
Schweinsburg et al ⁸⁰ (fMRI)	n = 13	18	NR	2.7	515
Medina ⁹²	n = 31	18	NR	2.91	541
Fried et al ⁷⁴	n = 19	18	16	1.8	122
Block et al ¹⁰⁹ (PET)	n = 18	NR	NR	3.9	NR
Long-term cannabis users (cannabis use > 15 years)					
Pope ⁷³	n = 63	36	NR	19 (median)	18,720 (median)
Messinis et al ⁸³	n = 20	33	NR	15.6	NR
Battisti et al ⁸⁴	n = 24	36	17 (median)	17.0	NR
Solowij et al ³³	n = 51	41	NR	23.9	NR
Late-onset cannabis users (≥17 age of onset)					
Fontes et al ⁸²	n = 49	30	21	8.7	5160
Pope et al ⁸⁵	n = 63	44	≥17	NR	12,480 (median)
Early-onset cannabis users (<17 age of onset)					
Solowij et al ³¹	n = 52	19	16	2.4	NR
Fried et al ⁷⁴	n = 19	18	15	2.6	1884

Joints/month (M)	Days of use/month (M)	Abstinence period	Controlled confounder ^a	Memory tests ^b
≤2 last 3 months	NR	7 days	DU, PC, PsyM, A, G, IQ	BVRT ^{''} BSRT ^{''} WAIS-PS ^{''} WMS ^{''}
0	NR	Day of testing (NS)	DU, PC, PsyM, A, G, SES	
NR	NR	1 week	DU, PC, MC, PsyM, A, G, IQ	SMT ^{''}
NR	NR	NU	DU, PC, MC, PsyM, A, G, IQ	PMT ^{''}
NR	12	NR	DU, PC, A, G, SES, E	CANTAB-OTSC* CANTAB-RVIPT ^{''} CANTAB-SWM ^{''}
12 (median)	12 (median)	12 hours	DU, PC, A, G	CANTAB-RVIPT* CANTAB-SWM* RAVLT*
≥28	NR	NR	DU, PC, MC, PsyM, G, E	SDRT ^{''}
46	NR	<5 hours	DU, PC, IQ, PF	N-BACK ^{''}
≥16	21	123 hours (M)	DU, PC, MC, PsyM, G, IQ, E	BNT ^{''}
NR	27	17 hours (M)	DU, PC, A, G, IQ	RAVLT ^{''} WCST ^{''} AT ^{''} ON ^{''} PASAT ^{''} WAIS-VC ^{''}
51	NR	4.1 days (M)	PC, MC, A, IQ, E	WCST*
375	NR	28 days	DU, PC, A, G, IQ	CFT* PAL* WCST* RAVLT*
NR	13	48 hours	DU, PC, MC, PsyM, A	SWMT ^{''}
NR	14	3.3 days (M)	DU, PC, MC, PsyM, A, G, IQ, SES	SWMT ^{''}
NR	17	38 days (M)	DU, PC, MC, PsyM, A, G, IQ, SES	SWMT ^v
57	NR	28 days	PC, MC, A, G, SES, E	WMS* CFT ^{''} CVLT ^{''} WMS ^{''} WAIS-PS ^{''}
6	NR	Day of testing (NS)	DU, PC, PsyM, A, G, SES	
72	NR	16 hours (M)	DU, PC, PsyM, A, G, BV, HW	BSRT*
≥28	NR	7 days	DU, PC, PsyM, A, G, IQ	BSRT*
≥16	20	≥24 hours	DU, PC, MC, PsyM, G, IQ, E	BNT* RAVLT* VFT*
435 (median)	30 (median)	12 hours	PC, MC, A, G, E	VMT*
NR	28	17 hours (M)	DU, PC, A, G, IQ	AT* RAVLT*
45	NR	3.8 days (M)	PC, MC, A, IQ, E	WCST ^{''} WAIS-VC ^{''}
NR	NR	28 days	DU, PC, PsyM, A, G	WCST* BSRT ^{''} BVRT ^{''} WMS ^{''}
17.5	14 (median)	20 hours (median)	DU, PC, G, IQ, E	RAVLT*
12.4	NR	Day of testing (NS)	DU, PC, PsyM, A, G, SES	WAIS-PS* WMS*

(Continued)

Table 3 (Continued)

Author	Subjects	Age in years (M)	Age of onset of use (M)	Cannabis use in years (M)	Joints [episodes]/lifetime (M)
Hanson et al ⁷⁵	n = 19	18	16	NR	465
Ashtari et al ⁹⁷ (MRI)	n = 14	19	13	5.3	NR
Nestor et al ¹³⁸	n = 35	22	16.5	5.7	NR
Gruber et al ³²	n = 34	23	15.5	7.24	≥2500
Pope et al ⁸⁵	n = 69	36	<17	NR	17,368 (median)
Jager et al ¹⁰² (fMRI)	n = 21	17	13	NR	4006

Notes: *Poorer performance when compared to noncannabis users; [†]no differences in performance when compared to noncannabis users; [‡]controlled though exclusion, matching, or statistical methods; [§]see Table 1.

Abbreviations: M, mean; n, number; NR, not reported; DU, other drug use; PC, psychiatric condition; PsyM, psychoactive medication; A, age; G, gender; IQ, Intelligence Quotient; BVRT, Benton Visual Retention Test; BSRT, Buschke Selective Reminding Test; NS, not further specified; SES, socioeconomic status; WAIS-PS, Wechsler Adult Intelligence Scale (Processing Speed Index); WMS, Wechsler Memory Scale; MC, medical condition; SMT, Sternberg Memory Task; NU, negative urine toxicology; PMT, pictorial memory task; E, education; CANTAB-OTSC, Cambridge Neuropsychological Test Automated Battery One-Touch Stockings of Cambridge; CANTAB-RVIPT, Cambridge Neuropsychological Test Automated Battery rapid visual information processing task; CANTAB-SWM, Cambridge Neuropsychological Test Automated Battery Spatial Working Memory; RAVLT, Rey Auditory Verbal Learning Test; CANTAB-SS, Cambridge Neuropsychological Test Automated Battery spatial span; WAIS-WM, Wechsler Adult Intelligence Scale (Working Memory Index); CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery Paired Associate Learning Test; SDRT, short-delay response task; PF, personality factors; N-BACK, N-back task; VFT, verbal fluency task; BNT, Boston naming test; WCST, Wisconsin Card Sorting Test; AT, alphabet task; ON, omitted numbers; PASAT, Paced Auditory Serial Addition Test; WAIS-VC, Wechsler Adult Intelligence Scale (Verbal Comprehension Index); CFT, Rey–Osterrieth Complex Figure Test; PAL, paired associate learning test; SWMT, spatial working memory task; CVLT, California Verbal Learning Test; PET, positron emission tomography study; BV, brain volume; HW, height and weight; VMT, verbal memory task; HVLT, Hopkins Verbal Learning Test; MRI, magnetic resonance imaging study; FNPL, face–name pair learning; COWAT, controlled oral word association test; fMRI, functional magnetic resonance imaging study.

cannabis use especially in young populations,³ particularly with high $\Delta 9$ -THC concentration.²⁵

Underlying neural mechanisms

Over the last couple of decades, advanced neuroimaging techniques have allowed investigation of the neural mechanisms underlying the effects of acute and chronic cannabis exposure in humans *in vivo*. While structural magnetic resonance imaging allows for the display of brain morphology *in vivo*, functional imaging techniques allow an indirect estimation of regional neural activity by utilizing the fact that neuronal activation results in regionally increased blood flow and metabolism. The application of functional magnetic resonance imaging (fMRI), single photon emission tomography, and positron emission tomography (PET) allow the investigation of brain activity changes in response to a study participant performing a specific cognitive task.

In pharmacological challenge studies, the acute effects of cannabinoids on memory function can be analyzed, while imaging studies comparing subjects with and without a history of cannabis use allow the investigation of changes in neural function associated with chronic cannabis exposure in humans.^{17,114} Cannabinoids exert their effects by binding to specific endogenous cannabinoid receptors, including the CB1 receptor and the CB2 receptor,²⁴ both of which are G-protein-coupled receptors for cannabinoid ligands. However, the receptors differ in their

structure, affinity for ligands, and distribution in the human body. CB2 receptors are mainly expressed in the immune system and in peripheral nerve tissues, and are not considered to affect cognition.¹¹⁵ Given the high densities of the CB1 receptors present in brain regions that are critically involved in learning and memory functions, particularly the prefrontal cortex (PFC), hippocampus, basal ganglia, anterior cingulate, and cerebellum,^{116,117} the endogenous cannabinoid (eCB) system is thought to modulate the neural substrates accompanying memory functioning after exposure to cannabis.¹¹⁸

Most of the major cannabinoids present in the extract of the cannabis plant act presynaptically as agonists at CB1 receptors,¹¹⁹ and thereby cause alterations in neuromodulator systems (eg, dopaminergic, cholinergic, serotonergic, GABAergic, and glutamatergic systems) that in turn affect molecular mechanisms relevant to cognitive processes and prevent long-term potentiation – a process that is widely believed to underlie learning and memory.^{120–123} In contrast, CB1 antagonists/inverse agonists such as CBD or rimonabant may reverse some of the neurobiological and behavioral effects of $\Delta 9$ -THC in animals and humans.^{19,20,124–126} The particular vulnerability of the adolescent brain to the adverse cognitive effects of cannabis use may also be related to the increased sensitivity of the eCB system during this developmental stage due to the synaptic pruning and myelination that still occur, particularly in the frontal regions of the brain.¹¹⁸ Pharmacological studies

Joints/month (M)	Days of use/month (M)	Abstinence period	Controlled confounder ^a	Memory tests ^b	
NR	16	3 days	PC, MC, A, G, IQ, SES	HVLT* WAIS-WM*	
174	NR	6.7 months (M)	DU, PC, A, G, IQ, SES, BV		CVLT''
NR	23	15 hours (M)	DU, PC, MC, PsyM, A, G, IQ	FNPL*	
77	NR	12 hours	DU, PC, MC, PsyM, A, IQ	WCST*	CFT'' CVLT'' COWAT''
NR	NR	28 days	DU, PC, PsyM, A, G	BSRT* WCST*	BVRT'' WMS''
NR	NR	5.1 weeks (M)	DU, PC, MC, PsyM, IQ		PMT'' SMT''

have shown that both the acute and chronic administration of $\Delta 9$ -THC or CB1 agonists caused morphological and functional changes in the hippocampus in rats,^{127,128} and the modulation of hippocampal CB1 receptors after the administration of $\Delta 9$ -THC significantly disrupted memory performance in rats.¹²⁹ Moreover, it was found that microinjection of a CB1 receptor antagonist into the hippocampus blocked spatial memory deficits caused by $\Delta 9$ -THC administration, indicating that the disruptive effects of $\Delta 9$ -THC on memory function are mediated through its effects on hippocampal CB1 receptors.¹³⁰

Studies that have investigated human cannabis users employing structural imaging have reported morphological alterations in the parahippocampal, hippocampal, and thalamic areas,^{131,132} while larger hippocampus volumes have been related to higher memory scores in controls, but not in frequent cannabis users.⁹⁷ Despite these structural imaging findings, there is modest evidence of a major effect of cannabis use on the brain structures relevant to memory function,^{114,133} and structural imaging studies lack the ability to display the dynamic neural processes underlying memory function. In this context, functional neuroimaging (single photon emission tomography, PET, and fMRI) studies of cannabis users have been used to assess neural activation during the resting state or during the performance of memory tasks. Resting state neuroimaging studies provide evidence of alterations in regional cerebral blood flow (rCBF) and cerebral metabolism related to acute and chronic

cannabis exposure,^{114,134–136} while brain activation may normalize after a period of abstinence.¹³⁷ Conversely, fMRI imaging studies using paradigms that engage memory and learning processes in cannabis users have reported both hypoactivation and hyperactivation in parahippocampal regions,^{78,96,102,103,138} despite nonsignificant differences in task performance between cannabis users and noncannabis users.

Another fMRI study reported working memory-related hypoactivation in the inferior frontal and temporal regions, including the anterior cingulate cortex (ACC) and right inferior frontal and superior temporal areas; however, hyperactivation was noted in the medial temporal areas in cannabis users when compared to nonusers,⁷⁹ despite similar task performance. Similarly, in a PET study, Eldreth et al¹³⁹ found hypoactivation in the left perigenual ACC and the left lateral prefrontal cortex (LPFC) and bilateral hyperactivity in the hippocampus. While on the one hand, these studies support the notion of “hyperactivity,” indicating that increased brain activation reflects a higher neurophysiological effort or a compensatory mechanism to achieve similar performance levels, on the other hand they also tend to suggest that such compensatory mechanisms may no longer be sufficient during the performance of more challenging tasks.^{96,140} Moreover, parahippocampal activity appeared to be dependent on the frequency of previous cannabis use when performing an activation task.⁸⁶ Jacobsen et al¹⁴¹ found that adolescent

cannabis users performed poorer in the working memory task compared to controls, and that the former group failed to deactivate the right hippocampus, as opposed to controls. It has been suggested that this failure may reflect dysfunction of inhibitory interneurons within the hippocampus in cannabis users during mnemonic processing.

The acute administration of $\Delta 9$ -THC and its neurocognitive correlates have only been studied recently, using sophisticated neuroimaging techniques with better spatial resolution.³⁹ Bhattacharyya et al¹⁶ provided the first human evidence that memory impairments induced by $\Delta 9$ -THC were mediated through its acute effects on brain activation in the medial temporal and prefrontal areas. In this study, a modest dose of orally administered $\Delta 9$ -THC was found to augment task-related activity in the parahippocampal cortex during the encoding condition of a verbal learning task, thereby disrupting the linear decremental change in neural activity associated with repeated presentations of verbal stimuli and the relationship between parahippocampal activity and task performance in healthy occasional cannabis users, indicating that increased neurophysiological efforts are necessary under the acute effects of $\Delta 9$ -THC in order to meet the demands of the task during encoding.

During the recall condition, $\Delta 9$ -THC attenuated the task-related activity in the LPFC and ACC. These findings are in line with an electrophysiological study that reported an attenuation of stimulus-locked event related potentials (ERPs) in response to increased memory-task difficulty and impaired task performance after the acute administration of marijuana; additionally, a higher degree of intoxication (measured in terms of heart rate and subjective ratings) was related to a more dramatic reduction in ERP amplitude.¹⁴² In a recent fMRI study, Bossong et al¹⁴³ reported that $\Delta 9$ -THC attenuated activity in the insula and inferior frontal gyrus on the right side and in the middle occipital gyrus on the left side during the encoding condition of an associative memory task. These effects were unrelated to task performance, implicating that neural activity patterns associated with $\Delta 9$ -THC administration could not be explained by differences in task performance and suggest that $\Delta 9$ -THC may affect neural activity in brain regions critical to learning new information. During the recall condition, $\Delta 9$ -THC resulted in a network-wide increase in activation, with the strongest effects being observed in the cuneus and precuneus. Given the opposite effects of $\Delta 9$ -THC on brain activity during the encoding and recall conditions, the authors suggested that $\Delta 9$ -THC affects memory more directly at an early stage (ie, during encoding), while changes during recall were more likely to be reflective of a mechanism to compensate for the effect of the drug during encoding.

Moreover, Bossong et al¹⁴⁴ showed that a rising working memory load was related to a linear increase in activity in brain areas that mediate working memory in subjects under the placebo condition. In this way, $\Delta 9$ -THC disrupted this linear relationship by inducing hyperactivity and decreasing task performance at low working memory load. In keeping with behavioral evidence suggesting differential vulnerability to the adverse effects of cannabis, preliminary evidence has emerged pointing to the neural mechanisms that may underlie this genetically mediated variable sensitivity to the effects of $\Delta 9$ -THC.³⁹ This study reported that the effects of $\Delta 9$ -THC on medial temporal, striatal, and midbrain function during the encoding and recall conditions of a verbal memory task were moderated by variations in the AKT1 and the dopamine transporter (DAT1) genes that regulate central dopaminergic neurotransmission. Furthermore, the effects of $\Delta 9$ -THC on brain activation during the encoding and recall condition were greater in those carrying the risk variants of both genes compared to the rest, indicating that the impact of $\Delta 9$ -THC on the neural activity that may underlie memory function might depend on individual genetic profiles.

Another factor that potentially determines the level of vulnerability to the harmful effects of cannabis on cognitive functioning is the relative proportion of the different cannabinoids, particularly the relative proportion of $\Delta 9$ -THC to CBD. While, at a behavioral level, the acute administration of $\Delta 9$ -THC is thought to have adverse effects on memory and induces anxiety and psychotic-like symptoms in humans,¹⁰⁰ CBD has not been associated with these adverse effects,^{39,60} and might even reverse the deficits induced by $\Delta 9$ -THC.¹²⁶ For instance, Morgan et al²⁰ reported that impairments in episodic memory induced by $\Delta 9$ -THC were prevented by a higher level of CBD. Moreover, at a neurobiological level, Bhattacharyya et al¹⁹ reported opposite effects of $\Delta 9$ -THC and CBD on activation in the ACC, medial PFC, and the LPFC during verbal recall in healthy men with minimal previous cannabis exposure. These findings further implicate the involvement of CB1-rich brain regions on memory through the potential adverse effects of cannabinoid agonists such as $\Delta 9$ -THC, and also propose protective effects of cannabinoid antagonists/inverse agonists such as CBD on memory function and learning in humans.

Conclusion

In conclusion, evidence regarding the acute impairments in memory function induced by cannabis is generally robust, particularly for those using cannabis with a lower proportion of CBD and higher proportion of $\Delta 9$ -THC. In other words, the effects are likely to depend on the type of cannabis used

(ie, the greater the dose of $\Delta 9$ -THC, the greater the memory impairment).⁹ However, whether those with a history of frequent cannabis use may develop tolerance to the acute impairments caused by $\Delta 9$ -THC is not entirely clear. Although some studies have reported recovery from cannabis-induced cognitive impairments in long-term users,^{73,74} deficits in verbal and working memory, as well as alterations in brain function and structure associated with cannabis use, are likely to persist beyond the acute intoxication state, particularly when heavy cannabis use is started at an early age. These findings emphasize the need for further investigations regarding the role of early-onset cannabis use on neurodevelopmental processes.

Since higher $\Delta 9$ -THC concentrations are now dominating the market,²³ and given that high prevalence rates exist particularly among teenagers,^{1,3} its consumption represents a major public health concern. Although the precise neurocognitive and neurochemical mechanisms underlying the marijuana-induced memory impairments remain to be elucidated, cognitive neurobiological studies suggest that cannabinoids may affect functioning in memory-relevant brain areas by interfering with the homeostatic role of the eCB system. While the hippocampus appears to have the highest density of CB1 receptors, and since this has been shown to play an important role in the disruptive effects of $\Delta 9$ -THC on memory,^{130,145} studies have highlighted that these effects may also be related to the effects of $\Delta 9$ -THC on prefrontal and parahippocampal function,^{16,46} implicating the involvement of a network of brain areas affected by $\Delta 9$ -THC.¹⁴³ In this context, the increased brain activation noted in cannabis users while performing hippocampus-dependent memory tasks may reflect compensatory mechanisms that could be activated in order to achieve similar performance levels comparable to those observed in nonusers. Moreover, these effects may depend on individual genetic profiles,^{39,42} suggesting interesting avenues for future genetic studies to investigate the modulatory role of susceptibility genes with regard to the memory impairments caused by cannabis.

Overall, further research elucidating the precise neural mechanisms underlying the heterogeneous and sometimes opposite effects of cannabinoids will be useful, not only in order to facilitate the development of treatments that may prevent the deleterious effects of cannabis, the most widely used illicit drug worldwide,² but also to identify potential candidate targets for memory impairments in conditions such as schizophrenia or dementia. Given the therapeutic potential of cannabinoids such as $\Delta 9$ -THC in the management of medical conditions including neuropathic pain or spasticity due to multiple sclerosis (for a review see Grant et al¹⁴⁶), an understanding of the neural mechanisms underlying the effects

of cannabis on memory function also has a wider implication beyond psychiatric disorders, as it may lead to the identification or synthesis of related molecules with the desired therapeutic effects, but without the undesired side effects.

Disclosure

The authors report no conflicts of interest in this work.

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