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Rolled into one?

Weeding out evidence on cognitive impact of marijuana from that of THC

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Introduction

Cannabis (also known as Marijuana), an umbrella term encompassing natural and bred plant varieties, contains over 100 distinct cannabinoids and other bioactive molecules in varying ratios, yet all are commonly conflated with the prime euphorigenic cannabinoid, Δ-9 tetrahydrocannabinol (THC).[1] A lack of appreciation for this distinction, along with media sensationalism, have created misinformation about the biological actions of specific cannabinoids, for instance, that regarding the cognitive impact of THC versus cannabis in general. Restrictions have stalled investigating the cognitive impact of cannabinoids per se, but shifting federal and state legislation may, at last, open avenues for systematic research.[1] Whereas all cannabinoids were once considered Schedule 1 under the Controlled Substances Act, with no medicinal value and high abuse liability, enactment of the Agricultural Improvement Act of 2018 (2018 Farm Act) seemingly removed hemp-derived cannabinoids from research restrictions. Although cannabis and THC remain listed as Schedule 1 substances, select synthetic formulations subject to rigorous clinical trials are US Food and Drug Administration-approved under less restrictive scheduling (eg, dronabinol, marketed as Marinol and Syndros). We summarize findings from English-only, peer-reviewed original articles and meta-analyses of specified cannabinoids' effect on cognition in preclinical and clinical literature, where known, to guide practitioners with proper evidence and highlighting gaps in knowledge for future research.

Most human literature is based on cannabis preparations and fails to characterize cannabinoid composition, potency, and consistency; is not controlled; varies in duration of use; and does not account for potential underlying neuropsychiatric differences or comorbid drug use. Preclinical studies in rodents offer a cleaner, well-controlled method to assess the effects of THC on cognition, with the goal of extrapolating to potential clinical relevance. Exploring cognition in animals involves numerous testing paradigms that assess attention processes, learning, and memory. Equating these studies to human exposure poses a significant challenge, given differing administration route, consequent bioavailability, dosage employed, and exposure duration. Additionally, anatomical differences and the methods of assessment warrant cautious interpretation.

Preclinical literature

Studies considered in this review are limited to doses (<10 mg per kg) that do not exceed an equated dose known to impair an adult human. It is vital to recognize that most rodent studies do not correspond to human "chronic" use patterns. The **eTable** (available at www.mdedge.com/THCandCBD) summarizes cognitive

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function tested, testing methods, and their outcomes in the murine models.

Pre-pulse inhibition (sensorimotor gating) deficiencies suggest disturbances in pre-attentive processes for rodents and humans. Available evidence suggests that repeated, brief THC exposures at clinically relevant doses does not affect pre-attentive processes.[2-6] Tasks mimicking human attentional capacity (accuracy and speed of task performance) and control (eg, impulsivity, perseverance), however, show impaired attention and slower temporal perception with repeated exposure to THC.[7-10]

Maze navigation challenges evaluate the effects of cannabinoids on learning and utilizing spatial cues. Evidence, especially from the Morris Water Maze paradigm, demonstrates that acute exposure to THC consistently impairs maze learning. Adolescent animals, especially females, appear more susceptible to THC-induced learning impairment, whereas adult animals develop rapid tolerance to these effects, suggesting an age-related effect. However, a significant confounder in these studies is that impaired acquisition of spatial learning could be secondary to THC-induced place aversion common to rodents.[11-26]

Delayed match (or nonmatch)-to-sample models investigate the effect of THC on nonspatial working memory tasks and have found dose-dependent disruption with acute or repeated THC exposure.[27-29] When rodent short- and long-term recognition memory is tested through interaction time with novel versus familiar objects, both acute and repeated THC exposure appear to impair novel object recognition in adolescent but not adult animals, again suggesting some age-dependent effects of THC. In contrast, cognition related to fear conditioning appears largely unaffected following repeated exposure to THC, even in adolescent animals.[30,31] Ultimately, these data are considered inconclusive.

Few rodent studies investigate the cognitive effects of combined THC and cannabidiol (CBD), particularly in a 1:1 ratio. This becomes important to the clinician because nabiximols, available as a commercial product (Sativex) in the United Kingdom and European Union, is being studied in clinical trials in the United States. Nabiximols contains CBD and THC as the most abundant cannabinoids, together with other minor cannibinoids and terpenes. In behavioral studies, combined treatment with THC and CBD prevented THC-induced sensorimotor deficits, place aversion, and impairment of novel object recognition in both adolescent and adult animals.[30,32,33]

Clinical literature

Although our focus is the relationship between cannabinoids and cognition, human studies are not well-controlled, with individual cannabinoids rarely analyzed. Therefore, in building a more complete picture of the cannabinoid–cognition interaction (memory, attention, psychomotor performance, impulsivity, and decision-making), here we include studies of cannabis without describing specific levels of cannabinoids present in the preparation.

Testing cognition in humans involves varying methodologies, reflecting the challenge of reducing complex processes to measurable units of performance. Central nervous system structures associated with cognition are extremely diverse and complex, making it difficult to draw inter-experimental comparisons. Differing tasks, even those testing within the same domain (ie, memory), might not be directly comparable. Existing literature of cannabis effects seldom account for such confounding factors, such as small sample size, psychiatric differences, comorbid drug use, genetics, and sex differences. Although these issues do not negate the findings, they might explain some of the ambiguous, often conflicting, results.[34-43] Our review is by no means comprehensive, but provides a solid background on current information.

Verbal learning and memory are often measured with tasks in which the participant must learn and recall words immediately and after a delay. Other tasks require participants to differentiate target words from distractors. Comprehensive reviews suggest that these tasks are particularly sensitive to both acute[44-46] and chronic[47] effects of cannabis, but are limited by the confounding variables mentioned above.

Dose-dependent impairment in verbal recall is observed after acute administration of THC[34,35,39,48-50] and vaporized cannabis[51,52] in adults, affecting both immediate and delayed recall.[34] Impairment appears greater in occasional users compared to heavy users, suggesting tolerance to effects.[35] In adolescents, impaired acquisition, storage, retention, and retrieval of various words is observed with chronic use.[53] Word-recall deficits are associated with increased cerebral blood flow on functional magnetic resonance

imaging (fMRI), a measure of neuronal activity, to regions important for memory.[54] Effects persist even when trials control for alcohol use, depression, intellectual ability[53,55] and abstinence periods[56]; however, conflicting evidence suggests possible recovery with extended abstinence for adolescents who had approximately 4 cannabis uses a week.[57]

Pre-dosing with oral CBD prior to acute THC ameliorates THC-induced verbal learning and memory deficits in some studies[49,58] but not in others.[50] Using fMRI, investigators have observed decreased activity of the striatum and lateral prefrontal cortex, regions implicated in verbal learning and memory during verbal recall, when acute THC was administered to adults.[59] Cannabidiol produces the opposite effect on activity in these brain regions, leading authors to conclude that perhaps CBD rescues verbal recall performance by negating the decrease in activity brought on by THC.[59]

Whether working memory (WM) is impaired by cannabinoids remains unclear. Acute doses of THC impair WM inconsistently. THC impairs Sternberg Memory Task (STM) performance[36,52,60] but not when combined with CBD.[61] fMRI during STM performance shows a reduction in the linear relationship between WM difficulty and activation of several brain regions implicated in WM (eg, cerebellum and frontal, parietal, and temporal cortices), suggesting impairment. THC impairs delayed match-to-sample performance in some investigations[34,37] but not in others,[35,39,62] and there are mixed findings regarding spatial WM impairment.[35,38,39] It should be noted that acute effects of cannabinoids on WM, whether paired with CBD or alone, are diminished in heavy users (more than 5 times per week) compared to light (less than once a week) or naïve users.[62] However, this is not a universal rule, as no effect on WM was observed in naïve patients taking a mixture of THC and CBD.[63] Last, adolescent and adult long-term heavy cannabis users showed altered activity in frontal and parietal cortical regions during STM performance, despite a lack of behavioral differences.[64,65]

Studies in adults and adolescents broadly suggest that acute exposure to cannabinoids impairs a variety of attentional processes, including attentional allocation, divided attention, and sustained attention.[34,36,52,66-69] Adolescents who use cannabis regularly have deficits in sustained attention in comparison to naïve or occasional users,[70,71] and attention deficits present in adolescent cannabis users appear to persist even after an extended (3-week) abstinence period.[55,57] However, after controlling for other predictors, such as alcohol or tobacco use, other work indicates that attention measures are not associated with cannabis use.[72]

In adults with previous occasional cannabis use, acute exposure to THC attenuates the amplitude of the P300 event-related potential, an electroencephalographic marker of attentional allocation, during performance of an auditory oddball task.[66,69] Other works find no effect on P300 amplitude in heavy cannabis users.[73,74] Impaired performance on a divided-attention task has been reported following administration of a high THC dose (500 µg/kg) in occasional but not heavy users.[75] These findings indicate, first, impaired attentional processes following acute high dose THC ingestion and, second, that these effects might be less apparent in more entrenched users, possibly due to tolerance.

Acute oral administration of THC in adults impaired psychomotor function, including finger tapping, critical tracking, and choice reaction time tasks in most,[35,76-79] although not all,[80] studies. When THC and CBD were combined, finger tapping was inconsistently affected.[81] High-dose combined THC and CBD was not associated with any impairment of motor function.[61] Chronic cannabis use effects on psychomotor function are inconsistent, with some studies reporting impairment in adults and adolescents,[82-84] improvement in adolescents,[85] and no change in adolescents[71] or adult daily users.[62] Although findings are mixed, they indicate that psychomotor performance is likely affected by acute administration of THC, but not acute THC and CBD.

Cannabis use is linked to impulsive and risky decision-making, in which users are more likely to make immediately rewarding choices over delayed rewards, despite a high probability of future adverse outcomes. Researchers employ a variety of tasks to test these phenomena in the lab.[86] Acute and long-term results are mixed, with some suggesting that acute administration of THC (1) adversely impaired decision-making by altering reward and punishment sensitivity and (2) increased risky choices in both infrequent[87] and regular adult users.[88] In other studies, no effect on these aspects of decision-making has been found.[75,89] Long-term cannabis use across all age groups (adolescents, young adults, and older adults) was shown to induce poor decision-making performance[62,85,90-93]; after controlling for tobacco and alcohol use, differences in performance were not found.[72,94-96] Therefore, whether acute or long-term use of cannabinoids impacts decision-making remains unresolved and requires further study.

Takeaways for the practitioner

Animal models remain the cornerstone of evidence concerning cannabinoids and cognition, highlighting the importance of better human-controlled studies. Although human and animal studies indicate that acute THC exposure can transiently alter learning, memory, and psychomotor performance, other findings suggest the possibility of tolerance to these effects, an interaction with age, and potential ameliorating effects of CBD if present in equal amounts to THC.

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eTABLE. Effect of Δ-9 tetrahydrocannabinol on executive cognitive processes in murine models[2-31]

Function	Performance test	Species	Sex	Age	Treatment type	Dose, mg/kg (route)	Estimated human equivalent dose, mg	Outcome	Reference
Sensimotor gating	Pre-pulse inhibition	Mouse	M	Adult	Acute pretreatment Acute pretreatment Subchronic (18 d)	5 (IP) 0.3-3.0 (IP) 0.3-3.0 (IP)	24.3 1.5-14.6 1.5-14.6	NC ↑ NC	Boucher et al., 2007[2] Long et al., 2010[3]
			F	Adult	Acute pretreatment	5 (IP)[a]	24.3	NC	Long et al., 2010[4]
		Rat	M	Adolescent	Acute pretreatment	0.3-3.0 (intravenous)	2.9 – 29	NC	Malone, Taylor, 2006[5]
				Adult	Acute pretreatment Subchronic (20 days)	1 (IP) 1 (IP)	9.7 9.7	NC ↓	Tournier, Ginovart, 2014[6]
Impulsivity (visuospatial task)	Five-choice serial reaction time	Mouse	M	Adult	Acute pretreatment	3 (IP)	14.6	↓	Cope et al., 2016[7]
		Rat	M	Adult	Acute pretreatment	2 (IP)	19.4	↓	Wiskerke et al., 2011[8]
					Chronic (14 d x 8 cycles, with 9 drug-free intervals)	0.6, 6 (IP)	5.8-58.3	↑	Irimia et al., 2015[9]
Attention (visuospatial task)	Lateralized reaction time	Rat	M	Adult	Acute pretreatment	1, 2 (IP)	9.7, 19.4	↓	Presburger, Robinson, 1999[10]
Working and reference memory (spatial task)	Morris Water Maze	Mouse	M	Adult	Acute pretreatment	0.3-3.0 (subcutaneous)	1.5-14.6	↓	Varvel et al., 2001[11]
					Acute pretreatment	4, 6 (IP)	19.4, 29.2	↓	Da et al., 2002[12]
					Acute pretreatment	0.3-3 (IP)	1.5-14.6	↓	Varvel, Lichtman, 2002[13]
					Acute pretreatment	1, 3 (IP)	4.9, 14.6	NC	Niyuhire et al., 2007[14]
					24-h pretreatment Subchronic (13 d)	1 (IP) 1 (IP)	4.9 4.9	↓ ↓	Boucher et al., 2009[15]
					Acute treatment and tested after 3 wk	0.001 (IP)	4.9 mg	↓	Tselnicker et al., 2007[16]
					Acute treatment and tested after 3 wk	0.002 (IP)	9.7 mg	↓	Amal et al., 2010[17]
		Rat	M	Adult	Subacute treatment	2.5 (IP)	24.3	↓	Cha et al., 2006[18]
					Acute posttreatment	0.5, 2 (IP)	4.9, 19.4	↓	Fadda et al., 2004[19]
			F	Adult	Subacute treatment	2.5 (IP)	24.3	↓↓	Cha et al., 2007[20]
	Eight-arm radial maze	Rat	M	Adolescent	Acute pretreatment Chronic (90 d) Repeated, escalating, and subchronic	1.25 (IP) 5 (IP) 2.5-5 (IP)	12.2 48.6 24.3-48.6	↓↓[b] ↓[c] ↓	Nakamura et al., 1991[21] Rubino et al., 2009[22]
				Adult	Acute pretreatment	1, 3 (IP)	9.72, 29.2	↓	Lichtman et al., 1995[23]
					Acute pretreatment	2 (IP)	19.4	↓	Mishima et al., 2001[24]
	T-maze	Rat	M	Adult	Acute pretreatment	2.5 (IP)	24.3	↓	Nava et al., 2000[25]
	Lashley III maze	Rat	F	Adult	Acute pretreatment	2.5 (IP)	24.3	↓	Carlini et al., 1970[26]
Working memory (nonspatial task)	Delayed nonmatch-to-sample	Rat	M	Adult	Acute pretreatment	2 (IP)	19.4	↓	Mallet, Beninger, 1998[27]
					Acute pretreatment	0.5-2 (IP)	4.9-19.4	↓	Hampson, Deadwyler, 2000[28]
	Delayed match-to-sample	Rat	M	Adult	Acute pretreatment	0.75-2 (IP)	7.3-19.4	↓	Heyser et al., 1993[29]
Recognition memory (nonspatial task)	Novel object recognition	Mouse	M	Adolescent Adult	Subchronic (20 d) Subchronic (20 d)	3 (IP) 3 (IP)	29.2 29.2	↓↓ ↓	Murphy et al., 2017[30]
				Adolescent Adult	Subchronic (28 d) Subchronic (28 d)	3 (osmotic pump) 3 (osmotic pump)	14.6 14.6	↓↓ ↓	Bilkei-Gorzo et al., 2017[31]

Abbreviations and symbols: F, female; IP, intraperitoneal; M, male; NC, no change; ↑, increased; ↓, decreased; ↓↓, greatly decreased.

[a]Dronabinol.

[b]Long-term working memory unaffected.

[c]Reference memory unaffected.