Review

Biological Psychiatry

Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review

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ABSTRACT

Cannabis use has been associated with impaired cognition during acute intoxication as well as in the unintoxicated state in long-term users. However, the evidence has been mixed and contested, and no systematic reviews of the literature on neuropsychological task-based measures of cognition have been conducted in an attempt to synthesize the findings. We systematically review the empirical research published in the past decade (from January 2004 to February 2015) on acute and chronic effects of cannabis and cannabinoids and on persistence or recovery after abstinence. We summarize the findings into the major categories of the cognitive domains investigated, considering sample characteristics and associations with various cannabis use parameters. Verbal learning and memory and attention are most consistently impaired by acute and chronic exposure to cannabis. Psychomotor function is most affected during acute intoxication, with some evidence for persistence in chronic users and after cessation of use. Impaired verbal memory, attention, and some executive functions may persist after prolonged abstinence, but persistence or recovery across all cognitive domains remains underresearched. Associations between poorer performance and a range of cannabis use parameters, including a younger age of onset, are frequently reported. Little further evidence has emerged for the development of tolerance to the acutely impairing effects of cannabis. Evidence for potential protection from harmful effects by cannabidiol continues to increase but is not definitive. In light of increasing trends toward legalization of cannabis, the knowledge gained from this body of research needs to be incorporated into strategies to minimize harm.

Keywords: Attention, Brain, Cannabis, Cognition, Executive function, Memory

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Shifts in public opinion and policies toward legalization of cannabis are poised to result in an increase in the prevalence of cannabis use beyond the 178 million users estimated to exist today (1–3). Although most individuals who try cannabis do not go on to use it regularly (1,2), individuals who do so risk adverse effects to physical and mental health (4). Negative sequelae that have been attributed to regular and prolonged cannabis use include alterations to brain morphology (5–7) and function (8–11); psychosis risk (12,13); poor psychosocial outcomes (4,14–17); and impaired cognition, especially deficits in attention, learning and memory (18–21), and executive functions (9,22). Morphological and connectivity changes in brain structures with high amounts of cannabinoid receptors (e.g., hippocampus, prefrontal cortex, cerebellum) (23) may mediate observed cognitive deficits in cannabis users (5–7, 9–11,24), although direct structure/function relationships are not readily demonstrated.

A substantial number of studies have been published in recent years, prompted by renewed interest in understanding the effects of cannabis on the brain partly as a result of mounting evidence for links between cannabis use and psychosis (25–28) and recognition of similarities between cognitive impairment in cannabis users and deficits observed in patients with schizophrenia (19). Interest has emerged in examining the effects of different compounds within cannabis plant matter, specifically (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), the primary psychoactive constituent considered to be psychotogenic, and cannabidiol (CBD), the second most abundant cannabinoid, shown to have antipsychotic properties (29) and to attenuate the psychotogenic effects of THC, with opposite effects on brain function (30). Recent critical reviews have focused on neuroimaging outcomes from acute cannabinoid challenge (9,31) and on brain morphology in chronic users (5,7,32). However, to date, the literature on neuropsychological task-based measures of cognition has not been examined in the form of a systematic review. We systematically review the empirical research published in the past decade. We identify core themes that have emerged from the recent literature or continue to plague this field and study limitations and future directions for this research area.

METHOD

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1) (33). The search strategy and

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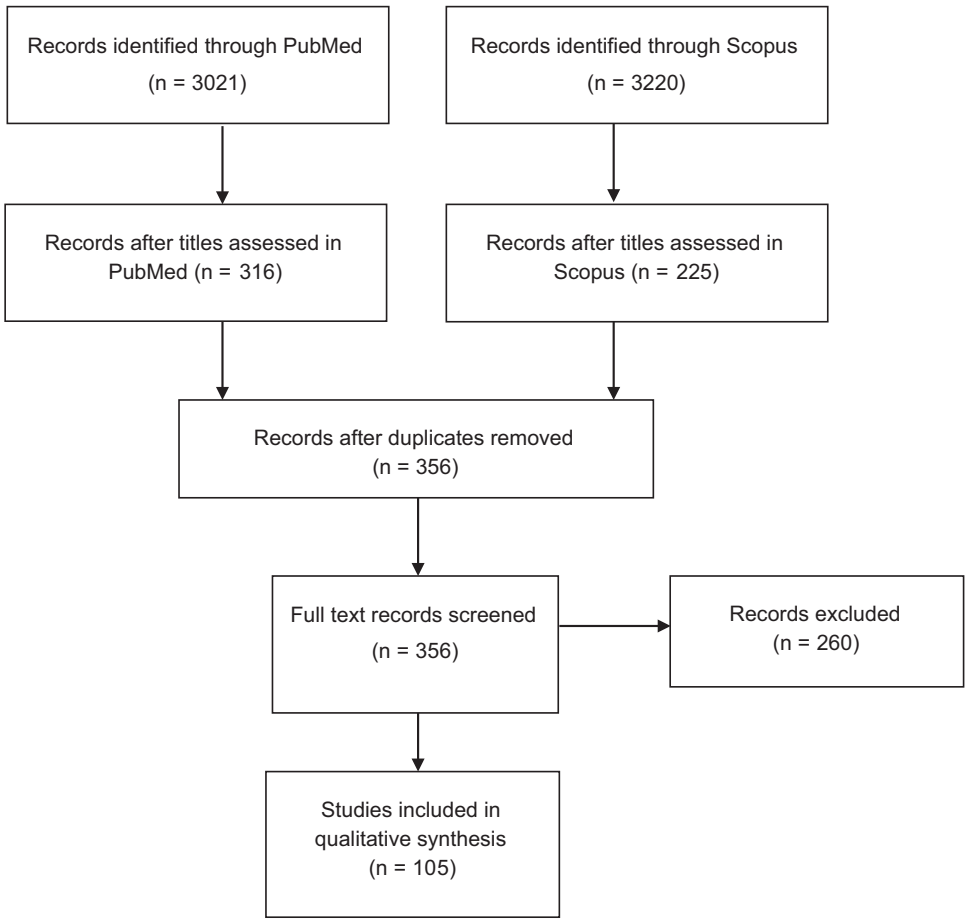

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for systematic search and identification of studies meeting inclusion criteria for systematic review. Selection criteria were as follows: 1) neuropsychological or cognitive experimental tasks administered to regular or former cannabis users or after acute administration of cannabis or synthetic or phytocannabinoid compounds; 2) cannabis (or cannabinoids) as the primary drug of interest; and 3) human participants. Exclusion criteria were as follows: 1) studies in which cannabis was not the primary drug of concern; 2) questionnaire (trait) measures of cognition; 3) major psychopathology or neurologic conditions within assessed sample; 4) animal research; 5) neuroimaging, electrophysiologic, or autonomic measures as primary outcome variables; 6) treatment (e.g., cognitive-behavioral therapy) as the primary focus; 7) real-world multiplex tasks requiring simultaneous use and integration of multiple aspects of cognition, such as driving; and 8) case studies.

data extraction are detailed in Supplement 1, and selection criteria, resulting in 105 studies included for review, are provided in the legend of Figure 1. From each study, we extracted participant demographics (age, sex, IQ), cannabis use metrics (e.g., age of onset and duration, frequency, and quantity of use), period of abstinence before testing, extent of other substance use (including alcohol and tobacco), dosing details for acute administration studies, cognitive domains investigated, experimental tasks employed, and key cognitive findings. The primary results of interest for qualitative synthesis of findings were group differences in performance and associations with cannabis use metrics.

RESULTS

We provide a summary appraisal of findings organized by primary cognitive domain in order of evidential strength from most to least consistently impaired. A more detailed account of findings from all studies is provided in Supplement 1, and detailed data extracted from each article are tabulated in Table S1 in Supplement 2. Within each cognitive domain, we address first acute administration studies, then studies of chronic exposure to cannabis, followed briefly by abstinence studies. Further consideration is given to the important issue of persistence or recovery of function separately in the Discussion. Table 1 provides a qualitative summary of findings across all cognitive domains examined.

Memory

Memory function has been the most consistently impaired cognitive domain affected by cannabis, and studies from the past 10 years continue to extend the evidence base. The most extensive evidence for impairment is within verbal learning and memory.

Verbal Learning and Memory. Most often measured using word list learning tasks, with several immediate and delayed recall trials and a recognition trial, verbal learning and memory tasks have been identified as particularly sensitive to the acute (20,34,35) and chronic (18) effects of cannabis. Further clear evidence has emerged for impairing effects of acute intravenous (IV) THC (36–40), vaporized cannabis (41,42) and oral nabilone (43) on immediate and delayed recall and sometimes recognition accuracy. Predosing with CBD or greater CBD content in cannabis may protect against some THC-induced verbal learning and memory deficits (40,44). Impaired verbal learning and memory continues to be consistently observed in chronic cannabis users, including adolescents (45–47) and young adults (48–52) [with some