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Does Cannabis Use Cause Declines in Neuropsychological Functioning?: A Review of Longitudinal Studies

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Abstract

Cannabis use has been linked to impairments in neuropsychological functioning across a large and continually expanding body of research. Yet insight into underlying causal relations remains limited due to the historically cross-sectional nature of studies in this area. Recently, however, studies have begun to use more informative design strategies to delineate these associations. The aim of this article is to provide a critical evaluation and review of research that employs longitudinal designs to examine the link between cannabis use and neuropsychological functioning. In summarizing the primary findings across these studies, this review suggests that cannabis use leads to neuropsychological decline. However, across most studies, these associations were modest, were present only for the group with the heaviest cannabis use, and were often attenuated (or no longer significant) after controlling for potential confounding variables. Future studies with neuropsychological data prior to and after initiation of cannabis use, along with careful measurement and control of "shared risk factors" between cannabis use and poorer neuropsychological outcomes, are needed to better understand who and under what conditions is most vulnerable to cannabis-associated neuropsychological decline.

Keywords

cannabis; cognition; marijuana; neuropsychology; longitudinal; drug abuse

Introduction

Use of cannabis is prevalent. During 2015, 44% of Americans over 12 years of age reported ever having used the drug and 8.3% endorsed past month use (Center for Behavioral Health Statistics and Quality, 2016). Among 12th graders, 45% have used cannabis and 23% have used in the past month (Johnston, Miech, O'Malley, Bachman, & Schulenberg, 2016). Annual prevalence of use rose from 24% during 1991 to 36% during 2016 among 12th graders. Historically, this remains much lower than estimates from 1977 to 1980, when it hovered near 50% (Johnston et al., 2016). Despite a higher prevalence of use during the late 1970s, public opinion toward legalization of cannabis has become more favorable. When the Pew Research Center began surveying public opinion toward cannabis legalization during

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1969, 12% supported legalization, whereas 84% did not (Pew Research Center, 2016). A reversal occurred recently, with 57% of Americans supporting and 37% opposing cannabis legalization during 2016. Support for legalization appears to be transgenerational, with the largest shift observed in generations born during or after the 1940s (i.e., Baby Boomers, Generation X, Millennials), but also observed to a lesser extent among those born from mid-1920 to mid-1940 (i.e., the Silent Generation). Consistent with these trends, 28 U.S. states have passed medical marijuana laws and 8 have legalized recreational use for adults over the age of 21.

Cannabis and its constituents are also the subject of research efforts focused on medical applications. As of February 2017, ClinicalTrials.gov listed 108 ongoing clinical trials with "cannabis" as the intervention. Results from studies examining the effectiveness of cannabis as medicine suggest that it may be effective for treating nausea among patients with cancer, anorexia among those with cancer or HIV, pain among patients with HIV or multiple sclerosis (MS), and urinary dysfunction in those with MS (Borgelt, Franson, Nussbaum, & Wang, 2013; Koppel et al., 2014). A recent meta-analysis examined 79 clinical trials and concluded that cannabinoids may be beneficial for nausea and vomiting, pain reduction, and reduced spasticity (Whiting, Wolff, Deshpande, & et al., 2015). However, adverse events were not uncommon across trials and cannabis formulations. These included dizziness, dry mouth, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucinations. The data from adverse events was not amenable to meta-analysis and suggests that further work is needed to better understand the circumstances under which they emerge (e.g., formulation, route of administration, dosing, disorder treated).

These side effects, as well as the recreational and medical effects of cannabis on the central nervous system, occur primarily through activity at cannabinoid receptor type 1 (CB1) (Pertwee, 2006; Pertwee, 2008). CB1 are located throughout the cortex and densely concentrated in numerous brain regions important for cognition and psychomotor functioning (Glass, Dragunow, & Faull, 1997). Not surprisingly, the effects of cannabis on neuropsychological functioning have been a topic of considerable interest for many decades. Given that this article is part of a Special Issue of JINS commemorating 50 years of the International Neuropsychological Society (INS), it is prudent to mention that at least three prior INS presidents (i.e., Paul Satz, Jack Fletcher, and Igor Grant) made early contributions to this literature (Fletcher et al., 1996; Grant, Rochford, Fleming, & Stunkard, 1973; Satz, Fletcher, & Sutker, 1976). Despite numerous studies, the onset, magnitude, and duration of the effects of cannabis on neuropsychological function, and the conditions under which adverse effects are exacerbated, continue to be debated. Understanding its adverse effects on neuropsychological functioning continues to be critically important.

Two meta-analyses help synthesize results from studies examining associations between cannabis use and neuropsychological functioning. Both focused on non-acute use (i.e., when participants were not acutely intoxicated) and included only studies that attempted to control for critical confounds that would otherwise hamper interpretation of findings. The meta-analysis by Grant, Gonzalez, Carey, Natarajan, and Wolfson (2003) included 15 studies resulting in data from 704 cannabis users and 484 non-using controls. Overall, evidence

emerged for a “residual cannabis effect” that was statistically significant but small in magnitude (Effect Size[1] [ES] = −.15, 99%CI [−.29, −.02]), suggesting that cannabis users’ neuropsychological performance was about one-fifth of a standard deviation (SD) worse than that of controls. For individual neuropsychological domains, the only statistically significant effects were observed for Learning (ES = −.21, 99%CI [−.39, −.02]) and Forgetting (ES = −.27, 99%CI [−.49, −.04]).

A more recent meta-analysis by Schreiner & Dunn (2012) used guidelines for study inclusion and grouping of neurocognitive domains that was similar to those used by Grant et al. (2003), but included only studies published since 2000 to minimize overlap. Their analyses included 33 studies, yielding 1,010 cannabis users and 839 controls. An overall negative association between cannabis use and neuropsychological functioning was also observed (ES = −.29, 95% CI [−.46, −.12]). Significant detrimental effects of cannabis use were also observed for Learning (ES = −.35, CI 95% [−.55, −.15]) and Forgetting/Retrieval (ES = −.25, CI 95% [−.47, −.02]), Abstraction/Executive functions (ES = −.21, CI 95% [−.38, −.05]), Attention (ES = −.36, CI 95% [ES = −.56, −.16]), Motor skills (ES = −.34, CI 95% [−.57, −.11]), and Verbal/Language (ES = −.23, CI 95% [−.47, −.001]). Thus, both meta-analyses suggest that cannabis use is associated with poorer neuropsychological functioning, with the magnitude of these effects hovering around 1/3 of a SD.

It is worth noting that a recent evidence-based consensus report from the National Academy of Sciences (2017) concluded there was moderate evidence for acute effects of cannabis on cognitive abilities, but limited evidence for associations under abstinence. When considering the aforementioned results, it is important to keep in mind that the majority of the current literature on cannabis use and neuropsychological functioning consists predominantly of cross-sectional studies and convenience samples of modest size. Although such studies have been valuable in advancing research in this area, they have an important limitation – they preclude making strong causal inferences between use of cannabis and declines in neuropsychological functioning. They do not answer the question, “Does cannabis use cause declines in neuropsychological functioning?” Studies that assess how changes in cannabis use prospectively influence changes in neuropsychological functioning, compare neuropsychological performance before and after onset of cannabis use, or make use of cotwin designs are more apt for inferring causation. Cotwin designs are very effective at controlling for measured and unmeasured confounds given that twins share genetic and environmental factors (e.g., comparing twins that differ on their history of cannabis use when trying to link cannabis use to neuropsychological functioning). Such studies have been rare, but are rapidly emerging in recent years. This manuscript presents a detailed review of these studies to better understand the strength of the evidence for or against the assertion that cannabis use causes declines in neuropsychological functioning.

Scope of the Current Review and Literature Search Process

A PubMed search was conducted during December of 2016 with variations of the terms ((cannabis OR marijuana OR THC) AND (neuropsy* OR neurocog* OR cognitive) AND

[1]We use the term Effect Size (ES) to refer to various different measures of standardized mean differences (e.g., Cohen’s d, Hedge’s g).

longitudinal). The retrieved studies were reviewed to identify those that used longitudinal designs to specifically examine associations between use of cannabis and changes in neuropsychological functioning. This yielded seven studies, most of which had large samples and data on neuropsychological performance prior to and after initiation of cannabis use. Below, we review each of these studies in detail and, whenever possible, include data on factors that may influence interpretation of study results. Key characteristics of these studies are provided in Table 1. By design, the scope of the review precluded inclusion of studies focusing on acute effects, psychosocial consequences, academic performance, or neuroimaging outcomes, which are discussed by others (Batalla et al., 2013; Broyd, van Hell, Beale, Yücel, & Solowij, 2016; Hall & Degenhardt, 2009; Lorenzetti, Solowij, & Yücel, 2016; Matthijs, Gerry, Sagnik, & Paul, 2014; Volkow, Baler, Compton, & Weiss, 2014; Volkow, Swanson, Evins, & et al., 2016).

Review of Longitudinal Studies on Cannabis Use and Neuropsychological Functioning

Studies without Neuropsychological Data Prior to Cannabis Use Initiation

Two longitudinal studies examining how use of cannabis changes neuropsychological performance were published with data from “PATH through Life”: a sequential cohort study using a representative sample of adults from the Canberra/Queanbeyan area of Australia randomly selected for participation from electoral roll samples. The first of these (Tait, Mackinnon, & Christensen, 2011) examined data from 1,499 participants (ages 20 to 24 at baseline) who completed 3 measurement waves, each 4 years apart. At baseline, 29% of participants had never used cannabis (never users, n = 699), 43% reported prior use but not in the last 12 months (former users, n = 1031), 18% reported current monthly or less frequent use (current light users, n = 427), and 9% reported current and at least weekly use (current heavy users, n = 226). Age of first cannabis use was < 16 years of age for 29% of users, between 16 to 17 years of age for 39%, and > 18 years of age for 32% of users. Neuropsychological performance was assessed at each measurement wave with the Symbol Digit Modality Test and Digit Span Backwards from the Wechsler Memory Scale, the Spot-the-Word task (a measure of premorbid estimated verbal abilities), and a modified CVLT (i.e., list read once, with only immediate and short-delayed recall assessed). Participants were classified based on their cannabis use across the three waves of data collection, resulting in 6 groups: “never” users (28% who with no use; n = 420); “always former” (44% who reported use before wave 1, but not thereafter; n = 657); “former light” (15% who were light users at wave 1, had no use at wave 3, and had no use or light use at wave 2; n = 231); “former heavy” (4% who were classified as heavy users at wave 1 and had no use at wave 3, regardless of wave 2 use; n = 60); “remain light” (5% classified as light users at wave 1 and 3, with light or no use reported at wave 2; n = 71); “remain heavy” users (4% with heavy use at wave 1 and 3, regardless of wave 2 use, n = 60). Analyses consisted of mixed-model repeated measures ANOVA with cannabis group and sex as fixed factors, education as a covariate, and neuropsychological test performance as the repeated measure. Group X Wave, Sex X Wave, and Sex X Group interactions were examined. The Group X Wave interaction was significant only for the CVLT Immediate Recall trial. Specifically, CVLT Immediate Recall was found to improve across all groups, with the exception of the “remain light” and

"remain heavy" groups, both of which evidenced declines in performance from wave 2 to wave 3. Planned contrasts of between-group differences from wave 3 to wave 1 revealed significant differences only between the "remain heavy" and "former heavy" groups, such that the "former heavy" group's performance improved relative to the "remain heavy" group's. Significant interactions with sex were not observed and analyses examining age of first use as a covariate were not significant.

The second study from "PATH through Life" focused on their middle-aged cohort (ages 40 – 46 at baseline), which consisted of 1,653 individuals with data at all three measurement waves, each which was four years apart (McKetin, Parasu, Cherbuin, Eramudugolla, & Anstey, 2016). At baseline, 10% of the sample (n = 576) reported having used cannabis at one of the three waves and 2% (n = 106) reported using weekly or more. Participants were classified as non-users, less than weekly users, and at least weekly users. Neuropsychological tests included those from the aforementioned "PATH through Life" study, with the addition of a Simple and Choice Reaction Time task. Linear random effects regressions examined relationships between cannabis use and neuropsychological function. The time-varying neuropsychological measure was used as the outcome variable and the time-varying level of cannabis use (based on group) was the categorical predictor. Time-varying Group X Wave interactions were tested to determine whether cannabis use affected age-related changes in neuropsychological function. Covariates included age at baseline, sex, years of education, tobacco smoking, current risky drinking, heaviest past drinking, BMI, depression, and premorbid verbal ability. Adjusted models examining between-subject effects revealed significant effects of cannabis on Immediate and Delayed trials of the CVLT, only between those using cannabis weekly or more and nonusers, with effect sizes of .55 SD and .44 SD, respectively. Within-person effects were not significant, nor were Group X Wave interactions.

Jacobus et al. (2015) conducted a three-year study with 108 participants recruited from San Diego area schools. The sample consisted of 49 adolescent cannabis users with ≥60 lifetime cannabis use episodes at baseline and concomitant alcohol use, and 59 controls with ≤9 lifetime cannabis use episodes at baseline and minimal alcohol use. At baseline, drinks per month ranged from 0-248 for cannabis users, and from 0-58 for controls. Cannabis users were consistent in their cannabis use patterns, with over 80% continuing to report >60 yearly cannabis use episodes at study completion. Participants completed a comprehensive neuropsychological battery at each of the 3 measurement waves, which were 1.5 years apart, assessing the domains of complex attention/working memory, processing speed, verbal memory, visuospatial functioning, and executive functioning. Data analyses consisted of repeated measures ANCOVAs with Group, Wave, and Group X Wave as predictors, lifetime alcohol use as a covariate, and neuropsychological performance as the repeated measure. Results indicated that cannabis users performed significantly worse than controls across all waves in the domains of complex attention/working memory (2 of 7 measures significant, ES = .4 to .7), verbal memory (2 of 8 measures significant, ES = .5 to .8), and visuospatial functioning (1 of 3 measures significant, ES = .4). A significant Group X Wave interaction indicated that users performed worse than controls in the CVLT-II at the 1.5 year, but not the 3-year follow-up. Another set of analyses were conducted with users classified as early (regular cannabis use before age 16) or late onset, but these results were less consistent.

Thus, this study found evidence for poorer performance associated with cannabis use on 5 of the 26 neurocognitve tests/subtests administered, with little evidence for worsening performance among cannabis users during the relatively short time frame that was examined during adolescence.

Studies with Neuropsychological Data Prior to Cannabis Use Initiation

To our knowledge, the first published longitudinal study published to report on associations between cannabis use and neuropsychological functioning among an adolescent sample transitioning to young adulthood was conducted by Fried, Watkinson, and Gray (2002) with data from 113 participants in the Ottawa Prenatal Prospective Study. Participants were excluded from analyses if they reported use of any substances other than alcohol, nicotine, or cannabis, which was also confirmed with urinalysis. Four groups based on self-reported cannabis use history were created for analyses: current regular heavy marijuana smokers (≥ 5 joints/wk; 21% of the sample; n = 15), current regular light smokers (< 5 joints/wk; 13% of the sample; n = 9), former regular users (no regular use for ≥ 3 months and ≤ 2 joints in the past 2 months; 13% of the sample; n = 9), and never used marijuana regularly (53% of the sample, n = 37). A comprehensive neuropsychological battery included measures of IQ, processing speed, memory, vocabulary, attention, and abstract problem solving. Neuropsychological data was collected when participants were 9 to 12 years old (prior to initiation of cannabis use) and at 17 to 21 years of age. ANCOVAs were used to examine associations between cannabis use and neurocognitive performance at ages 17 to 21, controlling for performance at ages 9 to 12 and for several confounds, including: parental income and education, mother's age at child's birth, as well as child's preteen IQ, age, sex, academic history, passive marijuana exposure, and prenatal exposure to drugs. Analyses revealed significantly poorer performance on Immediate Memory, General (delayed) Memory, Processing Speed indices, and overall IQ (about 5 points), but only between the "current heavy use" group and the "never used" group. All other group comparisons were not significant.

One of the most comprehensive studies to date on this topic has been conducted by Meier et al. (2012), which approached the question of the effects of cannabis use on neurocognitive functioning by analyzing data from 874 individuals from the Dunedin Multidisciplinary Health and Human Development Study, a longitudinal study of an entire birth cohort from Dunedin, New Zealand. Participants completed assessments at ages 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years of age. A comprehensive neuropsychological evaluation was completed at ages 7, 9, 11, 13 and 38. For analyses, change scores were calculated between the average of IQs during ages 7, 9, 11, and 13, and the IQ obtained at age 38. Participants were categorized into one of five groups based on a combination of ever having used cannabis and the number of assessment waves during which they met criteria for cannabis dependence: those who never used (28%), those who used cannabis at least once but never met dependence criteria (55%), those who met dependence criteria at only one wave (9%), those with dependence at two waves (4%), and those with dependence at three or more waves (4%). Linear regressions were conducted with the five levels of persistence of cannabis dependence predicting change scores, controlling for childhood IQ and sex. More persistent cannabis dependence was associated with declines in IQ, such that those with

dependence at 3+ waves experienced the most decline (ES = −.38, or approximately 6 IQ points). ES estimates for change on individual IQ subtest scores for the 3+ diagnoses group were largest for Digit Symbol Coding (−.62), Vocabulary (−.45), Similarities (−.44), and Information (−.15). A similar pattern emerged for the other neuropsychological measures, with significant effects observed for approximately half of the measures examined. The largest effects for the 3+ diagnoses group were evident on Months of Years Backwards from the Wechsler Memory Scales (−.63), WAIS-IV Processing Speed Index (−.61), RAVLT Learning Total Recall (−.48), CANTAB Rapid Visual Information Processing Vigilance (−.45), RAVLT Learning Delayed Recall (−.31), as well as the WAIS-IV Verbal Comprehension Index (−.23), Working Memory Index (−.16), and Perceptual Reasoning Index (−.12). To determine potential influence of confounds, the analyses were carried out again by sequentially excluding participants with schizophrenia, past 24-hour cannabis use, past week cannabis use, and persistent use (diagnosed with dependence on at least three measurement waves) of tobacco, alcohol, or other “hard-drugs” prior to computing difference scores. The number of participants excluded from the analyses based on the presence of these confounds ranged from 7 to 126. The pattern of significant results remained unchanged. Another set of analyses also considered whether cannabis dependence criteria was first met prior to or after age 18. No statistically significant differences emerged between the 1 or 2 diagnoses groups. Among those meeting 3+ diagnoses, those who met dependence criteria prior to age 18 (n = 23) showed a significantly greater decline in IQ (ES = −.55) relative to those who met cannabis dependence criteria for the first time after age 18 (n = 14). Indeed, the analyses revealed no significant decreases in IQ among the groups that were first diagnosed after age 18, regardless of the number of waves at which they met cannabis dependence criteria. Although multiple analyses and results were presented in this study, when taken together, the major findings were that persistent, frequent cannabis use or dependence were associated with declines in IQ (ES ≈ .5) and neuropsychological functioning when heavy-use/dependence began during adolescence.

Mokrysz et al. (2016) conducted a study with 2,235 participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who had data on all key variables needed to examine associations between cannabis use and IQ, while controlling for pertinent confounds. ALSPAC is a prospective study following women and their children since pregnancy in Bristol, UK. IQ scores were obtained for youths at age 8 via the Wechsler Intelligence Scale for Children (WISC) III and at age 15 via a two-subtest Wechsler Abbreviated Scale of Intelligence (WASI). Cumulative lifetime cannabis use data was collected from youths at age 15 and used to categorize participants into one of five levels of use: never, less than 5 times, 5-19 times, 20-49 times, 50 times or more. Although 23.5% of the sample (n = 526) reported having tried cannabis at least once, cumulative use of more than 50 times was reported only among 3.3% of the sample (n = 74). Across cannabis using groups, average age of first use ranged from 13.1 to 14.3 years of age. Multiple nested linear regressions tested for associations between lifetime cannabis use and IQ at age 15, using a progressively more exhaustive list of potential confounds, which included IQ at age 8, maternal and early life factors, adolescent mental health, and other drug use (including alcohol and nicotine). After controlling for IQ at age 8, lifetime cannabis use was found to be associated with IQ at age 15, with more cannabis use associated with lower IQ. The

group with the most cannabis use (50 times or more) was estimated to have an IQ 2.9 points (about 1/5 of a SD) lower relative to the never users. However, when the fully adjusted model was tested, cannabis use and IQ were no longer associated.

Of the existing studies, perhaps the study by Jackson et al. (2016) best addresses the issue of causal relationships between cannabis use and neuropsychological functioning due to its large sample size and cotwin design. The authors examined data from 3,066 twins from two longitudinal cohort studies: The Risk Factors for Antisocial Behavior (RFAB) study and the Minnesota Twin Family Study (MTFS). Twins were first assessed between the ages of 9 to 11, with follow-up assessments every 2 to 3 years. For RFAB, IQ was assessed via the WASI at ages 9 to 10 and then again at ages 19 to 20. Participants from the MTFS were administered four subtests from the WISC-R (Vocabulary, Information, Block Design, and Picture Arrangement) at ages 11 to 12 and then again at ages 17 to 19. Based on their self-report, participants were classified as “users” or “non-users,” whether they ever used cannabis 30 or more times, and whether they were ever daily users for a 6 to 12 month period. Among participants in the RFAB, 60% reported ever using cannabis (n = 475), with 50% of users reporting having used 30 or more times (n = 234) and 21% reporting daily use for more than 6 months (n = 99). Among those in the MTFS, 36% reported ever using (n = 822), with 37% of users endorsing 30 or more occasions of use (n = 304) and 22% reporting daily use for more than 6 months (n = 186). Data were analyzed separately for the RFAB and MTFS cohorts using mixed-effects linear regressions. Time X Group interactions were tested to determine whether changes in IQ differed between groups. For both cohorts, users showed significant decreases in Vocabulary subtest performance relative to non-users, corresponding to a decline of a little more than a 1/4 of a SD. A significant, but smaller, decrease in performance was also observed on the Information subtest. When controlling for covariates (i.e., age, sex, race, zygosity, SES), this difference persisted for participants in the RFAB, but not the MTFS cohorts. No other significant changes in performance between users and non-users were observed. Changes in test performance were not significantly different when participants were grouped as those who used 30 or more times and those who did not, or when grouped as those who used daily and those who did not. The cotwin control analyses revealed that changes in task performance did not differ between twin pairs discordant for cannabis use history. Results were the same regardless of whether MZ and DZ twins were considered separately or in the same analyses, or when comparing performance change between twin pairs where one sibling never used cannabis and the other used greater than 30 times.

Summary & Discussion

In recent years, a growing number of studies have emerged with strong longitudinal designs that better address the question: “Does cannabis use cause declines in neuropsychological functioning?” We reviewed seven such studies and offer conclusions based on their findings. Generally speaking, most (but not all) of these studies found that cannabis use was prospectively associated with poorer neuropsychological performance. However, findings from this review suggest a more nuanced conclusion.

Across studies, IQ and episodic memory performance were the measures most likely affected, although results varied depending on the study. Regardless of the neuropsychological ability assessed, it is important to consider the magnitude of effects observed across studies, which ranged from about 1/5 to 1/2 of a SD unit. However, it is important to keep in mind differences in “statistical significance” and “clinical meaningfulness.” The magnitude of these effects falls short of cut-points typically used by clinicians (i.e., 1 SD to 1.5 SD) to establish significant impairments in neuropsychological functioning (Heaton, Miller, Taylor, & Grant, 2004). Nonetheless, adverse consequences of cannabis use, including on psychosocial and academic outcomes, are well documented (Lynskey & Hall, 2000; National Academies of Sciences & Medicine, 2017; Volkow et al., 2014). It may be that the relatively small effects observed in the reviewed studies contribute to some of these outcomes. Alternatively, the relationship between neurocognitive functioning and academic performance is likely more complex and may be bi-directional. For example, adverse consequences on academic performance, school engagement, and psychosocial functioning that are experienced as a result of cannabis use may, at least in part, influence later neuropsychological outcomes.

Longitudinal studies with data on neuropsychological performance prior to cannabis use initiation help address one of the biggest limitations of prior work; that is, an inability to establish a temporal association between cannabis use and neuropsychological outcomes. That said, such studies are not immune from methodological challenges. It remains imperative to carefully control for relevant confounds, the most pertinent of which include other substance use, mental health, and psychosocial variables. Results from the studies reviewed underscore the importance of controlling for “third variables” or “shared risk factors” associated both with cannabis use and neuropsychological functioning. When controlling for pertinent confounds, associations between cannabis use and neuropsychological performance were often attenuated or no longer significant. Thus, lack of control for relevant confounds likely leads to overestimates of a “cannabis effect” or erroneous conclusions (Pope, 2002). Future longitudinal studies should also consider that predisposing factors contributing to cannabis use initiation and escalation may be independently associated with different neurocognitive trajectories; that is, regardless of whether cannabis use takes place (Rogeberg, 2013). One of the most comprehensive ways to control for potential confounds (both genetic & environmental) is the use of cotwin designs. It is noteworthy that the only study in our review with a cotwin design found no neuropsychological differences between twins discordant for cannabis use history, consistent with results from a prior cotwin study (Lyons et al., 2004). However, it will be informative to see if findings emerging from such a study design are similar in a sample with much higher levels of cannabis use.

Finally, it is important to note that almost all of the studies examined classified participants based on levels (frequency/quantity/dependence) of cannabis use, but across most studies, cannabis use was associated with declines in neuropsychological performance only in the highest levels of use. Perhaps the exception is the study by Meier et al. (2012), which found that declines in performance showed a range from those with 1 to 3+ measurement waves at which cannabis dependence criteria was met. Nonetheless, effect sizes were largest (but rarely > than .5 SD) among those with the most persistent histories of cannabis dependence.

This suggests cannabis use is most likely to cause declines in neuropsychological functioning among the heaviest of users, which represents a small subset of all individuals who endorse having used cannabis. Indeed, those classified as “heavy” users represented approximately 5% to 20% of participants in the studies reviewed.

In summary, based on our review of the current longitudinal literature examining relationships between cannabis use and changes in neuropsychological functioning, our answer to the question, “Does cannabis use cause declines in neuropsychological functioning?” is a qualified “yes.” The available evidence suggests that declines in neuropsychological functioning are most likely to manifest among daily (or almost daily) cannabis users and the magnitude of these declines are relatively modest (though not necessarily insignificant). It is worth noting that the studies reviewed consisted primarily of otherwise healthy individuals. Our conclusions may not generalize to neurologically (or otherwise) vulnerable populations that may be at greater risk for neuropsychological decline nor do they suggest an absence of more subtle effects on brain structure and function. Furthermore, it is well documented that the potency of cannabis has continued to rise in recent years, with use of more potent products growing (e.g., extracts, “wax” and “shatter”), which may have over 60% THC (e.g., Smart et al., 2017; Mehmedic et al., 2010). Whether the current findings generalize to individuals using such formulations, which were not likely represented in the reported cohort studies, will need to be determined with future research. Finally, numerous individual differences may influence who most is at risk for experiencing cannabis-related declines in neuropsychological functioning, which were not explored in the reviewed studies. Though, we note that consistent findings on sex differences or age of first use were not observed among the studies reviewed here (c.f. Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crane, Schuster, & Gonzalez, 2013; Crane, Schuster, Mermelstein, & Gonzalez, 2015; Ketcherside, Baine, & Filbey, 2016; Lisdahl, 2013). Nonetheless, these studies represent the vanguard of ongoing research in the area, with arguably the strongest research designs to detect such effects. Continued progress will likely be made with the recently launched Adolescent Brain Cognitive Development (ABCD) project. Supported through several NIH institutes, ABCD employs a prospective longitudinal design with a representative sample of 10,000, 9- to 10-year-old youth, prior to initiation of any drug use, who will be followed for 10 years. Across multiple time points, data will be collected on genetics, stress hormones, physical activity, mental health, environment (family, school, cultural), substance use, neuropsychological functioning, and brain structure and function. Through studies such as these, we will continue to come closer to understanding who, and under what conditions, is most vulnerable to neuropsychological declines from cannabis use.

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Table 1.

Characteristics of Longitudinal Studies on Cannabis Use and Changes in Neuropsychological Functioning.

Study	Sample Characteristics	Sampling Method	Time Points Considered	Criteria for Classification	CU Groups	CU Amount/ Frequency	Other SU Data Collected	Other SU Amount/ Frequency	NP Domains Assessed	NP Domains Associated with CU
Fried et al. (2005)	N=113; primarily White; 55.8% male; $\bar{x}$ age at follow-up = 18	Random selection	2 assessments (ages 9-12 and 17-21)	Current CU status and frequency	Controls; Former regular users; Current light users; Current heavy users	Current CU ($\bar{x}$ joints/wk)/ Cumulative CU ($\bar{x}$ joints total): Current light users: 1.4/122; Current heavy users: 12.4/1884; Former regular users: 0/2203	Current alcohol use ($\bar{x}$ drinks during wk before testing), current tobacco use ($\bar{x}$ cigarettes per day)	$\bar{x}$ drinks wk before test: Controls: .3; Current light users: 2.5; Current heavy users: 2.1; Former users: 3.1. $\bar{x}$ cigarettes per day: Controls: .2; Current light users: 2.2, Current heavy users: 9.6; Former users: 6.2	IQ, Vocabulary, Memory (immediate and delayed recall, working memory), sustained attention, abstract reasoning	Overall IQ, processing speed, immediate and delayed recall
Meier et al. (2012)	N=1,037; primarily White; 52% male; $\bar{x}$ age at last follow-up = 38	Rep. birth cohort	CU: 5 assessments(ages 18, 21, 26, 32, 38) NP: 2 assessments (ages 13 and 38)	A) Total assessments participant met criteria for cannabis dependence B) Total assessments when participant CU 4+ days/wk	A) No CU; Used but never diagnosed; Diagnosed at 1 wave; Diagnosed at 2 waves; Diagnosed at 3 or more waves B) No CU; Used but never regularly; Regular CU at 1 wave; Regular CU at 2 waves; Regular CU at 3 waves	Median days of past year use among persistent users: infrequent adolescent-onset CU = 14; frequent adolescent-onset CU = 365; infrequent adult-onset CU = 6; frequent adult-onset CU = 365.	Number of assessments when participants met criteria for tobacco, alcohol, and other drug dependence	N/A	IQ, memory, executive functioning, processing speed, perceptual reasoning, verbal comprehension	IQ, memory, executive functioning, processing speed, perceptual reasoning, verbal comprehension
Tait et al. (2011)	N=2,404; race = N/A; 45% male; $\bar{x}$ age at baseline = 23	Rep. sample with random selection	3 assessments (baseline, 2 follow-ups at 4 year intervals)	Current CU status and frequency	Never used; Always former; Former light; Former heavy; Remain light; Remain heavy	N/A	N/A	N/A	Memory (immediate and delayed recall, episodic memory, working memory),	Immediate Recall

Study	Sample Characteristics	Sampling Method	Time Points Considered	Criteria for Classification	CU Groups	CU Amount/ Frequency	Other SU Data Collected	Other SU Amount/ Frequency	NP Domains Assessed	NP Domains Associated with CU
									verbal ability, attention and motor speed	
McKetin et al. (2016)	N=1,897; primarily White; 42.5% male; $\bar{x}$ age at baseline = 43	Rep. sample with random selection	3 assessments (baseline and 3 follow-ups at 4 year intervals)	Past year CU frequency	No use in past year; < wkly past year use; ≥ wkly past year use	N/A	Tobacco use (never/past/ current), alcohol consumption (AUDIT score, levels based on heaviest past drinking frequency and amount)	No past year CU group mean AUDIT score = 4.2; Less than wkly CU group mean AUDIT score = 7.1; Wkly or greater CU group mean AUDIT score = 6.6	Memory (immediate and delayed recall, working memory), premorbid verbal ability, attention and motor speed	Immediate recall, but no within subject effects
Jacobus et al. (2015)	N = 108; 62.6% white; 65.3% male; $\bar{x}$ age at baseline = 18	Community Sample	3 assessments (baseline, 2 follow-ups at 1.5 year intervals)	A) Lifetime CU and alcohol use frequency; B) Age of onset of CU	A) Marijuana users with concomitant alcohol use; Controls B) Early onset of regular CU; Late onset of regular CU; Controls	$\bar{x}$ lifetime CU episodes: Users: 1086.4 Controls: 87.2; $\bar{x}$ CU episodes from Baseline to Year 3: Users: 292.4 Controls: 26.0; $\bar{x}$ days of past month CU at baseline: Users: 15.5 Controls: 0.1. $\bar{x}$ days of past month CU at Year 3: Users: 13.3 Controls: 3.7	Current alcohol use (drinks per month), lifetime number of alcohol use episodes, lifetime other drug use episodes, average number of cigarettes per day in past wk	Drinks per month at baseline: Users: 47.8, Controls: 5.1; Drinks per month at Year 3L Users: 51.2, Controls: 32.3; Lifetime number of alcohol use episodes: Users: 644.9, Controls: 180.2; Lifetime other drug use episodes: Users: 84.4, Controls: 7.5; $\bar{x}$ cigarettes per day at baseline: Users: 0.8, Controls: 0.1; Average cigarettes per day at Year 3: Users: 0.8, Controls: 0.3	Complex attention, memory (working memory, verbal memory), processing speed, executive functioning, visuospatial functioning	Complex attention, memory, processing speed, visuospatial functioning
Mokrysz, et al. (2016)	N=2,235; primarily White; 46.6% male; $\bar{x}$ age at baseline = 8	Rep. birth cohort	CU: 1 assessment (age 15) NP: 4 assessment (ages 8, 11, 15, 16)	Lifetime CU frequency	No CU; CU < 5 times; CU 5-19 times; CU 20-49	% reported typically smoking 1/16th ounce in less than 1	Cumulative tobacco and alcohol consumption (number of	CU > 50: 97.3% used alcohol >20 times, 83.8% used tobacco >	IQ, educational outcomes	None

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Study	Sample Characteristics	Sampling Method	Time Points Considered	Criteria for Classification	CU Groups	CU Amount/ Frequency	Other SU Data Collected	Other SU Amount/ Frequency	NP Domains Assessed	NP Domains Associated with CU
					times; CU ≥ 50 times	day: CU < 5 times: 14.3%; CU 5-19 times: 18.1%; CU 20-49 times: 30.2%; CU ≥ 50 times: 38.9%	times), number of other recreational drugs used	20 times, 67.3% used other drugs. CU 20-49: 71.8% used alcohol and tobacco >20 times, 54.9% used other drugs. CU 5-19: 77.4% used alcohol >20 times, 52.6% used tobacco >20 times, 43.6% used other drugs. CU < 5: 63.7% used alcohol >20 times, 34.3% used tobacco >20 times, 28.6% used other drugs. No CU: 26.4% used alcohol >20 times, 4.5% used tobacco >20 times, 5.7% used other drugs		
Jackson et al. (2016)	RFAB: N = 789; 37% Hispanic, 27% White, 14% Black, 5% Asian, 17% Mixed; 48% male; 46% monozygotic; $\bar{x}$ age at baseline = 10 MTFS: N = 2,277; 93% White; 49% male; 63% monozygotic $\bar{x}$ age at baseline = 12	Comm. & population based sample	5 assessment points over 10 years (ages 9-10, 11-13, 14-15, 16-18, 19-20)	A) CU initiation B) CU frequency	A) Users; Nonusers B) CU more than 30 times; Daily CU for at least 6 months	N/A	Maximal binge drinking (number of drinks), cumulative other drug use (dichotomous)	$\bar{x}$ maximal binge-drinking: 2.7 for nonusers, 7.6 for users. Other drug use: 1.6% of nonusers, 38.3% of users	IQ	IQ (verbal ability and general knowledge)

*Notes. Comm. Sample = Community Sample; Rep. = Representative; CU = Cannabis use; NP = Neuropsychological.