Supplemental Methods

This systematic review was conducted in accordance with PRISMA guidelines (1) (Flow diagram in Figure 1 of main manuscript).

Search Strategy

Electronic searches were performed using PubMed and Scopus (2004 to current) with the following key words: (cannabi* OR marijuana) AND (cognit* OR memory OR attention* or learning OR inhibit* OR impuls* OR reward OR decision making OR executive function* OR information process* OR performance OR functional brain imaging OR fMRI OR event related potential OR electroencephalogram) NOT (rats OR mice OR review OR MDMA OR ecstasy OR amphetamine). The focus of this review was specific to neuropsychological / cognitive studies. The initial search strategy was, however, designed to be as exhaustive as possible and therefore included reference to neuroimaging, so that any article that referred to functional magnetic resonance imaging, electroencephalogram or event related potentials, but examined a cognitive measure separately as the primary outcome, would be captured in the search results. Scopus results were limited by Research Article type. Searches were conducted on the 18th February 2015 to capture all studies published from 1st January 2004.

Selection Criteria

The search strategy resulted in 3021 results in PubMed and 3220 in Scopus. Titles were reviewed and 316 and 225 articles respectively identified as consistent with our inclusion criteria. Once duplicates were removed, 356 articles remained, from which abstracts and full text were assessed for inclusion based on the following criteria: (i) neuropsychological or cognitive experimental tasks administered to regular or former cannabis users or following the acute administration of cannabis, or synthetic or phytocannabinoid compounds; (ii) cannabis (or cannabinoids) as the primary drug of interest, and (iii) human participants. Exclusion criteria were: (i) studies in which cannabis was not the primary drug of concern; (ii) questionnaire (trait) measures of cognition; (iii) major psychopathology or neurological conditions within the assessed sample; (iv) animal research; (v)
neuroimaging, electrophysiological or autonomic measures as primary outcome variables; (vi) treatment (e.g., cognitive behavioral therapy) as the primary focus; (vii) ‘real world’ multiplex tasks requiring simultaneous use and integration of multiple aspects of cognition, such as driving; and (viii) case studies. Following this assessment, 105 articles were included for summary and qualitative synthesis.

**Data Extraction**

Data were extracted by three reviewers (HVH, SJB, CB) and in the case where consensus was required the senior author (NS) was consulted. Cannabis users were defined as per the original study criteria. From each study we extracted participant demographics (age, gender, IQ), cannabis-use metrics (e.g., age of onset, duration, frequency and quantity of use), period of abstinence prior to testing, extent of other substance use, dosing details for acute administration studies, cognitive domains investigated, experimental tasks employed and key cognitive findings. The primary results of interest were group differences in performance and associations with cannabis use metrics.

**Supplemental Results (more detailed description of study findings)**

**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. Memory is a complex domain, encompassing a diverse range of processes and measured by means of a wide range of tasks. The most extensive evidence for impairment is within verbal learning and memory.

**Verbal Learning and Memory**

Verbal learning and memory is most often measured using word list learning tasks (e.g., Rey Auditory Verbal Learning Test (RAVLT), California Verbal Learning Test (CVLT), Hopkins Verbal Learning Test (HVLT)), with several immediate and delayed recall trials and a recognition trial. These tasks have been identified as particularly sensitive to the acute (2–4) and chronic (5) effects of cannabis in previous reviews.

Acute administration studies of the past decade confirm impaired verbal recall after intravenous (IV) THC (6–10) and vaporized cannabis (11,12), with occasional users more impaired than frequent users (13) and impairments in immediate and delayed recall affected in a dose dependent manner (6). CBD may protect against some THC-induced verbal learning and memory deficits: pre-dosing with oral CBD prior to IV THC attenuated impairment of delayed but not
immediate recall (9) and high relative to low CBD content cannabis improved immediate and delayed prose recall, but not recognition or source memory (14). Acute oral nabilone treatment impaired immediate and delayed recall and recognition accuracy with dose-dependent effects (15), whereas escalating doses of oral dronabinol for 5 days had no effect (16).

Impairments in verbal learning and memory continue to be consistently observed in chronic cannabis users, including adolescents (17–19) and young adults ((20–24) but not (25,26)), even in only occasional users (27). Significant associations between poorer performance and frequency, quantity, duration and age of onset of cannabis use have been reported (19,21,28,29), sometimes without overt group differences between controls and less entrenched cannabis users (28). Consistent with previous findings (30), long-term users appear more affected than short-term users (31,32), and females may be more impaired (33). Verbal learning and memory deficits may associate with self-reported memory problems (34) and motivation (24), and were found to be greater in daily users with high THC concentrations in hair, whereas the presence of CBD in hair was associated with better recognition memory (35).

There is evidence for recovery of function after abstinence, but this remains under-researched. In young adults or adolescents, memory performance improved from 4 to 8 weeks abstinence (36) and recovered after 2 weeks abstinence in occasional users (27) or after 28 days in a more entrenched group for word list learning, but verbal story memory remained impaired (37). In a large prospective study (38) former heavy users showed improved immediate verbal recall compared to ongoing heavy users, and performance appeared to normalise to control levels. In contrast, persistent recall discrimination and long delay cued recall deficits were observed in adolescents with a mean 35 days abstinence (39). Fewer studies have assessed older adult users with long durations of use; one study found recovery after >28 days (28), but trend level impairment on long delay cued recall remained after a year of abstinence in cannabis using monozygotic twins relative to their non-using counterparts (40).

In summary, dose-dependent acute and chronic effects of cannabis exposure on immediate and delayed verbal recall highlight one of the strongest results in the literature. Of note, is the general consistency of tasks used across studies. Whilst further research is necessary, evidence is accumulating for potential recovery with cessation of use and for a protective role of CBD.

**Working Memory**

Whether working memory (WM) is impaired by cannabis is less clear. Acute administration of THC, dronabinol or nabilone affected WM inconsistently: THC (12,41) and dronabinol (42,43) impaired Sternberg task performance; THC impaired Delayed Matching to Sample task performance in some studies (6,44) but not others (7,10,45), and inconsistently impaired spatial WM (7,10,46) and
immediate but not delayed digit recall (47), and digit span (8,9,48) (the latter not ameliorated by CBD (9) and not impaired by nabilone or dronabinol (49)). THC alone or in combination with nabilone or dronabinol affected performance but not acquisition (50,51). THC (52) and nabilone (15) increased reaction time (RT) during n-back and numeric WM tasks, whereas daily dronabinol for 5 days increased RT on a 1-back but not other n-back conditions, which the authors argue reflects dronabinol-related suppression of cannabis withdrawal (16).

Chronic effects of cannabis impairing WM have been reported in young adults on immediate recall (53), verbal reasoning (54) and verbal n-back (55) WM tasks, but not on spatial WM (20,56) or digit span (24,25), whereas spatial WM (but not spatial or digit span) was impaired in adolescent users (18). Cannabis use-related problems correlated with Trails B but not digit span performance in young regular users (57). In older users, two studies reported no impairment on letter-number sequence and spatial span tests of the Wechsler Memory Scale (WMS) (58) or on an n-back task (59), whereas recent or heavy users were impaired on a range of WAIS WM tasks, with greater frequency and quantity of use correlated with poorer performance (28).

Adolescent or young adult former users showed trends toward poorer digit span and WMS WM performance after at least 23 days abstinence (37) but not impaired digit span at (35 day abstinent, 39,53 day abstinent, 60)). WAIS letter-number sequencing was impaired at 2-weeks abstinence, resolving by 3-weeks in one sample (27) but Trail making switching remained impaired in another at 53 days abstinence (61). No impairment in auditory WM indices was observed with (no regular use ≥ 3 months, 53). WM performance was better in >28 day abstinent than recent adult users (28), and WM measures did not differ between 1 year abstinent and non-user adult twins (40).

In summary, despite diverse study designs, neurocognitive tasks employed, sample characteristics and administration methods, several patterns emerge. First, acute doses of THC impair a broad range of neuropsychological measures of working memory more consistently than does chronic exposure to cannabis. Acute doses of synthetic cannabinoids (nabilone and dronabinol) were not impairing, possibly due to the oral route of administration, and other null effects may possibly be explained by tolerance in entrenched users (e.g. 13,45). There is little evidence that overt WM task performance is affected beyond the period of intoxication and any impairment appears to resolve with longer abstinence, but performance may worsen with cumulative exposure (28) and be differentially affected in the developing brain (18). Further, intact performance may nevertheless mask altered underlying brain activation (62).

Other Memory Function Including Wide Ranging Memory Assessment Batteries

Impairing acute effects of cannabis have been reported in regular users for semantic memory after smoking (63) and on RT in a prospective memory task (in conjunction with vardenafil, 12)). More
studies have examined chronic effects of cannabis use, reported to adversely affect visual recognition and delayed recall in current young adult regular users (64), memory scores on Brown-Peterson total recall in adolescents (17), prospective memory (64) including in >10 day abstinent adolescents (65), and subjective self-reports, but not objective time- or event-based tests of prospective memory (21). In contrast, others have found no effect of chronic cannabis use on semantic memory function (54) or pattern recognition memory (45). Abstinence of more than 28 days was associated with improvements in memory broadly (53,66) and in visuospatial memory (37) in adolescents or young adults. Moderating factors include length of abstinence (36), age of onset (66), and type of memory investigated (e.g., verbal story memory persistently impaired (37)).

In summary, adverse effects of regular cannabis use on a broad range of other memory functions have been identified, but few investigations of acute effects have been performed. The evidence largely suggests recovery of function, but the limited abstinence studies have been conducted entirely in adolescent/young adult users and further assessment of older adults with long duration heavy use is required.

**Attention and Attentional Bias**

Traditionally, impaired attention has been considered a hallmark of the intoxicating effects of cannabis. Further evidence has accumulated over the past decade in support of acute exposure to cannabinoids impairing attentional processes measured using tasks that require participants to focus, divide or sustain their attention. Dose-dependent effects on errors in continuous task performance tasks (CPT) and divided attention tasks (DAT), and slowed RT during simple RT and attentional control tasks (e.g., Eriksen task), have been reported following acute administration of THC or cannabis (6,7,12,13,41,52,67). Where no impairment was observed, this may be due to the development of tolerance among daily users (47,68,69). Near daily users made more errors on the secondary attention task of a DAT soon after smoking, but not 1.5 hours later which the authors interpreted as being due to tolerance (69). Impairing effects on divided attention were reported after acutely administered dronabinol (42,49), and to a lesser extent taranabant (a CB1 inverse agonist) (42) and nabilone (15,49) in some studies, but not others (16,43). Overall, these findings indicate impaired attentional processes following acute cannabinoid ingestion, especially THC and to a lesser extent dronabinol, taranabant and nabilone, and that these effects may be less apparent in more entrenched users due to tolerance.

The previous evidence for deficits in attention following chronic cannabis exposure had been mixed but recent studies provide some clarity. A large number of studies report greater impairment in regular or chronic cannabis users relative to controls on measures of sustained and divided
attention, processing speed, rapid visual information processing, visual search, tracking, paced serial addition, digit span, and letter number sequencing (18,26–28,32,70–73). Samples in these studies included adolescent and adult cannabis users with a wide range of exposure to cannabis and the majority were abstinent for several days to several weeks. Others report mixed findings with impaired performance on some tasks but not others (e.g., CPT and rapid visual processing, respectively (17)), no impairment in chronic users (54), moderation by genotype (59), or no difference between abstinent former users and controls on broader measures of attention (28,36,40,53,66). Despite this, associations remain between poor attentional performance and a younger age of onset of cannabis use after 30 days (66) or 23 days abstinence (70), where former users remained impaired relative to controls despite improvements in sustained and divided attention with increasing abstinence (withdrawal effects also impacted performance up to 16 days abstinence) (70).

In summary, attention is impacted adversely by cannabis acutely but may be moderated by tolerance. Cannabis-related attentional impairment may reflect residual effects that dissipate gradually as cannabinoids are cleared from the body, supported by high levels of urinary THC metabolites being associated with greater deficits in attention (73), and not associated with the duration of cannabis use (32) (although others have reported associations with duration of use (74), previously using subtle brain markers (eg.,75)). The weight of the evidence suggests that attentional impairment may be present in chronic, regular cannabis users for a period of 30 days or more, and the detection of impairment may depend on the experimental tasks utilized to capture attentional processes, as well as on the age of onset of cannabis use.

**Attentional Bias**

There is only a limited literature examining attentional bias in cannabis users, an area of research which investigates the degree to which attention is automatically drawn to a stimulus often linked with reinforcing properties of drug use, which is commonly measured using visual or dot probe and modified Stroop-like tasks with cannabis-related stimuli. Greater attentional bias has been noted in chronic cannabis users (76–80) (including stronger negative implicit memory associations; (81)), associated with levels of craving and frequency of use (82), problematic cannabis use (77) and, during acute intoxication, with lower CBD:THC ratios in hair (80). Investigation of attentional bias during the intoxicated state is limited and there are no studies of abstinent users following cessation of use. The latter may be a particularly important target for future research to strengthen the efficacy of treatment programs aimed at maintaining abstinence.
Psychomotor Function

Finger tapping, critical tracking, choice reaction time tasks, and digit-symbol substitution tasks have been used to measure psychomotor function. In infrequent users, smoked or vaporized cannabis impaired critical tracking (12,68,83,84), affected RT and motor control in a dose-dependent manner (41), and disrupted motor function in a task with a motivational component (85). In heavy users, high dose smoked cannabis resulted in more collisions in a virtual maze task (86) but did not affect critical tracking (68,69). Oral administration of THC, nabilone or dronabinol impaired psychomotor function in six out of seven studies (15,16,47,49,51,87, not 50) and IV THC impaired motor performance (7). Oral THC and CBD inconsistently affected finger tapping (88), whereas higher doses of each in a sublingual spray (nabiximols) did not affect motor function (43).

Findings regarding the chronic effects of cannabis on psychomotor function are mixed, being reported as impaired (23,26,54,89), improved (in a high functioning young sample) (20), and unaffected (in simple motor screening or RT tasks) in adolescents (18) or daily users (45). Nevertheless, psychomotor function was shown to be impaired in 23- to 35-day abstinent users (28,37,39,70), with a trend also after 12 months abstinence (finger tapping) (40). Abstinence after 4 weeks (with acetylcysteine treatment) was associated with moderate increase in psychomotor speed scores (36).

In summary, the weight of the evidence suggests psychomotor function is affected by acute intoxication and that that this likely persists for some time following chronic cannabis exposure.

Executive Function

Executive function comprises a broad range of cognitive functions, grouped into subdomains below, that have been widely investigated in the cannabis literature, although the patterns of findings are complex.

Planning, Reasoning, Interference Control and Problem Solving

Using a range of similar tasks, THC administration was found not to affect performance (10,67,68), or to impair performance (8,11,83,84,86,90) equally across samples of occasional, moderate and heavy users. Neither THC nor CBD or their combination (9) nor dronabinol treatment (16) affected problem solving. Impaired performance may depend upon extent of prior exposure, route of administration, dose delivered and blood cannabinoid concentrations at baseline and following dosing (e.g., 68).

There are also mixed findings with regard to the chronic effects of cannabis on these aspects of executive function, again across studies using similar measures. A number of studies reported null findings in case-control comparisons (18,26,38,55,61,66,77,91). Several others found cannabis-
related deficits in heavy users (25,45,58,92), including adolescents (93), early but not late onset adult users (94), recent older users (28), and associated with persistent use in a longitudinal study (31). Sometimes impaired executive function was evident despite intact performance on other cognitive tasks (20,56) and associated with self-reported cannabis use-related problems (57). Studies where executive dysfunction was detected tended to comprise older samples than the predominantly adolescent-young adult users where no impairments were observed. It may be that executive dysfunction becomes more evident beyond the period of maturation of the frontal lobes, perhaps reflecting perturbed neurodevelopment.

Consistent with this interpretation, three abstinence studies reported no group differences relative to controls in younger samples (37,60,66) but in another, abstinence was not associated with improvement in executive functioning in young treatment seekers (despite concomitant treatment with acetylcysteine) (36). Persistent executive dysfunction was observed in ≥28-day abstinent users aged ~35–50 (28), and in 12-month abstinent users aged 38–51 (40) impaired performance on Block Design was the only significant difference detected between abstinent users and their non-user twins (with intact performance on the Stroop and Wisconsin Card Sorting Test).

**Inhibition**

Measures of inhibition are derived from paradigms such as Go/No-Go or Stop-Signal tasks. Acute administration of THC has consistently been reported to increase Stop Signal RT in both occasional and heavier cannabis users (12,68,84,90). Findings in chronic users are more mixed. Dose-dependently impaired cognitive inhibition (26) and decreased inhibitory control across multiple inhibition tasks (95) were reported in young adult users (only when a motivational component was added (96)), and in adolescents during a two-choice inhibition paradigm (17), whilst four studies found no performance differences in Go/Stop or Stop-Signal tasks (17,22,33,56), or better performance in cannabis users (97).

**Verbal Fluency**

Three studies reported no effect on verbal fluency during acute intoxication with THC or cannabis (6,8,14), but there has been little consistency regarding chronic effects. In young frequent users, verbal fluency was shown to be either increased (in a high functioning college sample (20)), not affected in current (14,25,26,91) or >28-day abstinent adolescents (37,39,60), or impaired in both current (23,64) and >7 day abstinent users (64), and impaired in older samples (32,72), associated also with the duration of use (32). The findings suggest that if verbal fluency is impaired in cannabis users, it is more likely to be in older individuals with longer durations of exposure, whereas in younger users may depend on intellectual functioning, and on the task employed.
**Time Estimation**

The subjective effect of cannabis distorting time is well known, but methodological variation in studies of time estimation provides inconclusive evidence regarding the nature of this distortion or its underlying mechanisms (98). There is limited evidence for an impairing effect of acute THC, nabilone or dronabinol on temporal processing (16,50,51), whereas smoked cannabis may lead to time overestimation or underproduction (67,99), possibly only in occasional but not heavy users (100). Only one study examined chronic and abstinence effects in adolescence, finding none (27).

In summary, executive function subdomains are differentially affected by acute administration and chronic exposure to cannabis. There are clear acutely impairing effects on inhibition, whereas planning, problem solving, reasoning and interference control are inconsistently impaired and the moderators of impaired performance require further investigation. The latter subdomains may be more affected in older chronic users, or with greater exposure to cannabis. There is a very sparse literature assessing recovery of executive functions with abstinence, which is an important area for optimizing treatment programs for cannabis dependence. For example, one study found that poor neurocognitive performance was associated with relapse to cannabis use at 1-year follow-up in adolescents (66).

**Decision Making, Reward Processing and Delay Discounting**

Substance use, including cannabis use, is often associated with impulsive decision making involving the selection of positive and immediately reinforcing choices over delayed rewards despite the possibility of future adverse outcomes. Common measures of risky and impulsive decision making include performance on the Iowa Gambling task (IGT), delay discounting tasks, and behavioral risk taking tasks including the Balloon Analogue Risk task (BART). Acute administration of THC adversely affected decision making by altering sensitivity to reward and punishment and increasing risk taking in infrequent (101) and regular users (86,102,103) (but not (83,90)).

Evidence for effects of chronic cannabis use on decision-making is mixed. Although several studies have reported poorer decision making performance across a range of tasks (20,45,56,95,104,105), and especially decreased sensitivity to loss and greater sensitivity to gains (104), clear group differences were not found in other studies (17,22,73,106–108). Associations between the degree of prior cannabis exposure and poorer decision making are reported (e.g., higher THC concentrations in hair (107) or urine (73), lifetime exposure, past year and past month use in males but not females (33), and DSM-IV symptoms of cannabis-use disorders (22)). In adolescents, earlier onset, longer duration, and increased frequency and quantity of use were
associated with poorer performance (105). Cognitive flexibility in decision making is also affected by chronic cannabis exposure (17,93,96) but may be moderated by genotype (59). Several studies reported no effect on behavioral risk taking (22,33,106), but greater risk taking in adolescents with a mean 53 days abstinence (60) and an association with extent of prior exposure in 25-day abstinence users (108) were observed. No delay discounting performance differences were found between current and abstinent users and controls (109), nor in the effect of monetary reward on performance in current users (110).

In summary, the evidence for increased risky decision making and sensitivity to reward is complex and mixed across acute, chronic and abstinence studies. Risky decision making was impaired in four of six acute administration studies, with evidence suggesting that higher doses affect the capacity to effectively weigh the probability of gains over losses and respond flexibly. Whether decision making is affected beyond the period of intoxication is much less clear, although a dose-response relationship is suggested between prior cannabis exposure and risky decision making, including in abstinent users. Further consideration of individual differences (e.g., genotype, gender, education level) as well as decision making context (monetary reward vs. behavioral risk taking) may elucidate the chronic effects of cannabis on decision making, with implications for recovery.

Miscellaneous

High (but not low) dose vaporized cannabis impaired creativity as measured by divergent thinking (alternate uses task), but not convergent thinking (remote associates task) in frequent users (111). Impairing effects of chronic use have been found in conditioned learning (eyeblink conditioning, including abstinent users) (112), information processing speed (which normalized during acute intoxication) (113) and IQ (31), but no effects were evident for theory of mind (114). In their large longitudinal study of 1037 individuals from birth in which cannabis use was ascertained through interviews at ages 18 through to 38 years, Meier et al. (31) have shown that cannabis users who commenced use prior to the age of 18 exhibited greater decline in IQ compared to adult onset users, an effect that was not ameliorated by a reduction/cessation of use.
Supplemental Discussion

Gender Issues

Gender issues continue to be insufficiently addressed in studies of predominantly male cannabis users (~75% of studies reviewed). Many argue that this overrepresentation matches the gender distribution of cannabis users in the general population (e.g., 115). Some studies matched user and control groups for gender ratio; in others females tend to be over-represented among controls; some controlled for gender in analysis; some recruited male (or rarely, female) cannabis users only; and surprisingly, about 6% of studies did not report participant gender (see Supplement 2). A minority of studies did recruit equal numbers of males and females and tested for gender effects but sample sizes were often small, whereas potential gender differences have been ignored in the analyses of some studies with large sample sizes where this could have been examined.

In general, where gender effects were tested (~12% of studies), very few were found (see Supplement 2). With acute administration, THC impaired working memory in young adult females but not males (46) and while no gender effects were reported in outcomes from another study of smoked cannabis, females consumed smaller a dose than males (67). One further study of acute administration reported females to be more impaired than males in finger tapping (88). Previous work suggested gender-specific cognitive effects in chronic cannabis users; female heavy users remembered fewer items and made more errors than female light users in a visuospatial memory task, whereas male heavy users were more impaired in attentional/interference tasks and in delayed recall (116,117). In a recent study specifically aimed at examining gender effects within users (no control group), no gender differences in cognitive performance were found overall, but the quantity of cannabis used was more consistently associated with memory impairment in females, but with poor decision making in males (33). No association was found between gender and self-reported memory problems, yet gender was reported to be a significant predictor of verbal and visual memory performance but without a specified direction (34). Trail making B performance was impaired in both genders, but females showed a stronger association between poorer performance and greater cannabis use than males (26). Under stereotype threat (of cognitive deficits being associated with cannabis use) male users were found to perform worse while females performed better (23), but in a similar study a motivational statement improved the motivation of male users than female users (24). No gender effects were found in five other studies of chronic users (19,38,53,64,94) where gender effects were specifically tested.

Since gender differences in cannabinoid metabolism and action may exist (118) and have been found in brain morphology in cannabis users (e.g., 119,120), future research should further
investigate gender differences in cognition, both following acute administration and chronic exposure.

Further Details Regarding Doses Administered and Route of Administration

Doses for acute administration vary considerably and different routes of administration result in pharmacokinetic and pharmacodynamic differences that hinder direct comparability of studies and complicate interpretation where results are conflicting. Oral doses between 10–40 mg of THC or synthetic analogues and IV administration of 1.5–5 mg THC were often employed, and vaporized cannabis or THC is increasingly used in studies, with doses ranging from 2–8 mg. However, most acute administration studies used a smoked route, with doses ranging from 2.5 to 69.4 mg THC, sometimes by body weight (e.g., 0.25–0.5 mg/kg), or expressed as a % THC (range 1.77–23.1%) but the weight of the plant matter and its composition in terms of other cannabinoid compounds are rarely reported (69). Entourage effects of the various other cannabinoid compounds require further investigation. Significant proportions of THC are lost in sidestream smoke and blood levels attained are also inconsistently reported (for whole blood, plasma or serum) and rarely investigated in relation to impairment. While cognitive outcome measures are generally not directly related to blood levels, concentration levels of between 2 and 5 mg have been reported to be required for impairment to manifest (68), with occasional users impaired at both low and high blood concentration levels but heavy users only at high levels (84) – further research is warranted.

The Confound of Other Substance Use

Greater attention is generally being given to the significant potential confounds of polydrug use, but a disconcerting number of studies still do not even report or consider the other substance use of their samples (e.g., 33% of studies do not report tobacco use; 8% do not mention other illicit drug use or exclusions). Most studies excluded participants with extensive other illicit drug use but the criteria for doing so were either not reported, or unspecified beyond a “history of other drug use” (19% of all studies). Otherwise, exclusion criteria ranged from lifetime illicit drug use of between 5 and 100 times, recent use ranging from same day through the past year, weekly use, positive urine drug screens (and two studies used hair or saliva assays), and participants having been in treatment or meeting criteria for dependence or abuse. The primary control for polydrug use was exclusion, with few studies actually covarying for or considering extent of other drug use further in analyses (with some exceptions, largely for MDMA, as detailed in Supplement 2, Table S1).
Of the studies that reported tobacco use, some excluded daily or dependent smokers (12% of studies), others ensured minimal tobacco use in the cannabis using sample and covaried for this in analyses (7.6%), some matched comparison groups on tobacco use metrics (14%) with occasional covariance nonetheless, while others acknowledged a significant difference between comparison groups and covaried (7.6%) or did not covary in analyses (7.6%). Mostly, the cognitively impairing effects of cannabis held after controlling for tobacco use, including in one of two studies that employed a tobacco using control group. Acute studies used varying methods to impose abstinence from tobacco and sometimes deal with withdrawal effects but tobacco was sometimes present in the cannabis administered and not always well accounted for. Despite acknowledging a difficulty in discriminating easily between the effects of prolonged exposure to tobacco versus cannabis, particularly when cannabis is often smoked together with tobacco, studies of chronic effects could aim to recruit cannabis users who do not use tobacco, include tobacco-using control groups for comparison, or continue to better document and covary for the extent of tobacco exposure in analysis.

More than 20% of studies did not report any details of the alcohol use of the sample, some providing information around abstinence prior to testing, some stating that they covaried for alcohol use nevertheless, but providing no alcohol use metrics. Significant differences in alcohol use between comparison groups were reported by some but not further addressed, while around 15% excluded alcohol dependence, 20% matched comparison groups on alcohol use, and 15% covaried for group differences in alcohol use, with two thirds of such studies showing that impairing effects of cannabis remained. Alcohol use metrics were found to have impairing effects on verbal learning and memory, prospective/retrospective memory or sustained attention in some studies (e.g., 26,54), while other studies found better performance associated with alcohol use (e.g., 19,20,37). Four studies included an alcohol-using control group to demonstrate cannabis-specific impairment, and one included cannabis user groups with and without concomitant extensive alcohol use, finding different cognitive measures to be impaired in each group relative to controls, but the two cannabis groups were not directly compared (39) (see 19 for attempts to examine interactive effects of cannabis and alcohol). Most of the acute administration studies excluded heavy drinkers and/or imposed a period of abstinence from alcohol prior to testing. The range of alcohol use metrics reported or used for matching or covarying is very heterogeneous, ranging from quantity/frequency measures, lifetime use, dependence or abuse scores or status, abstinence period and zero blood alcohol measures on the day of testing. Greater standardization of not only cannabis use metrics across studies, but also tobacco, alcohol and other drug use would enable better characterization of
the specificity of cannabis effects. Further research to examine additive, interactive or synergistic effects of cannabinoids with other substances is required.

The prospective study conducted by Meier and colleagues (31), as highlighted in the main manuscript, was exceptionally well controlled, ensuring specificity to persistent effects of cannabis by ruling out the decline in IQ being attributable to persistent tobacco, alcohol or other drug use, as well as schizophrenia. Increasing numbers of studies are now also excluding participants for other comorbid psychiatric disorders.
Supplemental References


