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A Meta-Analysis of Cannabis Research: Is there Evidence of Lasting Neurocognitive Effects?

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A META-ANALYSIS OF CANNABIS RESEARCH: IS THERE EVIDENCE OF LASTING NEUROCOGNITIVE EFFECTS?

By

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ABSTRACT

Cannabis use in the United States has generally increased over the past decade as more States have legalized recreational use. In conjunction with changes to the chemical makeup, which has made available cannabis more potent, the long-term effects experienced by cannabis users may have changed, and more individuals may be effected. The current study replicated the methods used in Schreiner & Dunn (2012) and Grant et al. (2003) to conduct a meta-analysis examining the neurocognitive effects of cannabis after abstinence lasting a period of at least 25 days. Previous research has found mixed results, with some studies finding significant differences between abstinent cannabis users and matched healthy controls, and others finding no evidence of significant differences. Results of the current meta-analytical study found no significant effects within the domains of overall effects, attention, forgetting/retrieval, learning, or verbal/language. Results identified a significant small effect size within the domain of abstraction/executive function. Results continue to add to the growing evidence there are no significant long-term neurocognitive effects associated with cannabis use.

Keywords: *Cannabis, long-term effects, neurocognition, meta-analysis*

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

Cannabis is the most widely used illicit substance in the world and rates of lifetime prevalence in the United States have been rapidly changing in recent years (Johnston et al., 2022; Substance Abuse and Mental Health Services Administration, 2020; UNODC, 2015). Understanding the potential adverse effects is becoming increasingly important as cannabis becomes more accessible due to changes in its legal status (Martins et al., 2021; Smart & Pacula, 2019). In addition to increased accessibility, there have been changes in the cannabinoid content of cannabis, which has a direct influence on the effects of the drug (Jikomes & Zoorob, 2018). Understanding the potential consequences of these changes (e.g., cognitive effects, residual effects, health outcomes) is valuable for decisions made regarding cannabis policies and regulations. While there are several domains of interest, the cognitive effects of cannabis are one of the most important to understand given its popularity with adolescents and young adults. Neurocognitive function is also a critical area of research as previous research has shown deficits in a variety of neurocognitive domains including executive functioning and memory impacts various factors such as employment (Kalechstein et al., 2003). Acute effects of cannabis are relatively well understood with several studies finding evidence that cannabis leads to cognitive deficits in several domains of cognitive function (i.e, attention, memory, learning, inhibition, and executive functioning) during and shortly after acute intoxication (Crean et al., 2011; Scott et al., 2018). However, there is less clear evidence when examining the lasting, or residual, effects of cannabis on cognitive function after a period of abstinence. Some studies have found support for deficits, while others have found nonsignificant differences when comparing past users to healthy controls (Dellazizzo et al., 2021; Figueiredo et al., 2020; Lovell et al., 2020; Schreiner & Dunn, 2012; Scott et al., 2018).

Many factors limit our current understanding of the long-term effects of cannabis. One predominant factor is the impact of racism, politicization, and the drug's legal classification as a schedule 1 drug, classifying it as higher risk than drugs like cocaine and fentanyl (Solomon, 2020). In addition to these problems, funding for cannabis research is often awarded to studies focused on the negative effects of the drug leading to bias not only in the projects completed but in the reporting of results (National Academies of Sciences et al., 2017). Approaching and reporting the results in an unbiased manner is necessary to advance our understanding of the long-term outcomes associated with cannabis use. Many cross-sectional studies also assert cannabis is a causal variable without having the necessary data to determine causality (Schuster et al., 2018). As a result, there is much we do not know about the effects of cannabis, particularly the long-term effects. The ambiguity of currently available results on the long-term effects of cannabis is only increased by studies, reviews, and meta-analyses that overstate their results or use unclear language (Dellazizzo et al., 2022; Lovell et al., 2020). The current study seeks to clarify what we currently know about the long-term effects of cannabis by clearly defining terms important to understanding the results, examining specific outcomes consistent with previous research, and implementing best practices for meta-analysis (e.g., *a-priori* power analysis; Jackson & Turner, 2017).

Changes in Cannabis Legislation, Use, and Production

The legal status of cannabis in the United States has had a long and complicated history which has impacted research efforts. Cannabis was grown for several uses in the American colonies including hemp for rope and cloth, as well as medicinal and recreational uses (Maisto et al., 2021). Cannabis became effectively illegal after the passing of the *Marihuana Tax Act* of 1937, which was eventually determined unconstitutional by the Supreme Court in 1969.

However, in 1970, the *Controlled Substances Act* was passed which labeled cannabis as a schedule 1 drug, indicating it is a drug with high potential for abuse and no known medical uses (*Drug Scheduling*, n.d.). This is despite several studies indicating there may be some medical benefits to cannabis (Banerjee & McCormack, 2019; Lim et al., 2017). In addition to this research, medicinal cannabis use is legal in the majority of states in the US, despite the drug's legal status at the federal level. Recreational cannabis use has also been legalized in 24 states plus the District of Columbia as of the beginning of 2024, indicating an important shift in how cannabis is viewed in the United States.

With increased legalization of recreational and medical cannabis use, we have also seen increased accessibility and rates of use (Martins et al., 2021; Smart & Pacula, 2019). Rates of use have seen several changes over recent years with fluctuations due to a variety of factors including a peak in use around 2019 and reductions during the COVID-19 pandemic lockdowns. However, the most recent data still shows a considerable number of adolescents endorse lifetime cannabis use with 10.20% of 8^{th} graders, 22.00% of 10^{th} graders, and 38.60% of 12^{th} graders indicating past use (Johnston et al., 2022). In addition, 49.60% of individuals aged 18 to 25, and 48.90% of individuals aged 26 or older have reported lifetime cannabis use (Substance Abuse and Mental Health Services Administration, 2020). Research has indicated the brain continues to develop well into young adulthood making the number of individuals 25 or younger who have used cannabis striking, and highlighting the importance of understanding how cannabis impacts cognitive functioning (Lebel & Beaulieu, 2011).

When examining the general effects of cannabis, the role of cannabinoids is an important factor to consider. Cannabinoids are compounds found in the cannabis plant and play a significant role in the experiences of individuals who use cannabis (Ameri, 1999; Grotenhermen,

2005; Levinsohn & Hill, 2020). The two most common and active cannabinoids found in cannabis plants are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and their effects are well understood (Jikomes & Zoorob, 2018). In the past decade with increased availability, there have also been significant increases in Δ9-tetrahydrocannabinol (THC) and decreases in cannabidiol (CBD; Smart et al., 2017). THC is best known for its psychoactive properties and the resulting "high" individuals experience, while CBD is most often seen in medical cannabis strains with effects including relaxation and pain relief (Levinsohn & Hill, 2020; Lorenzetti et al., 2016). Furthermore, there is evidence CBD mitigates some of the adverse effects of THC, which may increase the risk of adverse effects from new strains with higher THC and lower CBD levels. Preliminary evidence also suggests THC exacerbates changes in neuroanatomy while CBD protects against these negative effects (Lorenzetti et al., 2016). There is also evidence legalization of recreational and medical cannabis use has also increased rates of vaping and edible use which can vary even more in terms of potency than more traditional methods of use. Some concentrates used for vaping, dabbing, or edibles contain upwards of 60% THC (Borodovsky et al., 2016; Chan et al., 2017; ElSohly et al., 2021; Matheson & Le Foll, 2020). The increased accessibility of more discreet, and possibly more potent, methods of use is a question that needs to be examined in the literature. Research has demonstrated orally ingested cannabis also results in adverse effects on cognitive performance despite lower blood THC levels (Schlienz et al., 2020). Based on the available evidence what was previously found to be true regarding the effects of cannabis may no longer be applicable due to the significant changes in THC and CBD content which have occurred over the past decade.

Cognitive Performance and Cannabis

Due to the psychoactive properties of cannabis, there has been considerable research on its neurocognitive effects (Auer et al., 2016; Bosker et al., 2013; Bourque & Potvin, 2021; Broyd et al., 2016; Camchong et al., 2017; Crean et al., 2011; Hooper et al., 2014; Rabin et al., 2017; Schuster et al., 2019; Thames et al., 2014; Yip et al., 2014). The research on the cognitive effects of cannabis is complex, with many studies finding conflicting results with some finding evidence of significant cognitive deficits linked to use, and others finding negligible deficits. Lisdahl et al. (2021) highlights some of these complexities (i.e., quantity and frequency of use, length of abstinence, recreational or medicinal use), and emphasizes the effect sizes are often small to moderate. Another study found evidence effort mediated the relationship between frequency of cannabis use and memory performance (Hirst et al., 2017). Contrastingly, a meta-analysis of neuroimaging studies found significant differences between users and non-users in several brain regions including the hippocampus, and orbitofrontal cortex relative to controls (Lorenzetti et al., 2019). There is also some evidence that there may be differences based on biological sex when examining long-term, but not acute, effects of cannabis on various domains of neurocognitive functioning, with male cannabis users showing decreased performance on measures of psychomotor function relative to healthy controls, and females demonstrating decreased performance on visuospatial tasks (Crane et al., 2013). Additionally, there is evidence bias in the examiner's judgments of participants' cannabis use status affects performance, with participants who were believed to be users performing worse than perceived non-users regardless of use status (Sodos et al., 2018). Earlier age of onset has also been shown to be associated with worse performance on cognitive measures (Sagar et al., 2015). Given the complexity of the research on

the cognitive effects of cannabis, it is important for researchers to carefully examine and communicate findings.

Acute Cognitive Effects

Many studies have demonstrated the acute effects of cannabis significantly impair cognitive functioning in several domains, even shortly after the period of intoxication. Thames et al., 2014, identified differences in the cognitive domains of attention and working memory, information processing, and executive functioning with those who recently used cannabis performing worse on these tasks than non-users. In line with these results, one study comparing THC to placebo found evidence of visual working memory impairment in the THC group (Adam et al., 2020). Conversely, a study conducted by Murray et al. (2022) suggested age may play a significant role in the impact of cannabis on cognitive functioning with adolescents demonstrating greater impairment compared to adults. Another recent study of acute effects of medicinal cannabis use on cognitive performance found some evidence of improvement on neuropsychological tests during acute intoxication and recovery, suggesting cannabis use may not only lead to deficits (Olla et al., 2021). It is important to state medicinal cannabis tends to have higher CBD content than recreational strains, which may contribute to these results. Despite some contradictory evidence the data largely suggests cannabis results in deficits in performance on cognitive tasks during and shortly after the period of intoxication as highlighted in reviews and meta-analyses of the literature (Crean et al., 2011; Lovell et al., 2020; Scott et al., 2018). Studies examining the long-term effects of cannabis are less clear in their findings.

Long-Term or Residual Effects

Findings on the long-term effects of cannabis after abstaining from use on neurocognitive functioning have varied. There appear to be several reasons for the mixed results. One reason

seems to be how studies define the word residual. Depending on the study residual effects have been defined as anywhere from 24 hours abstaining from use to over a year abstaining from use, which leads to vastly different results (Hooper et al., 2014; Lorenzetti et al., 2021; Pardini et al., 2015; Thames et al., 2014; Winward et al., 2014). In addition, several studies focus on specific psychiatric populations including individuals with substance use disorders (Hooper et al., 2014; Roten et al., 2015), or schizophrenia (Rabin et al., 2017). As a result of these factors, among others (e.g., age of the sample, duration of use), it can be difficult to tease apart the residual effects of cannabis on cognitive functioning.

Within the currently available literature, several studies have found evidence of residual cognitive deficits among cannabis users. One study found deficits in verbal learning, but not visuospatial learning, in individuals who had been abstinent from cannabis use for approximately 2.5 years (Lorenzetti et al., 2021). However, this study only had 12 participants in the prolonged abstinence group, limiting the generalizability of the results. Another study that monitored abstinence for one month found a significant impact on inhibition tasks, verbal memory, and psychomotor speed (Winward et al., 2014). Thames et al. (2014) found no statistically significant differences between recent users and past users in terms of global neurocognitive function or individual cognitive domains. Past users in this study were defined as individuals who had not used in at least 28 days. These findings suggest there may be some adverse long-term effects of cannabis use on cognitive functioning.

Despite some studies presenting evidence of cognitive deficits associated with cannabis use even after cessation, other studies have found incongruous results. A study examining abstinent adolescents with cannabis use disorder (CUD) found there were no significant differences between abstinent CUD users, adolescents with other psychopathology but no

substance use disorders, and healthy controls when looking at IQ, attention, memory, or executive functions (Hooper et al., 2014). Participants in this study had to be in remission and were abstinent between 1 and 12 months, and results indicate other variables, such as psychopathology, better account for differences in performance. Similarly, a longitudinal study examining the relationship between working memory function and substance use found moderate to heavy use of several substances including cannabis did not result in changes to working memory function (Cousijn et al., 2014). Another study comparing participants with a history of problematic cannabis use found individuals who were abstinent in the past 30 days, as well as those who used less than or equal to 3 days per week, had better global health, appetite, and depression outcomes compared to heavy users, but did not include healthy controls (Mooney et al., 2018). This same study also found users who were abstinent in the past 30 days reported improved sleep, anxiety, and cognitive functioning.

There is also evidence some of the impacts of cannabis on cognitive function improve over time when users are abstinent (Bosker et al., 2013; Curran et al., 2016; Pardini et al., 2015; Rabin et al., 2017; Roten et al., 2015; Schuster et al., 2018; Vadhan et al., 2011; Wallace et al., 2020). A longitudinal study examining attention and academic functioning in adolescents found after a year of abstinence there was no evidence of residual effects of cannabis (Pardini et al., 2015). Similarly, Schuster et al. (2018), measured cognitive performance weekly throughout one month while monitoring cannabis abstinence and found improvements on the task each week, with the most significant improvement occurring one week after abstaining. Roten et al. (2015) found improvement in composite and verbal memory, as well as psychomotor performance during monitored abstinence with adolescents who met DSM-IV criteria for cannabis dependence. However, these studies did not include control groups limiting interpretation and

comparison. One study found psychomotor function in chronic daily cannabis smokers improved during 3 weeks of abstinence, but did not reach the level of the healthy control group (Bosker et al., 2013). Bosker et al. note chronic smokers and controls were not matched for several key variables (i.e., education, social-economic status), and state the results should be interpreted cautiously. Similar improvements were found among cannabis-dependent patients with schizophrenia and non-psychiatric control abstainers (Rabin et al., 2017). These improvements also appear in neuroimaging research. A recent neuroimaging study suggests the hippocampus recovers if users are exposed to CBD, or are abstinent from cannabis, indicating there may not be significant residual effects following abstinence, as well as highlighting the possible protective effects of CBD (Yücel et al., 2016). These neuroimaging studies are particularly important as structural changes to the brain have been identified as the mechanism through which cannabis impact long-term neurocognitive function (Thames et al., 2014; Winward et al., 2014). These longitudinal studies underscore the importance of clearly defining terms such as residual by demonstrating important changes occur after cessation of use.

Systematic Reviews and Meta-Analyses

The mixed results found in individual studies examining the long-term cognitive effects of cannabis make clear and structured meta-analyses vital to our understanding of the impact cannabis may have on cognitive functioning. To date, there are several systematic reviews and meta-analyses which have attempted to consolidate the results of various studies examining the long-term neurocognitive effects of cannabis (Crane et al., 2013; Curran et al., 2016; Dellazizzo et al., 2021; Figueiredo et al., 2020; Ganzer et al., 2016; Lovell et al., 2020; Scott et al., 2018). However, despite the plethora of research on this topic, many of these have conflicting findings or limitations that should be addressed. A review of the literature highlighted the controversial

nature of the results when looking at the long-term effects of cannabis on cognitive function, and indicated effects appear to subside after approximately one month of abstinence (Curran et al., 2016). This is supported by Schreiner and Dunn (2012), a meta-analysis which found non-significant differences between healthy controls and users who had been abstinent for at least 25 days, and further supported by Scott et al., 2018, a meta-analysis which found nonsignificant differences when studies required abstinence from cannabis for longer than 72 hours. Other studies have asserted there was evidence of minor to moderate effects with minimal effects of prolonged abstinence, defined as ≥25 days, on the results (Lovell et al., 2020). It is important to note Lovell et al. only included four studies after 2012 in their secondary analyses on prolonged abstinence and no studies past 2015, which may not capture changes or accurately portray more recent data. This highlights the importance of new meta-analyses to examine more recent studies.

Other meta-analyses and reviews examining this subject have focused on specific populations (e.g., chronic cannabis users) limiting the generalizability of the findings (Figueiredo et al., 2020; Ganzer et al., 2016). In addition, the language used in many meta-analyses and reviews make sweeping claims off of small effect sizes or use ambiguous language when defining important variables (i.e. residual). Dellazizzo et al. (2021), a systematic review of meta-analyses that examined acute and residual effects did not define what constituted residual effects (i.e., period of abstinence, currently sober). Despite being unclear in their definition of residual effects, they claim there is evidence of detrimental effects of cannabis on cognitive function that persist beyond acute intake, which is not clearly presenting important information. One consequence of using ambiguous language is the perpetuation of negative bias in popular media, which can influence how data is used, or understood by individuals unfamiliar with the literature (FeaturedNeurosciencePsychology, 2022). This demonstrates the importance of being clear in

the language used in academic papers, and how the use of ambiguous language can contribute to the spread of misinformation. Cognitive domains are also defined differently in various meta-analyses. This is important because without consistent domain definitions, it is difficult to compare current meta-analyses with previous studies and meta-analyses, thus limiting our understanding of how the effects of cannabis on cognitive function may have changed (Lovell et al., 2020; Schreiner & Dunn, 2012). The conflicting results of these meta-analyses suggest there needs to be more clarity in our understanding of the currently available literature.

CHAPTER TWO: PRESENT STUDY

The primary aim of the current study was to conduct a meta-analysis of studies examining the cognitive effects of cannabis use after prolonged abstinence (≥25 days) to determine if there is currently significant evidence of long-term, or residual, cognitive effects. The focus on studies with prolonged abstinence was to account for the pharmacokinetics of cannabis. Unlike other substances THC, one of the primary psychoactive cannabinoids in cannabis, is fat-soluble and can be stored in body fat and slowly released into the bloodstream for months (Ellis et al., 1985; Grotenhermen, 2003; Maisto et al., 2021). To account for this, only studies with prolonged abstinence for a period of at least 25 days were included. This is in line with previous research which has suggested that despite possibly continuing to be detectable in urine, on average cannabis is no longer detectable after 25 days of abstinence with several factors contributing to the range (Gretenhermen, 2003). This was done to minimize the effect of residual THC and provide a clear definition of residual effects and ensure any residual effects are being analyzed after significant THC levels have left the system. The threshold of 25 days was also chosen to be in line with previous definitions of prolonged abstinence (Lovell et al., 2020; Schreiner & Dunn, 2012). Additionally, the present meta-analysis only included studies published after 2010 to account for changes in cannabis (i.e., THC and CBD ratios, methods of use) which may contribute to changes in the cognitive effects in the years since Schreiner and Dunn's meta-analysis (2012). The cognitive domains, search terms, and other study criteria were consistent with previous meta-analyses on the topic to ensure results of the analyses are clear and allow for comparison with previous meta-analyses (Grant et al., 2003; Schreiner & Dunn, 2012).

Research Question

The primary aim of the current study was to identify if there is evidence of significant long-term effects of cannabis on neurocognitive function. Specifically, we hoped to better understand if there are significant differences between individuals who have abstained from cannabis use for at least 25 days, and healthy, non-using controls. It was expected results would be in line with previous research on the topic (Grant et al., 2003; Schreiner & Dunn, 2012) with differences in cognitive functioning decreasing with abstention. The current meta-analysis did not test hypotheses, and the goal was to better understand the currently available data and identify if and how the effects of cannabis have changed in the past decade.

CHAPTER THREE: METHOD

The current study examined the cognitive effects of cannabis after prolonged abstinence, which will be defined as a period of at least 25 days. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines first outlined in Moher et al. (2009) and updated in Page et al. (2021). The PRISMA guidelines have been used in several meta-analyses across a variety of topics and domains (Ferrari et al., 2013; Figueiredo et al., 2020; Finnerup et al., 2015; Lovell et al., 2020; Schreiner & Dunn, 2012). Our literature review was limited only to data not included in Schreiner & Dunn (2012) and published during or after 2011 to account for potential changes in THC and CBD content in strains of cannabis as well as changes related to the legal status of cannabis in the United States (i.e., access, rates of use, methods of use). This was done to include more recent data than currently available meta-analyses (Lovell et al., 2020; Scott et al., 2018). Additionally, the methods and procedures were pre-registered on PROSPERO (ID#: CRD42023466560) prior to completing any data extraction or analyses.

The literature search was completed using the online databases PsycInfo, PsycArticles, PubMed, and Medline to identify all relevant studies. The search terms were (marijuana or marihuana or tetrahydrocannabinol or THC or cannabis) AND (neuro* or cognit* or assess* or abilit* or effect* or process* or impair*) AND (residual or long-term or abstinen* or abstain* or lasting or non-acute or persist*), consistent with previous meta-analyses on the topic (Schreiner & Dunn, 2012). Titles and abstracts were reviewed to ensure they broadly fit the research question (i.e., examine cognitive effects of cannabis). Articles deemed relevant or for which relevance could not be determined were reviewed further. For this stage of review, full-text articles were collected and reviewed by members of the research team including graduate

students, post-bac research assistants, and undergraduate research assistants. Studies were included if majority consensus was reached. After studies meeting the inclusion criteria of the present study were selected, references for the included studies and reviewed meta-analyses or systematic reviews were further reviewed to identify other potentially relevant studies following the same procedures previously outlined. Studies were selected for inclusion in analyses based on the criteria outlined in Grant et al. (2003) and followed in Schreiner & Dunn (2012; see Table 1). Additionally, to assess risk of bias in individual studies, studies were checked using the Joanna Briggs Checklist for Analytical Cross-Sectional Studies in line with previous meta-analyses (Joanna Briggs Institute, 2016; Lovell et al., 2020).

Participants

The proposed study did not recruit any participants. Studies included in the analyses had varying sample sizes and demographic makeups. Studies were selected only on the inclusion and exclusion criteria listed in Table 1. However, key demographic variables in the included studies were examined to determine if additional analyses (i.e., metaregression) were needed.

Power Analysis

An *a-priori* power analysis was completed using the R statistical package *metapower*, which can be used to estimate the power for both fixed effects and random effects meta-analysis models at various levels of assumed heterogeneity (Griffin, 2021). While many meta-analyses do not report conducting *a-priori* power analyses, research has indicated it is a crucial step to ensure power is increasing through the use of meta-analytical techniques (Jackson & Turner, 2017). The expected effect size, expected study size, expected heterogeneity, and expected number of studies are required to complete the calculations. Study size was estimated to be 112 based on the average number of participants from previous studies examining the residual effects of

cannabis on cognitive function (Hooper et al., 2014; Matheson et al., 2020; Schuster et al., 2018; Thames et al., 2014), and heterogeneity was assumed to be high ($I^2 = 0.75$) based on previous research (Schreiner & Dunn, 2012). The results indicated to detect small effect sizes ($d = 0.2$) at least 28 studies would need to be identified and included to sufficiently power the analyses. Power analyses indicated a minimum of 6 studies would be needed to sufficiently power the analyses to detect a moderate ($d = 0.5$) effect size.

Proposed Analyses

In line with previous meta-analyses on the topic, the primary areas of analysis were overall and lasting effects of cannabis on cognitive functioning. Analyses were completed with R Statistical Software (v4.3.1; R Core Team, 2023). R Statistical Software is software for statistical analyses which contains several packages that can be used to complete meta-analyses and make adjustments and considerations for variables including sample size, number of studies, and heterogeneity. Packages that were used include dmetar, meta, metafor, metaforest, and ggplot2 (Balduzzi et al., 2019; Harrer et al., 2019; van Lissa, 2020; Viechtbauer, 2010; Wickham, 2016). A random-effects model was utilized to account for the heterogeneity of several factors within studies such as outcome measures, population characteristics, and abstinence length among others as used in previous meta-analyses on the topic (Figueiredo et al., 2020; Lovell et al., 2020; Schreiner & Dunn, 2012). Additionally, while standardized mean differences using Cohen's *d* are typically used to determine effect sizes, in studies with small sample sizes it is sometimes necessary to compute effect sizes using Hedge's *g* to correct for the overestimation of effect that can occur when using Cohen's *d* with small sample sizes (Borenstein et al., 2009; Schreiner & Dunn, 2012). The decision of whether to use standardized mean differences or Hedge's *g* was determined after assessing the studies included for analyses. In addition to using Hedge's *g*, the

estimator used was determined by the number of studies included in the analyses. The most common estimator by DerSimonian and Laird has been found in several studies to be biased by a small number of studies and high level of heterogeneity (Follman & Proschan, 1999; Hartung, 1999; Hartung & Knapp, 2001a, 2001b; Makambi, 2004). Heterogeneity was assumed and found to be high ($I^2 \geq 0.75$), and the restricted maximum-likelihood estimator was used in line with prior research (Veroniki et al., 2016).

To determine effects on neurocognitive performance, several outcomes were assessed. To assess overall effects on neurocognitive functioning broadly, effect sizes were averaged across different outcomes. This was done to create an overall neurocognitive performance outcome to analyze due to studies using different neuropsychological measures. In addition, since studies included a variety of measures to assess outcomes, the current study followed the guidelines initially described in Grant et al. (2003), and subsequently outlined and followed in Schreiner and Dunn (2012) to determine eight additional outcome variables. These outcomes were abstraction/executive (e.g., decision making, ability to understand abstract concepts, impulse control), attention (e.g., ability to focus on a task), forgetting/retrieval (e.g., ability to recall learned information), learning (ability to encode information), motor, perceptual-motor, simple reaction time, and verbal/language (e.g., knowledge of language and vocabulary; Grant et al., 2003). Upon completion of the literature review only the domains of overall effects, abstraction/executive, attention, forgetting/retrieval, and learning were included in analyses (see Table 2 for more details). The included domains represent important areas of function within various settings such as school, interpersonal relationships, and work (Aronen et al., 2005; Kalechstein et al., 2003; Mar Gómez-Pérez & Calero, 2022).

Past users currently in prolonged abstinence were compared to the healthy controls to identify if there is evidence of significant group differences. In addition to the primary analyses outlined above, metaregression analyses were planned to account for year of data collection and age of sample . These analyses were completed to account for possible moderation of effect sizes caused by these variables. Metaregression analyses were completed in R Statistical Software..

Tests of heterogeneity were conducted to evaluate the variance in effect sizes across studies. The Q statistic, which is the sum of squared deviations on a standardized scale, and the I^2 statistic, which is used to determine the proportion of observed variance due to true effects and not sampling error, were examined for these purposes (Borenstein et al., 2017). Additionally, due to publication bias, Orwin's Fail-safe N test was conducted for statistically significant results. Fail-safe N tests computes the number of missing studies with insignificant results (i.e., mean effect of 0) which would need to be added to the analysis to result in an overall statistically insignificant effect (Borenstein et al., 2013; Long, 2001).

Diversity

While the current study did not recruit participants, there are significant diversity factors that need to be considered when conducting cannabis research. With the history of cannabis legislation and research being affected by racism, it is important research on cannabis takes extra steps to reduce bias (Solomon, 2020). The negative bias found in cannabis research has real-world implications on legislation which has disproportionately hurt individuals of various racial and ethnic backgrounds. Most significantly Black communities have been affected, with Black individuals being arrested at nearly 4 times the rate of White people in America despite similar rates of use (American Civil Liberties Union, 2021). With the racial biases related to cannabis use still having a significant impact on the lives and freedoms of People of Color in America,

researchers must report results accurately and without bias due to the potential consequences of changing cannabis legislation. The current study clearly and accurately reports the results of the analyses to further support this goal.

In addition to differences in cannabis consequences experienced by minoritized racial groups, there are also potentially important differences based on sexual identity. Studies have suggested individuals who identify as a sexual minority are at higher risk of meeting the criteria for cannabis use disorder (CUD; Boyd et al., 2020). Understanding all the risks associated with cannabis use, especially long-term effects, is beneficial to our understanding of how CUD may impact cognitive functioning and could be particularly beneficial to people who identify as sexual minorities. Due to the apparent disproportionate risks associated with cannabis use for various minoritized groups, it is crucial research is clear in reporting results, and takes steps to minimize bias throughout the entire research process.

Ethical Considerations

No human subjects were enrolled in the current study. The methods and procedures were submitted for review by the IRB to ensure it met exempt status. The university IRB confirmed the current study is exempt from review due to the absence of human subjects. Additionally, study selection is an important ethical consideration. When selecting studies to include in analyses the inclusion and exclusion criteria were strictly followed and studies were examined for other potentially problematic factors (e.g., use of the same sample). Additionally, steps to examine the impact of bias in individual studies, and the effect of publication bias were taken to ensure ethical research practices. To that end, the current study assessed individual studies using the Joanna Briggs Checklist for Analytical Cross-Sectional Studies and for publication bias using

Orwin's Fail-safe N test. These additional steps help ensure results were not negatively impacted by bias within the individual studies, or by unpublished data.

Implications

Cannabis is the most widely used illicit drug in the world, and it is becoming more easily accessible each year as more countries re-evaluate their cannabis laws (Johnston et al., 2022; UNODC, 2015). As cannabis becomes more accessible understanding the potential long-term effects of cannabis use, even after cessation, becomes increasingly important. With the currently available data, it is difficult to draw conclusions, as each study contains only small samples of the population and have found contrasting evidence. A comprehensive meta-analysis with clear, and focused goals will increase our understanding based on the available data. Additionally, reporting based on the results was focused on accuracy and clarity, and not publication. The current study will additionally contribute to the literature by replicating previous methods and procedures which will enable comparison to previous analyses and help us understand how things have changed in the ensuing years. Regardless of how the legal status of cannabis continues to change in the United States and abroad, it is crucial to understand the possible adverse or beneficial effects to inform recommendations for use and inform clinical practice for individuals with cannabis use disorders.

CHAPTER FOUR: ANALYSES AND RESULTS

Study Selection and Review

The initial literature search identified 3,611 studies. Out of those 3,611 studies 170 were identified as possibly relevant to include in analyses based on titles and abstracts. These 170 studies were then reviewed by three members of the research team based on the inclusion criteria (see Table 1). If majority consensus could not be reached, a subject matter expert was consulted, and expert input was discussed by the research team. Out of the 170 studies initially pulled, 7 were identified as meeting inclusion criteria, and were included in the analyses. An additional 4 studies were identified through reference review, with one additional study meeting criteria identified (see Figure 1 for more detail).

After studies were selected, they were reviewed for specific behavioral assessments used. Upon review, there were several outcomes that could not be assessed because there were no relevant behavioral assessments included in the selected studies. The outcomes of perceptual-motor and simple reaction time were not included in any of the selected studies, and the outcome of motor was only included in one study. As a result, these outcomes were not analyzed. One study (Auer et al., 2016) used data collected prior to 2012. This study was included because it analyzed data collected in 2011, otherwise met criteria for inclusion, and had not been included in Schreiner & Dunn (2012). Additionally, studies were reviewed using the Joanna Briggs Critical Appraisal for Analytical Cross Sectional Studies to assess for risk of bias. All studies were determined to be low risk of bias.

Analysis Plan

After reviewing the included studies several decisions were made for the analysis plan. Due to the expected high level of heterogeneity ($I2 \geq 0.75$), a random effects model was used for

analyses. Additionally, due to the limited number of studies included in the analyses, as well as the variability in sample size within the included studies, the decision was made to use the restricted maximum-likelihood estimator, and to apply a Knapp-Hartung adjustment in line with prior research (IntHout et al., 2014; Langan et al., 2019). These decisions were made to reduce the risk of false positives. Lastly, due to the small sample size of some of the included studies, the decision was made to use Hedge's *g* in line with prior research, and standards (Borenstein, 2009; Schreiner & Dunn, 2012). Effect sizes were calculated using means and standard deviations reported in the selected studies. Models were also assessed for outliers, and re-run without identified outliers as needed. For significant results fail safe n and influence analyses were completed. Subgroup analyses were completed for age, and year of data collection. Duration of use and race/ethnicity were not consistently measured in included studies, and metaregression could not be completed on these variables.

Overall Effects

The first analysis completed looked at overall effects by calculating a summary effect size for all examined cognitive domains. The summary effect size was calculated by averaging across effect sizes for the assessed outcomes. All eight studies were included in this analysis. Results indicated the overall effect was not significant (ES = 0.17, 95% CI [-0.17, 0.50]). The tests of heterogeneity for this analysis were significant ($Q(7) = 19{,}233.47$, $p < .01$, $I^2 = 100\%$, $T^2 = 0.15$) Outlier analysis indicated two studies, Delibaş et al. (2018) and Winward et al. (2014), were outliers and analyses were rerun. Results of the second analysis including the remaining six studies were still not significant (ES = 0.12, 95% CI [-0.03, 0.28]). Tests of heterogeneity remained statistically significant after removing the outliers ($Q(5) = 16{,}445.48$, $p < .01$, $I^2 = 100\%$, $T^2 = 0.02$).

Subgroup analyses, a form of metaregression, were completed to examine the effect of age group (adult, adolescent), or year of data collection (before or after 2012) on the results. Results of the age subgroup analysis indicated overall neurocognitive effects were not significant in either adolescents (k = 2; ES = 0.53, 95% CI [-5.83, 6.88]), or adults (k = 6; ES = 0.06, 95% CI [-0.1834, 0.2944]). The between group analyses were also not significant (Q(1) = 0.86, p = .35). Results of the year of data collection subgroup analyses found that the effect size for studies collected after 2012 (k = 7) were not statistically significant (ES = 0.14, 95% CI [-0.26, 0.54]). Additionally, results of the between group analyses were not significant (Q(1) = 1.72, p = .19).

Abstraction/Executive Functioning

The next analysis examining abstraction/executive functioning included four studies. Results indicated the effect size was significant (ES = 0.27, 95% CI [0.06, 0.47]). Tests of heterogeneity were also statistically significant (Q(3) = 863.24, p < .001, I^2 = 99.70%, T^2 = 0.02). Outlier analyses indicated there were no outliers (see Figure 8 for influence plots). Results of the fail-safe N test indicated 10 additional studies with an effect size of zero would be needed to accept the null hypothesis.

Subgroup analyses for age and year of data collection were completed. The age analysis indicated results were not statistically significant for the studies examining adults (k = 3; ES = 0.29, 95% CI [-0.06, 0.65]). Results of the between group analyses were not statistically significant (Q(1) = 1.38, p = .24). Similarly, results were not statistically significant for the studies completed after 2012 (k = 3; ES = 0.30, 95% CI [-0.03, 0.64]). Between group analyses were not statistically significant (Q(1) = 2.87, p = .09).

Attention

Attention was included in five of the selected studies. Results of this analysis indicated the effect size was not significant (ES = 0.22, 95% CI [-0.27, 0.70]). Tests of heterogeneity were significant ($Q(4) = 2{,}709.19$, $p < .001$, $I^2 = 99.90\%$, $T^2 = 0.14$). Subgroup analyses examining group differences based on age were completed. Subgroup analyses revealed results were not statistically significant for adults (ES = 0.03, 95% CI [-1.05; 1.10], or adolescents (ES = 0.22, 95% CI [-0.27, 0.70]). Tests of between group differences were not significant ($Q(1) = 2.29$, $p = .13$).

Verbal/Language

Results of the Verbal/Language analysis were not significant ($k = 3$; ES = 0.41, 95% CI [-0.91, 1.74]). Tests of heterogeneity were significant ($Q(2) = 161.84$, $p < .001$, $I^2 = 98.80\%$, $T^2 = 0.28$). Subgroup analyses for age and year of data collection were also completed. The age analysis indicated results were not statistically significant for the studies examining adults ($k = 2$; ES = 0.25, 95% CI [-0.38; 0.88]). Between group analyses indicated a significant difference ($Q(1) = 21.99$, $p < .001$).

Forgetting/Retrieval

Results of the analysis examining Forgetting/Retrieval were not significant ($k = 4$; ES = 0.31, 95% CI [-0.35, 0.97]). Tests of heterogeneity were significant ($Q(3) = 41.16$, $p < .001$, $I^2 = 92.70\%$, $T^2 = 0.14$). Subgroup analyses for age and year of data collection were also completed. Age analyses indicated the effect size for adolescents was non-significant ($k = 2$; ES = 0.47, 95% CI [-5.37; 6.30]), and was significant for adults ($k = 2$, ES = 0.19, 95% CI [0.18; 0.20]). Tests of between group differences were not statistically significant ($Q(1) = 0.36$, $p = 0.55$).

Learning

Only two selected studies included assessments of learning. Results of this analysis were not significant (ES = 0.29, 95% CI [-2.75, 3.34]). Tests of heterogeneity were significant ($Q(1) = 2281.19$, $p < .001$, $I^2 = 100.00\%$, $T^2 = 0.12$). The two included studies did not differ in terms of population (i.e., adolescents vs. adults). One of the included studies (Auer et al., 2016) was collected prior to 2012. However, due to the analysis only have two included studies, outlier and subgroup analyses were not completed.

CHAPTER FIVE: DISCUSSION

The current study applied meta-analytic approaches to examine whether there is evidence of residual neurocognitive effects of cannabis. Residual effects have been defined as those lasting after the majority of THC has left the body after a period of approximately 25 days (Ellis et al., 1985; Grotenhermen, 2003; Maisto et al., 2021). The meta-analysis included 8 studies that contributed to the overall effect domain. Results indicated there were no significant effects on overall cognitive functioning. Similarly, in the domains of attention, forgetting/retrieval, verbal/language, and learning there was no evidence of lasting neurocognitive effects due to cannabis based on a 95% confidence interval. The domain of abstraction/executive function had a statistically significant, but small, effect size (Hedge's g = 0.27). In the domain of abstraction/executive functioning, the results indicate that healthy controls performed better than abstinent cannabis users. However, only one of these studies measured abstraction/executive functioning (or any other variables) before exposure to cannabis. Therefore, this difference could have existed prior to exposure to cannabis, or the difference could be evidence of residual effects of cannabis that last beyond 25 days of abstinence. The design of these studies prevents a conclusion one way or the other in relation to potential long-term impacts on executive functioning (e.g., decision making, abstraction). In sum, there was no evidence of residual effects in four of the five domains evaluated in these studies. There was a small but statistically significant difference in executive functioning, but the methodology of these studies could not control for pre-existing differences or the potential effects of other variables (e.g., lifestyle, exposure to other drugs, etc.).

The nonsignificant results for the overall effect indicate there are no statistically significant differences between past users and healthy controls when accounting for all the

domains included in the current analyses. This contradicts previous research, including meta-analyses, which found there were significant differences between abstinent cannabis users and healthy non-using controls (Dellazizzo et al., 2021; Lovell et al. 2020). The conflicting results with other meta-analyses could be due to less strict inclusion criteria in those analyses, bias within the included studies, or over-reporting of results. When considering the majority of cannabis research is funded by NIDA, an organization focused on identifying negative effects of substances including cannabis , it is not surprising meta-analyses and systematic reviews find some evidence of negative long-term effects (National Academies of Science, 2017; Solomon, 2020). Within this context it is imperative researchers conducting meta-analyses and literature reviews are balanced in their reporting and taking steps, to account for unpublished non-significant results such as conducting Fail Safe N tests. Lovell et al. (2020) only utilized a funnel plot for the 30 studies included in the primary analyses, and did not report any analysis of publication bias included for the subset of studies which looked at prolonged abstinence. Research has shown that funnel plots may not be the most accurate representation of publication bias, as they rely on subjective interpretation of visual data which may be influenced by factors other than publication bias (Kossmeier et al., 2019; Polanin et al., 2016). Despite not assessing publication bias on the subset of studies, they reported the significant results with certainty. The Lovell et al., (2020) meta-analysis also did not include an *a-priori* power analysis, limiting confidence in the results. When considering the findings of the current study in conjunction with the findings of other meta-analyses, there seems to be little or no evidence of residual effects.

Results of the current study also support other studies and meta-analyses which found as time of abstinence increases, effect sizes decrease or become non-significant (Schreiner & Dunn, 2012; Scott et al., 2018). The non-significant differences within the verbal/language domain is

consistent with previous longitudinal research that found improvements within this domain after one month of monitored abstinence (Roten et al., 2015). Roten et al. (2015) demonstrated that deficits in this domain improve and recovery occurs after cessation of use. The current study extends this by finding evidence that after a roughly equivalent period of abstinence (≥25 days) there are no statistically significant differences between past cannabis users and non-using healthy controls in all but one domain. Long-term cannabis use does not appear to be associated with deficits in verbal/language skills. Similarly, results of the current study within the domain of attention support previous research demonstrating after a year of no use, past cannabis users did not significantly differ from controls in attention (Pardini et al., 2015). This adds to the evidence that in many important areas of functioning past users do not differ significantly from non-using healthy controls. The non-significant results in overall effects, and the domains of learning, and forgetting/retrieval are consistent with previous meta-analyses (Schreiner & Dunn, 2012; Scott et al., 2018). The non-significant difference in overall effects is notable, as this analysis represented a summary of all the included domains. The current meta-analysis adds to the growing literature suggesting there is almost no evidence of long-term neurocognitive effects of cannabis after prolonged abstinence (i.e., ≥25 days), particularly in the domains of verbal/language, attention, forgetting/retrieval, and learning. And the design of studies that met criteria for inclusion in this meta-analysis prevents definitive conclusions because there was no measure of pre-exposure functioning to equate past users and non-users before cannabis exposure.

All but one of the analyses in the current study resulted in non-significant effect sizes. One small significant effect size within the domain of abstraction/executive function was found. This provides evidence there may be a small association between cannabis and long-term

outcomes on tasks including decision making, working memory, and complex attention. It should be noted the effect size was small, and the analysis was underpowered to detect moderate effect sizes, meaning the results should be cautiously interpreted. This result is also inconsistent with previous meta-analyses which found after prolonged abstinence (≥25 days) there was no evidence of statistically significant differences in abstraction/executive function (Lovell et al., 2020; Schreiner & Dunn, 2012). This suggests this finding is either spurious or represents a shift in effects since 2011. Without additional original studies and support in future meta-analyses, it is impossible to determining. Study design is also cause for concern within this domain. Two of the four included studies were not longitudinally designed, and only one estimated premorbid functioning (i.e., prior to first cannabis use; Thames et al., 2014). Methods of estimating premorbid functioning, are also limited by requiring comparison with a full WAIS-IV, or estimating full scale IQ scores and not scores within specific domains (Bright & Linde, 2017; Shura et al., 2022). The inability to control for pre-exposure functioning with certainty is a serious limiting factor. This is particularly important within the domain of abstraction/executive functioning. This domain, largely associated with the prefrontal cortex, is associated with decision making, complex attention, and the ability to understand and communicate abstract ideas (e.g., freedom, vulnerability). Previous research, including twin studies, has indicated poorer executive functioning in childhood predicts adolescent substance use, suggesting these differences may be present prior to use (Cavalli et al., 2023; Gustavson et al., 2017). Without being able to control for premorbid executive functioning, it is not possible to say cannabis caused these differences. There are also questions regarding size of the groups within studies and the utility of small effect sizes in determining the impact. Only two studies included in this analysis had sample sizes greater than 100 participants (Auer et al., 2016; Meier et al., 2022).

Auer et al. (2016) had 612 participants, but the control group had substantially more participants (n = 531) than the past-user group (n = 81). It should be noted, there were additional groups within this study, but they were not relevant to the current analyses. Meier et al. (2022) had 254 participants, with 196 participants in the non-using group and only 58 participants in the past-use group. The imbalanced groupings may have affected the outcomes as there is some indication sample size imbalances can impact power of statistical analyses (Liang et al., 2020). In addition to the group sizes, the difference between statistical significance and clinical utility is an important distinction. Clinical utility is the most pertinent question. If there is no clinical utility to these differences, then how do they matter? Answering this question requires confidence in the results. Based on the results within the other domains, methodological limitations, and previous research indicating poorer executive functioning predicts later cannabis use, we cannot definitively draw any conclusions about this result. . Lastly, results of the Orwin fail-safe n test indicated only 10 studies with non-significant results would be needed to fail to reject the null hypothesis for the effect on executive functioning. This means if there are 10 studies that have not been published due to disseminations bias, then the finding would no longer be statistically significant. Research has shown that roughly 56% of non-significant results are reported in studies, compared to 76% of significant results and this does not account for unpublished data (Polanin et al., 2016). Publication bias, a form of dissemination bias is a well-documented concern within research and based on estimates, it seems likely there would be at least 10 unpublished studies that found non-significant results within this domain (Ioanndis & Trikalinos, 2007; Polanin et al., 2016). Lastly, the analysis was underpowered based on *a-priori* power analyses which indicated a minimum of 6 studies would be needed to detect a moderate effect size. The power analysis assumed high heterogeneity ($I^2 \geq 75\%$), but this analysis indicated

substantially greater heterogeneity (I^2 = 99.70%), suggesting the analysis is more underpowered than expected. Due to the lack of power, this analysis may be spurious, and decrease the chances it can be reproduced because as power decreases the number of true positives decreases, resulting in underpowered studies having a higher proportion of false positives to true positives (Button et al., 2013). Executive functioning should continue to be explored in future studies that use experimental designs that allow conclusions to be drawn regarding lasting effects of cannabis if there are any.

The results of the current study support four previous meta-analyses on this topic (Curran et al., 2016; Grant et al., 2003; Schreiner & Dunn 2012; Scott et al., 2018), but does not support three previous meta-analyses on this topic (Figueiredo et al., 2020; Ganzer et al., 2016; Lovell et al., 2020). The continued mixed results indicate there may be several unaccounted variables impacting the outcomes of various studies. Some of these variables could include effort, psychopathology (e.g., depression, anxiety), or use of other substances such as alcohol (Crane et al., 2013; Hirst et al., 2017). A total of 32 studies that were identified by the search terms were meta-analyses and reviews that are capturing the same results and data without significantly changing the criteria, suggesting studies published prior to 2012 are continuing to influence results despite significant changes to the chemical makeup of available cannabis (Smart et al., 2017). These identified meta-analyses were all published within the last 10 years, suggesting this is an important area of research, however, the lack of original studies that properly control for the various confounding variables published within this time frame is cause for concern when considering the number of meta-analyses and reviews available. Additionally, several of the published meta-analyses (e.g., Lovell et al., 2020; Scott et al., 2018) were published after the National Academies of Science (2017) review of the literature, which concluded that within the

literature spanning from 2000-2016 there was limited to no data to support an association between the sustained effects of cannabis use following prolonged abstinence, and the cognitive domains of attention, memory, and learning (p. 274-275). In spite of this review conducted by the National Academies of Science, several meta-analyses and reviews, using the same studies included in their review, have reported significant evidence. This further demonstrates the influence of funding, and negative bias on reporting of results. Another major limitation to the current literature is a lack of clear mechanism through which cannabis effects neurocognitive functioning. Many studies examining the effects of cannabis on neurocognitive functioning do not address how cannabis may impact long-term neurocognitive functioning, and others highlight animal studies showing how THC has impacts on brain structure (Lovell et al., 2018; Thames et al., 2014; Winward et al., 2014). The current state of the literature suggests some researchers may believe this question has been answered, as evidenced by the number of studies that did not meet criteria for inclusion (see Figure 1).

Diversity of samples is another area of concern regarding the available literature. Many of the available studies include largely white, male, and right-handed individuals. One study, Auer et al. (2016) had a majority Black sample, but used data collected in 2011. Auer et al., controlled for the effect of race on results, but did not find any effect. While the results of Auer et al. (2016) suggest race may not have an impact on the findings, it is important that studies carefully consider the possible impact of race on performance generally. There is evidence some neurocognitive tests are biased against non-White individuals, and the norms used for comparison groups often under-represent individuals from minoritized groups (Gasquoine, 2009). The under-representation of marginalized groups in research, particularly when the research could influence legislation targeting them, is poor science and has lasting and far-

reaching consequences (i.e., incarceration). Of the studies included in the current meta-analysis four did not report race or ethnicity. It should be noted these studies were not conducted in the United States (Delibaş et al., 2018; Meier et al., 2022; Riba et al., 2015; Zimmermann et al., 2018). Only Auer et al. (2016) included a majority Black sample (n = 447). While this sample was more diverse than other included studies, they only had participants who identified as White or Black, and they did not clearly report the breakdown within all of the groupings, making it unclear how many of the past cannabis users fall into either group. Excluding Auer et al. (2016) the remaining studies had substantially more White participants (n = 168) than Black participants (n = 42), or "other" participants (n = 31). While there are enough participants who identify as White and Black in the included studies to evaluate potential differences, the lack of specificity for the remaining participants is concerning. This limits our ability to draw conclusions based on the variables race acts as a proxy for, and further contributes to White individuals being used as the standard comparison group, which may contribute to ongoing bias in research. Additionally, this indicates study inclusion criteria may be biased towards individuals who are White or Black. Due to inconsistent reporting of race/ethnicity data, metaregression analyses were not possible. While race/ethnicity have been shown to act as proxy variables for other variables including socio-economic status, it is important to be able to control for the impact of the variables underlying this construct as many neurocognitive assessments include demographic based norms (Gasquoine, 2022; Putzke et al., 2002). Race and ethnicity are important variables to consider, as studies have indicated that while cannabis use trajectories are similar for Black and White individuals, alcohol use starts earlier on average for White individuals (Finlay et al., 2011). This suggests that, particularly in studies with majority White individuals, alcohol use needs to be clearly and appropriately controlled for. Additionally, it could suggest that alcohol use and race

may interact to moderate results. If not controlled for, then differences may be due to alcohol, or polysubstance use and not cannabis. This is important when considering the fact alcohol is legal for consumption throughout most of the world including the United States. Previous research has demonstrated structural and related functional changes in the brain due to alcohol use with earlier use being associated with decreased performance (Squeglia et al., 2014). This suggests studies that do not assess or appropriately control for alcohol use are not necessarily reporting true results of cannabis on neurocognitive functioning. Increased diversity within study samples would help minimize this problem based on prior research.

Biological sex is another important variable to consider and appropriately control for in research on neurocognitive effects with previous research highlighting differences in performance within specific domains of function, particularly for children and adults up to age 21 (Roalf et al., 2014). Within the literature focused on the acute neurocognitive effects of cannabis, sex-related deficits have been previously identified for male cannabis users in the domain of psychomotor function, and in the domain of visuospatial tasks for female cannabis users (Crane et al., 2013). Within the current meta-analysis metaregression was not feasible due to lack of power. The included studies overall were well balanced in terms of sex, not counting Riba et al. (2015) which did not clearly report the demographics of the sample. The studies included 676 male participants, and 712 female participants. However, similar to race, Auer et al. (2016) did not clearly break down the past users group in terms of biological sex. With Auer et al. (2016), and Riba et al. (2015), not clearly reporting the demographic characteristics of the sample, and with Thames et al. (2014) reporting only rounded percentages, even if the study had been powered enough metaregression analyses on biological sex would have been difficult to run or would not have accounted for all of the studies. Additionally, while overall there was a

roughly even number of total male and female participants, the control and cannabis groups were imbalanced in terms of sex with the cannabis groups having substantially more male (n = 303) than female (n = 183) participants and the control groups having substantially more female (n = 529) than male (n = 373) participants. Most notable is there are considerably more female participants in the control groups, than there are female participants in the cannabis groups. This suggests any findings within the current meta-analysis cannot be clearly generalizable to biological men and women. Given past research demonstrating important differences based on biological sex, it is critical that studies balance their samples appropriately.

All these concerns with the existing literature contribute to stigma against past and current cannabis users. This could have negative effects on access to effective healthcare, particularly for those who have a history of substance use (Fraser et al., 2020; Nyblade et al., 2019; Thornicroft, 2008). This is compounded by a negative outcome bias in the literature and funding opportunities. This can manifest in several ways, including focusing on significant but small negative effects within abstracts, and overstating small effects. In the current study, the possibly spurious and small effect size found in the domain of abstraction/executive function is unlikely to be replicated due to methodological limitations within the original studies. Past research has also indicated there are several confounding variables that may account for these results, including pre-exposure functioning and effort (Crane et al., 2013; National Academies of Sciences, 2017; Scott et al., 2018). These questions need to be further explored within the literature, and future studies should similarly temper their discussion of results until more concrete or clear evidence is available, as the currently available data within all of the literature does not clearly support evidence of lasting neurocognitive effects associated with cannabis use.

There are several limitations to the current study. One major limitation is the lack of studies meeting criteria for inclusion. Some of the most common factors leading to studies being excluded included no prolonged abstinence requirement (n = 27), no standardized behavioral assessments (n = 23), and no healthy control group (n = 18; see Figure 1 for full selection flowchart). These are significant limitations to the published research. Studies continue to use terms such as residual, and long-term despite not requiring a full day of abstinence. This adds to misconceptions about long-term effects of cannabis on neurocognitive functioning. The use of survey data and not standardized behavioral assessments is also alarming, as self-report on cognitive function is subjective, and limits comparison between groups. Similarly, the lack of healthy controls limits any comparison to individuals who have never used cannabis. All of these limitations within the literature further limit the utility of meta-analyses to be fully powered. Based on *a-priori* power analyses, a minimum of 6 studies with high heterogeneity (i.e., $I^2 \geq$ 75%) would be needed to detect a moderate effect size, and 28 studies with high heterogeneity would be needed to detect a small effect size. The studies included in the analyses had considerably higher heterogeneity (I^2 = 100%), suggesting the number of studies needed to properly power the analyses to detect moderate and small effect sizes would need to increase. This means the results of the current study are likely under-powered and may only give some insight into the actual effects, however, based on the current results there is not significant evidence of lasting neurocognitive effects in any domain besides abstraction/executive function for which there is limited evidence. Another limitation was due to the high heterogeneity, small number of studies, inconsistent reporting, and lack of power for the analyses, metaregression analyses examining factors including duration of use, race/ethnicity, and biological sex were unable to be completed. Not being able to confidently run metaregression analyses limits our

ability to properly control for variables of interest, and further limits our ability to interpret the data with certainty.

While there are several limitations within the current study, these limitations highlight meaningful problems within this area of research. The problems are highlighted by the number of meta-analyses and reviews on this topic (n = 36) which utilize the same studies, do not have substantially different inclusion/exclusion criteria, and have reported conflicting results, further adding to the confusion. None of these meta-analyses clearly reported conducting *a*-priori power analyses raising concerns regarding reported small effect sizes found. If the purpose of conducting meta-analyses is to increase the power, and thus our confidence in the reported effects, it seems vital the meta-analyses are themselves properly powered. These meta-analyses and reviews have also not used consistent methods (e.g., domains examined, search terms used) which limits comparisons between them. This in turn highlights another primary issue, which is the number of studies being published on this topic. Several studies do not include key components such as behavioral assessments, or control groups which limit our ability to draw conclusions and make comparisons between groups. There are also a number of studies that did not require abstinence greater than 12 hours, and being labeled as "long-term," or "residual." However, due to the half-life of cannabis, 12 hours would more appropriately be labeled as part of the acute phase. Even among studies that meet criteria, they use different outcome measures, do not measure control variables consistently (e.g., duration of use), or had uneven group sizes all of which contribute to the heterogeneity and increase the number of studies needed to power the analyses. This limits the ability of meta-analytical studies to synthesize and analyze the data. Over the past 12 years, there have been hundreds of studies which are titled to indicate they examine the residual or long-term effects of cannabis on neurocognitive functioning. However,

when examining the available studies less than 10 included data that was collected since 2010, had healthy controls, or utilized standardized behavioral assessments allowing comparison. Additionally, several studies, some published as late as 2022, included data that was from the 1980's. While these results may be helpful to some degree, currently available cannabis has substantially higher levels of THC, lower levels of CBD, and may have more intense psychoactive properties as a result (Jikomes & Zoorob, 2018; Levinshon & Hill, 2020; Lorenzitti et al., 2016; Smart et al., 2017). While this may mean the data is still being processed, there is not enough data from the past 10 years to give a clear picture of the effects currently available cannabis may have on neurocognitive functioning.

The current state of research on neurocognitive functioning seems to clearly illustrate the long-term effects of systematic bias. Despite several studies and meta-analyses demonstrating there is no substantial evidence of long-term neurocognitive effects of cannabis after prolonged abstinence (Crane et al., 2013; Hooper et al., 2014; Schreiner & Dunn, 2012; Scott et al., 2018), popular media, and research continues to make broad statements purporting significant evidence, despite small effect sizes (FeaturedNeurosciencePsychology, 2022; Lovell et al., 2020). This is further demonstrated by a systematic meta-review of meta-analyses (Dellazizzo et al., 2022) reporting there is evidence of long-term effects on neurocognitive functioning persisting beyond acute intoxication, which contradicts a comprehensive overview of the literature conducted by the National Academies of Science in 2017 (p. 274-275) which found there was limited to no evidence of association between sustained abstinence and cognitive function. One factor that likely has contributed to the ongoing mixed results is the history of cannabis research and legislation being inherently biased (Solomon, 2020). The National Academies of Science overview of the current state of cannabis research published in 2017 identified several barriers to

research. One substantial barrier they discussed is funding and the authors highlight NIDA's mission to study the negative effects and outcomes associated with cannabis and other substances. The authors assert that "Because cannabis was historically perceived to only have negative effects, the majority of cannabis research has been conducted under the auspices of NIDA" (p. 384), arguing research funded by NIDA is biased by their mission to study negative outcomes. This suggests positive outcomes are not being reported, studied, or that studies that receive funding are biased to identify or examine only negative effects. This becomes even more problematic when considering what is needed in future research. To definitively answer this question, large scale longitudinal designs that match participants on age, race, gender, and premorbid neurocognitive functioning are necessary. Large scale longitudinal studies are very expensive and time-consuming. This makes the funding barrier even more impactful on our ability to study cannabis in a meaningful way, particularly when considering the long-term effects after cessation of use. Longitudinal studies looking at the neurocognitive effects of cannabis also need to take into account important confounding variables including duration of use, age, use of other substances, other psychopathology, and effort among others. These studies also need to ensure use of standardized assessments and matched healthy control groups. Standardized assessment is a core component of research in this area, as it provides further insight into the functional changes, and can be used to estimate effects on ability to function within work settings. Another key source of bias within research more broadly is publication bias. With researchers facing increased pressure to publish, there is likely to be increased focus on the statistical significance of findings without additional consideration of the functional or clinical applicability of those findings. When considering the negative bias in funding, what results is researchers ignoring the possibility of positive outcomes, which limits our

understanding of cannabis. Without well-designed longitudinal studies that allow researchers to control for baseline differences in functioning, we cannot answer this question.

In conclusion, the current state of the literature does not allow for researchers to draw meaningful conclusions positively or negatively about the long-term impact of cannabis on cognitive functioning. There are several glaring methodological issues with the currently available research. Additionally, even if there were an adequate number of longitudinal studies exploring this, methodological differences between these studies would continue to be a barrier due to the increased heterogeneity these differences create. These differences could include the domains measured, the criteria used for inclusion and exclusion criteria, survey items used to acquire self-report, or demographic makeup of participants among many others. Limiting between study heterogeneity, while including a seemingly never-ending list of variables needed to clearly answer this question is daunting. This is not to say that we cannot reach a point where we can more confidently or definitively answer this question, but that we currently appear to be far from that goal. Original research needs to make serious efforts to limit bias, and to increase access to all data, including non-significant results. Studies should also attempt to assess THC content of cannabis used by participants when possible. This would allow for the results to be further broken down and allow us more insight into possible dose-dependent effects and impacts. It is the job of scientists to strive well-controlled and meaningful research and to avoid sweeping and broad generalizations that are not well supported by data, and this unfortunately has been a pattern within cannabis research. As it stands now, there is no evidence of positive or negative effects of cannabis on long-term neurocognitive functioning, and we need to improve our methods as researchers before we can confidently and definitively answer this question.

Future Research

- Use of longitudinal designs to account for pre-exposure neurocognitive function
- Inclusion of healthy and demographically matched controls to allow for between subject comparison
- Clear communication of practical applicability of findings
- Relevant control variables including effort and assessor bias should be included
- Careful sampling to ensure balanced samples to account for important demographic variables including biological sex, gender, and race
- Consistent methodology, including use of assessments, among studies to limit heterogeneity between studies
- Use of standardized measures that are supported by research to allow us to extend results to other domains of life and functioning including work settings
- Monitored abstinence to ensure participants have been abstinent prior to follow-up testing
- Assessment of bias from external sources

APPENDIX A: TABLES

TABLE 1

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Includes group of cannabis only users	1. Study is a meta-analysis or review
2. Includes control group of nonusers or limited drug use	2. Study only examines acute effects of cannabis on cognitive function
3. Study reports necessary information for calculating effect size	3. Neuropsychological testing is not included in the study
4. Study uses a valid behavioral measure of neuropsychological functioning	4. Study does not have any human subjects (i.e., animal studies)
5. Participants are not under the influence of any substances during testing	5. Study focuses on specific psychiatric populations
6. The use of other substances both past and present is addressed	
7. History of psychiatric and neurological problems is addressed	

Note. Inclusion and exclusion criteria are based on previous meta-analyses examining the residual cognitive effects of cannabis (Grant et al., 2003; Schreiner & Dunn, 2012).

TABLE 2

8 Independent Samples Meeting Inclusion Criteria

Study	Users	Control	Abstinence Period	Domains	Age Group
Auer et al. (2016)*	81	531	30 days	Ex, L	Adults
Delibaş et al. (2018)	30	30	30 days	A	Adults
Hooper et al. (2014)	33	37	3 months	A, Ex, F	Adolescents
Meier et al. (2022)	59	196	30 days	Ex, F	Adults
Riba et al. (2015)	16	16	28 days	A, F	Adults
Thames et al. (2014)	41	49	28 days	A, Ex, L	Adults
Winward et al. (2014)	20	55	1 month	A, F, V	Adolescents
Zimmermann et al. (2018)	19	18	28 days	V	Adults

Note. Attention (A); Abstraction/Executive Functioning (Ex); Forgetting/Retrieval (F); Learning (L); Verbal (V).

*Study used data collected from 2011

TABLE 3

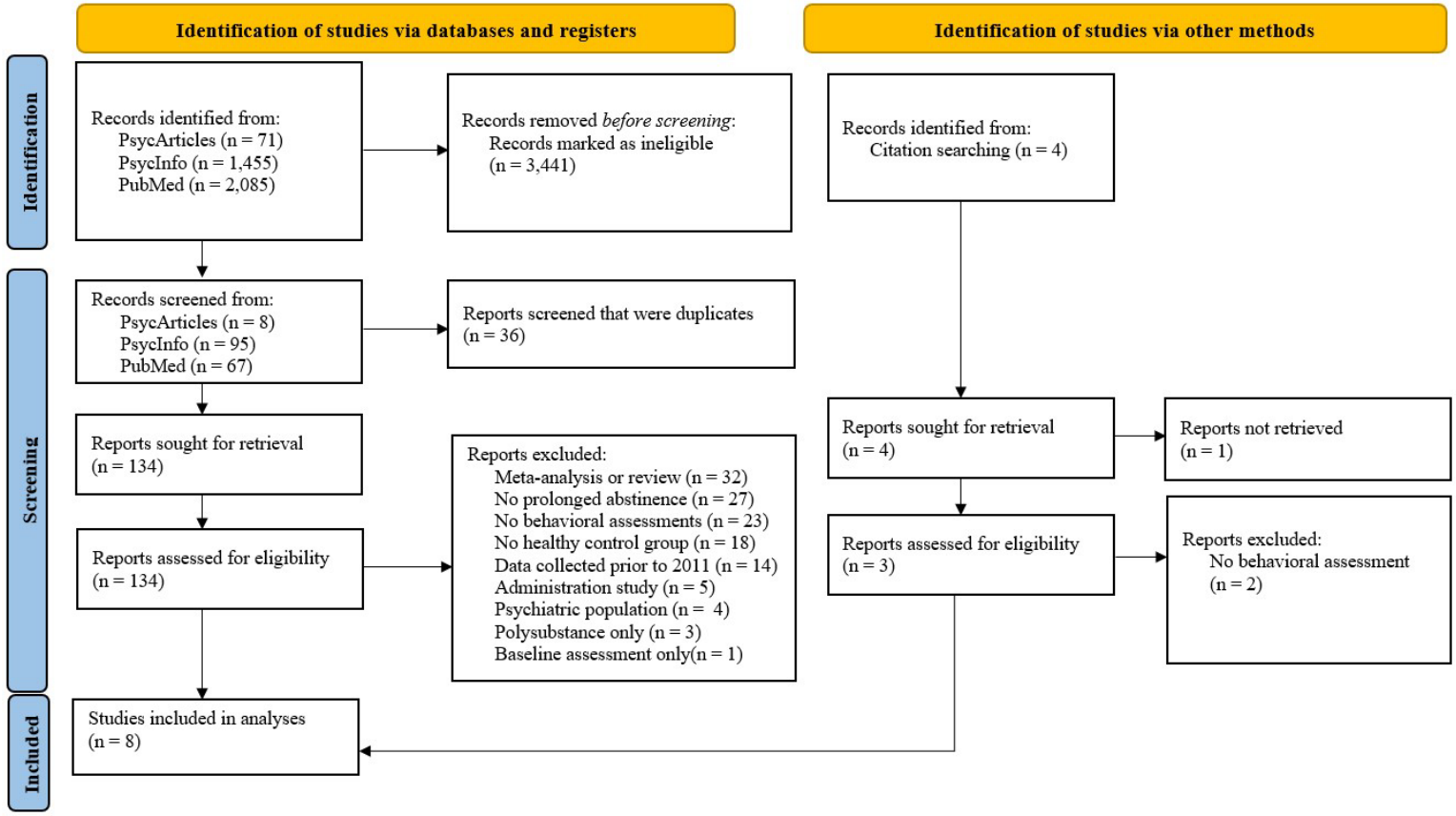
Outcome Measures in Assessed Domains

Neurocogntive domain	Outcome Measures
Abstraction/Executive	Digit symbol substitution test, digit, WAIS-IV digit span, Trail Making B, Stroop Test, DKEFS color-word interfence, DKEFS Trail Making Condition 4, CVLT intrusions, WJ-III Auditory Working Memory, Animal Naming, WMS Months Backwards
Attention	Trail Making A, Iowa Gambling task*, Continuous Performance Test II
Forgetting/Retrieval	CVLT-II Recall, BVMT-R, Rey-Osterrieth Complex Figure Delay, WRAML-2 Verbal memory, HVLT-R Delayed, Deese-Roediger-McDermott paradigm
Verbal/Language	WASI Vocabulary, WST, WAIS-IV Verbal Comprehension Index

Note.

*Previous research has indicated the Iowa Gambling Task loads more onto attention than executive functioning (Gansler et al., 2011; Schreiner & Dunn, 2012)

APPENDIX B: FIGURES



Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

FIGURE 1

Study Selection Flowchart

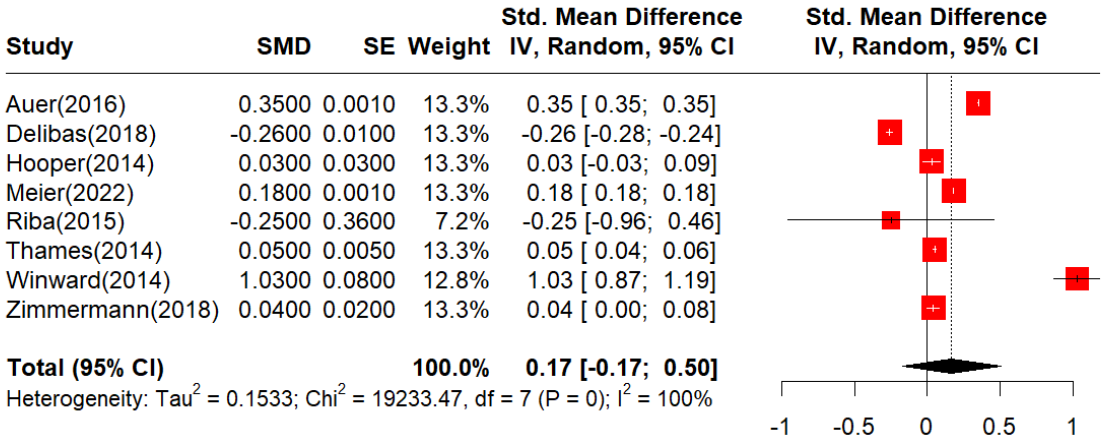


FIGURE 2

Forest Plot: Overall Effects

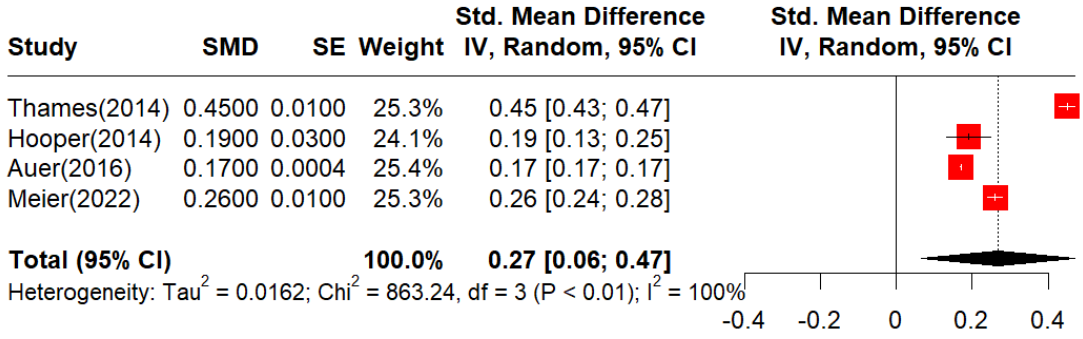


FIGURE 3

Forest Plot: Abstraction/Executive Functioning

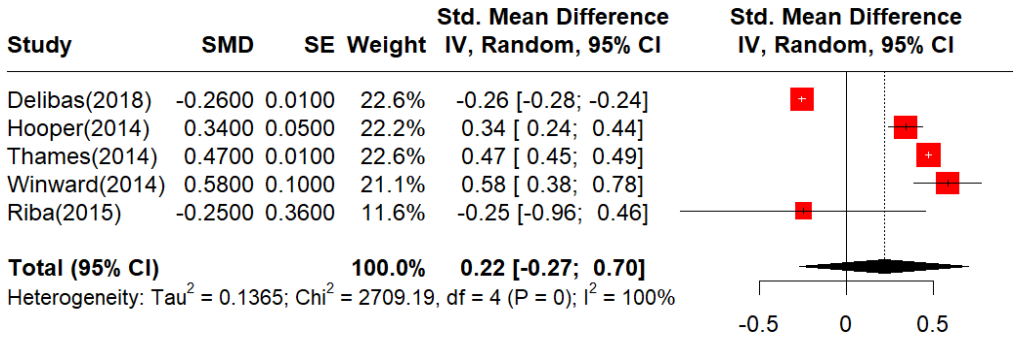


FIGURE 4

Forest Plot: Attention

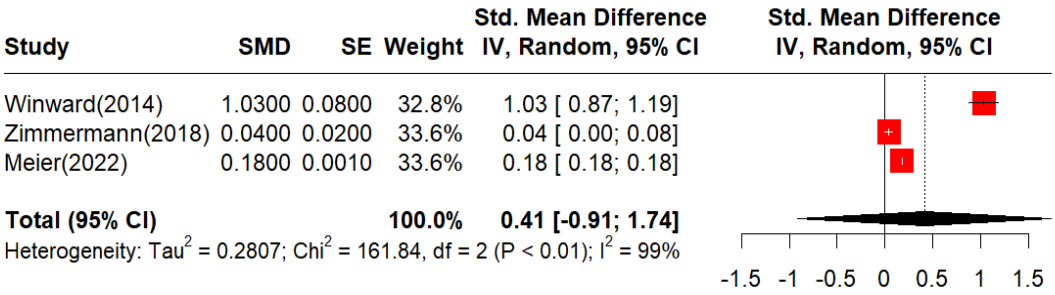


FIGURE 5

Forest Plot: Verbal/Language

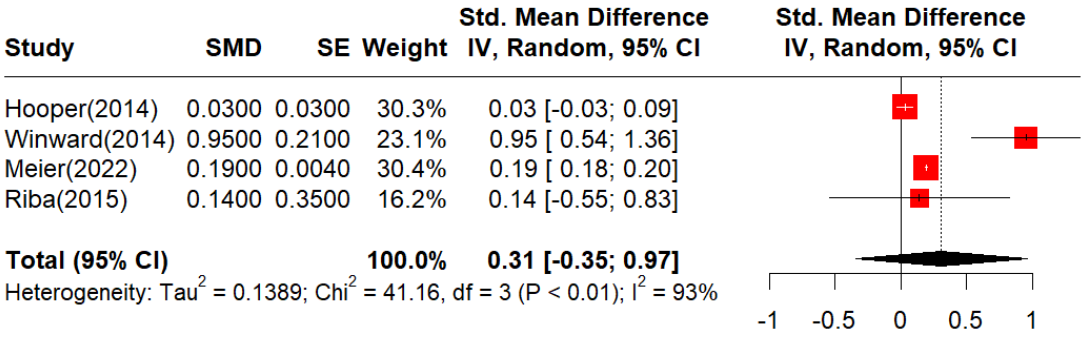


FIGURE 6

Forest Plot: Forgetting/Retrieval

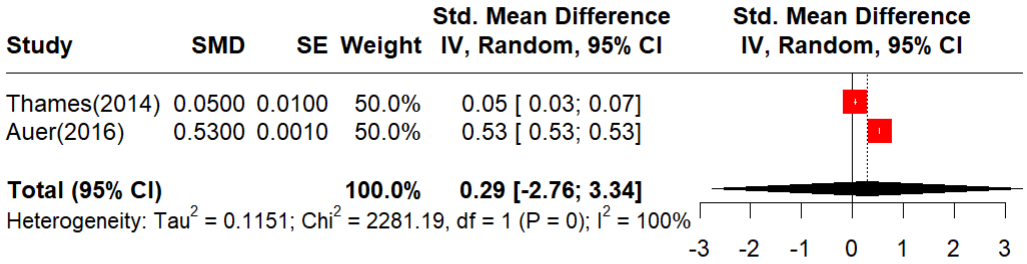


FIGURE 7

Forest Plot: Learning

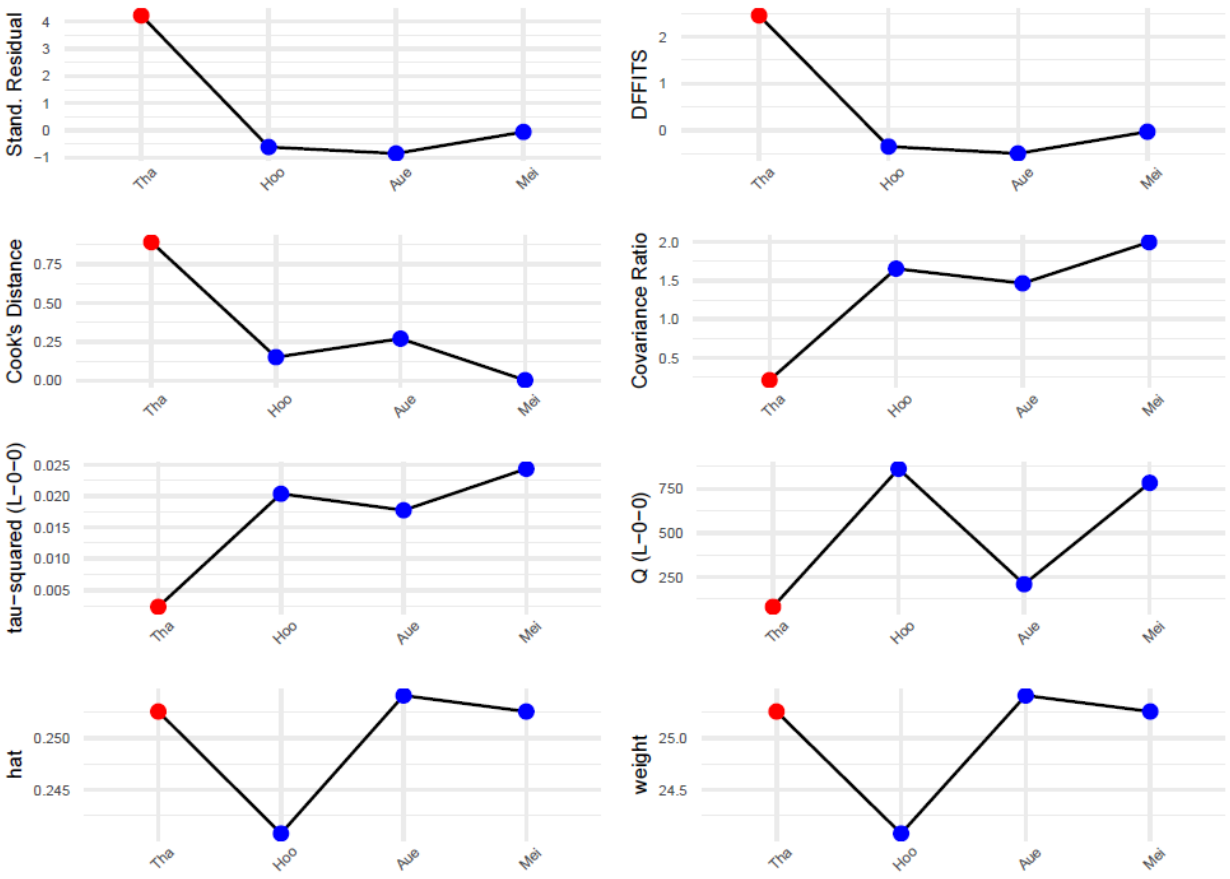


FIGURE 8

Influence Plots for Abstraction/Executive Functioning Analyses

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