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INTRODUCTION

Introduction to JINS Special Issue: Clarifying the Complexities of Cannabis and Cognition

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OVERVIEW

Cannabis remains the second most popular substance used among adolescents and young adults, with approximately 30.6% of teens and 52.4% of young adults having used in their lifetime (Johnston et al., 2020). Repeated cannabis use may lead to downregulation of the endocannabinoid system and result in subtle neurocognitive effects, especially during adolescent neurodevelopment (see Sagar & Gruber, 2018). For decades, the effects of cannabis on neurocognition were largely investigated by comparing chronic, heavy, cannabis users with those who do not use cannabis. In general, the majority of studies observed subtle alterations in performance among people who use recreational cannabis regularly, particularly on cognitive measures of executive function, verbal learning and memory along with structural and functional differences in prefrontal and limbic regions (see Blest-Hopley et al., 2019; Lisdahl et al., 2014; Nader & Sanchez, 2018; Sagar & Gruber, 2018; Scott et al., 2018; Yanes et al., 2018 for reviews and meta-analyses). More recently, researchers have begun to focus on the nuances of cannabis use, and the specific impact that cannabis-related variables may have on cognitive outcomes. This *JINS* Special Issue is aimed at highlighting the complexities of cannabis issues while identifying future areas of research that require further attention. This issue includes empirical studies that tackle factors that may influence cannabis-related outcomes, including age of initiation, frequency and magnitude of use, specific cannabinoid constituents, symptoms of cannabis use disorder (CUD), acute versus residual effects, comorbid substance co-use, as well as examining causality in longitudinal designs, identifying moderators and sex differences that may explain individual differences, and examining cannabis-related neurocognitive effects in medical cannabis users.

NEUROCOGNITIVE EFFECTS OF CANNABIS: CLARIFYING THE COMPLEXITIES

This special issue includes papers that examined multiple outcomes, primarily focused on executive function, attention and memory. In a study examining three attention networks (the alerting, orienting and executive control systems), Ortega-Mora and colleagues report that young adults and adults who use cannabis exhibited enhanced alerting, but decreased orienting, compared with those who do not use cannabis; interestingly, these effects were specifically noted in cannabis users who met DSM-IV criteria for cannabis dependence compared with both cannabis users without dependence and non-users. Moreover, age of onset of cannabis use predicted the efficiency of the orienting and executive systems, while other variables related to frequency of use, duration and length of abstinence did not. In contrast, Parlar and colleagues found that in young adults, frequency of cannabis use, especially daily use, was associated with significantly poorer working memory, impulsive delay discounting and greater reported ADHD symptoms while early age of initiation was not linked with these outcomes.

Wade and colleagues took the novel approach of specifically examining the links between a metabolite of THC, the primary intoxicating constituent of cannabis, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH), and cognitive outcomes in adolescent and young adult regular cannabis users. They found that THCCOOH concentration was significantly associated with poorer total learning and long delay recall, whereas self-reported cannabis use was linked with poorer initial learning and short delay recall. Although nicotine metabolite (cotinine) markers did not moderate cannabis effects on cognition, cotinine was uniquely linked with poorer short delay recall performance. Thus, their findings support designs that collect both self-report and drug toxicology to assess for recent THC and comorbid drug exposure, as the latter provided unique predictive utility.

Taylor and Filbey highlight the importance of exploring differences between acute and residual effects. In this study, the authors compared the performance of cannabis users and non-users on an effort-based decision-making task. While previous studies of acute cannabis intoxication revealed decreased effort allocation (Lawn et al., 2016; Silveira et al., 2016), Taylor and Filbey's data reveal that the residual effects of cannabis (i.e. after 24 hr of abstinence) are associated with greater effort allocation. The authors posit that these differences are likely related to the complex interaction between THC and the dopaminergic system, which is implicated in the valuation of effort and reward. Taken together, findings from these studies and others included in this issue underscore the importance of examining how cannabis-related variables [including age of onset, frequency of use, CUD symptoms, cannabinoid content (THCCOOH, THC, cannabidiol), co-use of nicotine and length of abstinence] may mediate cognitive performance, as each is likely to exert unique effects on various components of cognition.

POTENTIAL MODERATORS OF CANNABIS-RELATED EFFECTS

One explanation for inconsistencies in the literature regarding neurocognitive effects of cannabis is that there are moderating factors that remain understudied. There has been growing appreciation for the differential effects of cannabis in males and females from patterns of use to the presentation of CUD symptoms. Several studies report that women have worse withdrawal symptoms (Schlienz, Budney, Lee, & Vandrey, 2017) and have greater co-morbid mental and physical health problems (Brabete, Greaves, Hemsing, & Stinson, 2020), while male cannabis users may be more vulnerable to neuropsychological deficits (Lisdahl & Price, 2012). Still, most studies to date have been disproportionately male and/or neglected to report sex differences (Crane et al., 2013). Four papers in this Special Issue add to this important literature. Schnakenberg Martin and colleagues report on the interactions between sex and cannabis use in predicting neuropsychological functioning; they found greatest effects in male cannabis users relative to male non-users on tests of intelligence, psychomotor speed and verbal learning. Consistent with these findings, Hirst and colleagues found that male cannabis users performed poorer than female users on verbal learning and memory. However, female users were worse on an attention task. Savulich and colleagues expanded these findings to adolescents, and reported that female adolescent users also exhibited worse attention compared with male adolescent users. Male adolescent users, however, had poorer visual recognition memory compared with their female counterparts. Sullivan and colleagues examined whether sex moderated the impact of cannabis on brain morphometry and found that adolescent/young adult male cannabis users had smaller volumes in prefrontal, inferior temporal, paracentral and precuneus regions compared with male non-users while female users had the opposite pattern compared with their peers; notably, both patterns of structural findings were linked with disadvantageous cognitive performance. These findings converge on greater impacts of cannabis use on learning and memory in males, and on attention in females and sexually distinct patterns of brain structural effects in young users. Overall, this series of studies underscore the importance of adequately sampling both male and female cannabis users in research studies to more clearly determine sex-based differences in neurocognitive outcomes.

There are several other possible moderators of cannabis effects that have been proposed in the literature, including genetic differences in the endocannabinoid system (e.g. Filbey et al. 2021; Schacht et al., 2012; Taurisano et al., 2021), psychiatric comorbidities (e.g. Bogaty et al., 2018; Menendez-Miranda et al., 2019; Wallace et al., 2019), and lifestyle factors that influence brain health (Lisdahl et al., 2014). For the latter, this Special Issue includes an article by Sullivan and colleagues reporting novel relationships between aerobic fitness, cannabis use and brain volume in healthy adolescents and young adults. Overall, in both cannabis users and non-users, superior aerobic fitness was linked with greater brain volume in numerous cortical regions and superior neuropsychological performance. Cannabis users demonstrated a weaker link between aerobic fitness and volume in the left superior temporal region. These findings, coupled with a prior report of superior neuropsychological performance in aerobically fit cannabis users (Wade et al., 2019), reveal a potential low-cost prevention and treatment method that can be developed to reduce the neurocognitive consequences of repeated cannabis use.

LONGITUDINAL EVIDENCE

Despite mounting evidence of associations between cannabis use and cognitive deficits from cross-sectional studies, the issue of chronology of these putative effects remains. A longitudinal, prospective design is the gold standard for evaluations of causality; the emergent longitudinal findings on the association between cannabis and cognitive deficits suggest modest cognitive declines following initiation of cannabis use, particularly in heavier users (Gonzalez, Pacheco-Colon, Duperrouzel, & Hawes, 2017). However, to date, these studies have generally lacked specificity and do not consider potential confounding factors of other substance use. Two studies in this issue address these limitations in the current literature. Ajmera and colleagues addressed this specific problem in a longitudinal, prospective study of verbal learning and memory and decision making in adolescents. The authors measured and controlled for other substance use in addition to including an alcohol initiating sample to rule out contributions of alcohol use. Based on the premise that heavier cannabis users are associated with greater cognitive declines, the authors also divided the cannabis users based on severity of cannabis use. They found that learning and memory declined following initiation of moderate cannabis use and findings were not accounted for by potential

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confounds. The second study by Pacheco-Colon et al. applied a longitudinal design to determine the bidirectional relationship between cannabis use and motivation, which is often reported to be impaired in adult cannabis users (see paper in this Special Issue by Taylor et al.). Similar to Ajmera and colleagues, Pacheco-Colon and colleagues also controlled for other substance use in addition to depression and other individual factors. They did not observe prospective reductions in self-reported motivation in the adolescent cannabis users (findings that are consistent with Taylor et al. in this Special Issue). Consistent with Gonzalez and colleagues' (2017) review, these studies provide additional evidence that the initiation of cannabis is linked with modest reductions in learning and memory. Further, these important studies underscore the need for larger-scale prospective, longitudinal studies, such as the Adolescent Brain Cognitive Development (ABCD) Study®, that carefully assess individual/biological, family, peer, sociocultural factors, detailed substance use patterns and neurocognitive outcomes to determine whether previously reported neurocognitive deficits are predictors of cannabis use trajectories, or caused by escalation in cannabis use (Lisdahl et al., 2018).

NEUROCOGNITIVE IMPACT OF MEDICAL CANNABIS USE

Although many studies have examined the impact of cannabis use on cognitive function, these have almost exclusively focused on those using cannabis for recreational purposes (to feel high or altered), with few exceptions (Olla et al., 2019). Given the different goals of recreational cannabis users and medical patients, which drive cannabis product choice and use patterns, it is likely that those who use cannabis for medical purposes may experience differential effects on cognition. In this Special Issue, two studies highlight this critical point. Sagar and colleagues assessed prospective medical cannabis patients before initiating treatment with cannabis or cannabinoids, and again following 3, 6 and 12 months of use. The authors report that medical cannabis patients exhibited improved executive function and stable verbal learning and memory over time, with additional analyses suggesting that observed improvements appear to be related to concomitant improvements in mood, anxiety and sleep. In another study featured in this issue, Watson et al. examined pro-inflammatory biomarkers and cognitive performance among people with and without HIV who do and not use cannabis. Daily cannabis use was related to lower levels of pro-inflammatory biomarkers, and among those with HIV, lower levels of these biomarkers were associated with better performance on measures of learning. Importantly, both of these articles highlight important clinical changes that may occur in those using cannabis to address chronic conditions, which in turn may be related to improvements in cognitive performance.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, this Special Issue brings together a diverse cluster of empirical studies aimed at further clarifying the impact of cannabis use patterns on neurocognition. Scientists and clinicians will note that the picture is rather complicated, and may depend on the quantity, frequency, product type/potency, age of initiation, symptoms of CUD, sex of the user, length of abstinence, whether comorbid medical or psychiatric conditions are included and whether the individual is using cannabis recreationally or medically (which can also impact product type and age of initiation). Further, it is important to highlight that neurocognitive outcomes linked with regular cannabis use are generally in the small to medium-effect size range; accordingly, there may be a statistically significant difference between groups or in relation to cannabis variables that does not always indicate a clinical impairment. When communicating such findings to the public, the scientific community is urged to explain the extent of differences in layman's terms (e.g. 'performance was 10% below non-users', 'although they had lower scores, cannabis users were in the low-average to average range'), provide contextual information (i.e. typical use patterns in the sample), address potential limitations and alternative explanations, and caution against over-interpretation of neurocognitive group findings within the context of criminal justice policy or individual court cases (Cooper, 2015). Finally, this research provides some helpful clinical advice; studies looking at the impact of abstinence on cognition suggest that clinical neuropsychologists encourage clients to abstain from cannabis for 2 weeks before testing to reduce potential impact of recent withdrawal and acute drug effects.

There are several areas of cannabis research that remain understudied. Most critically, large-scale prospective studies, such as the ABCD Study®, are needed to determine causal links and provide more evidence regarding the fine-tuned timing of cannabis-related neurocognitive effects. For example are previously reported differences pre-existing, or directly due to cannabis exposure? Does light (i.e. less than weekly) cannabis use result in any neurocognitive changes during adolescent development? If an adolescent uses cannabis for a distinct period of time (e.g. 1–2 years) and then maintains abstinence into young adulthood, do they get back on their childhood-predicted neurocognitive trajectory? Is there a 'sensitive period' for cannabis exposure? Research is also needed to determine whether subtle neurocognitive deficits are considered short term and recover with sustained abstinence (Wallace et al., 2020). More information regarding the impact of co-use and simultaneous use is also needed, especially as comorbid use of cannabis, alcohol and nicotine use is highly common (Johnston et al., 2020; also see Wade et al., this Special Issue). As the popularity of alternate modes of cannabis use continues to increase, including the consumption of edibles and vaping concentrated oils (Johnston et al., 2020; Streck et al., 2019), which may confer additional risk, significantly more data are needed regarding the impact of potency, cannabinoid content, and route of administration on neurocognition. Finally, we need to further characterize

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factors that increase resilience or vulnerability to cannabis effects (i.e. studies are needed to identify potential moderators such as genetics, sex at birth, gender identity, racial/ethnic health disparities, sociocultural factors, psychiatric, physical and neurologic conditions, health and lifestyle factors and medical cannabis effects). Given the increasing popularity of cannabis, understanding risk and resilience factors will help create more targeted and accurate prevention and treatment programs to improve neurocognitive health and CUD treatment outcomes.

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