Looking for Interactions

Towards a More Complete Neurocognitive Model of Cannabis Use and Cannabis Use Disorder

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Colofon

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Chapter 1

General introduction

Cannabis use is complex: interactions between external and internal factors guide initiation of use, escalation towards heavy use, brain, and behavioral consequences of use, as well as the potential development of a cannabis use disorder (CUD). Unravelling how external and internal factors interact is a massive challenge, even more so considering every cannabis user is unique. Over the past decade, both medical and recreational cannabis use have been legalized in multiple countries and US states (UNODC, 2022), which has been paralleled by a decreased perception of harm (Buckner, 2013; Piontek et al., 2013; UNODC, 2021) and increased use (Holm et al., 2014, 2016). In particular, the increase in daily users who are at high risk (>30%; Leung et al., 2020) for the development of CUD highlight the need to move towards a more complete model of use and dependence that can inform prevention, intervention, and policy.

Cannabis use in the Netherlands and beyond

Cannabis is the most often used drug worldwide after alcohol and tobacco with over 200 million users – over 4 percent of the world population – annually (UNODC, 2022). In the Netherlands, 7.8% percent of the adult population reported using cannabis within the past year, with the numbers being as high as 24.5% in 18- to 19-year-olds and 26.4% in 20- to 24-year-olds (Trimbos-instituut & WODC, 2021). Of all users, close to 50% reported at least monthly use (Trimbos-instituut & WODC, 2021). Similar to global statistics (UNODC, 2022), cannabis use in the Netherlands is about twice as common in men than women, but increased legalization has been paralleled by increased use in women in multiple countries (UNODC, 2022). Furthermore, the ratio of the primary compounds found in cannabis, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has been changing (Chandra et al., 2019). THC is responsible for the psychoactive properties ('high') of cannabis while CBD is non-psychoactive and implicated in the potential medicinal effects of cannabis (Chandra et al., 2019). While medicinal use of cannabis is becoming more common and high-CBD products are increasingly available, THC levels in cannabis are increasing worldwide while CBD levels are decreasing. This could increase the harmful effects of cannabis use that are largely contributed to high THC levels (e.g., UNODC, 2022). In the Netherlands, though historically high, THC levels of Dutch grown weed (currently at about 14.6%) and imported hash (currently at about 24.3%) seem to be stabilizing after years of increase (Trimbos-instituut & WODC, 2021).

Born in the Netherlands in the 90's, the wide accessibility of cannabis was something I never really thought about. Cannabis has been decriminalized since 1976 and this policy is not likely to change in the foreseeable future. However, access to and the legality of cannabis use varies widely over countries and regions. Cannabis is rather

unique in that sense: while most countries have adopted similar laws to regulate most drugs (i.e., alcohol and tobacco are legal in most western jurisdictions, whereas MDMA, cocaine, heroin and other 'hard drugs' are illegal), cannabis legislation varies widely and is changing rapidly (UNODC, 2022). Despite inconclusive evidence regarding the potential harms and benefits of use, more and more countries and regions are moving towards legalization or decriminalization of medical and/or recreational cannabis use. For example, Canada legalized recreational use of cannabis in 2019, twenty years after they permitted exemptions for medical cannabis use in 1999 (UNODC, 2021). In the US, medical use of cannabis had been (partially) legalized in 47 states in 2020, with 17 of these states also legalizing recreational cannabis use before 2022 (UNODC, 2021). Furthermore, Canada and the US have been accompanied by several countries worldwide, including South Africa (2018), Malta (2021), Switzerland (2021), and Uruguay (2022) towards legalization of recreational cannabis use in the last five years (UNODC, 2022). Although data on the direct effects of these recent legislative changes is limited, both US and European data shows that while cannabis is becoming more readily available, perceived harm of cannabis use is going down (UNODC, 2021). This reduced perceived harm (Holm et al., 2014, 2016), combined with changing norms (Buckner, 2013) and increased availability (Piontek et al., 2013) increase the chance of initiation of use and put individuals at risk for persistent use and escalation.

From initiation to escalation

All substance use disorders start with initiation. While cannabis initiation is common in all age groups, most individuals initiate cannabis use during adolescence (UNODC, 2019) and the prevalence of cannabis use peaks during young adulthood (e.g., 26.4% in 20-24 year old Dutch; Trimbos-instituut & WODC, 2021). Adolescence is a crucial period for brain development in which brain plasticity is still relatively high compared to adulthood. While brain regions involved in socio-emotional and reward processes mature relatively early during adolescence, regions involved in behavioral control lag behind (Casey et al., 2008; Gladwin et al., 2011) resulting in a surge in risk-taking behavior. Suboptimal behavioral control can result in impulsive decision making in which small short-term rewards (e.g., drug use) might outweigh large long-term rewards (e.g., health and reduced risk for drug dependence; Crone & Dahl, 2012; Stanger et al., 2013). Substance use is common risk-taking behavior during adolescence that can be attributed to underlying brain maturation processes; however, social factors play a crucial role in cannabis initiation. During adolescence, the reliance on and importance of peers intensify (Marshal & Chassin, 2000; Sebastian et al., 2008). Hence, aside from the reward-related feelings that are a direct effect of cannabis use (Koob & Volkow, 2010), social rewards might also be crucial in both the initiation and

continuation of use (Walker et al., 2017). Especially during adolescence, interests and norms of the peer group play a large role in the behaviors one engages in, including cannabis use (Leadbeater et al., 2022). Participating in group behaviors might result in feelings of social reward such as increased peer affiliation (e.g., Caouette & Feldstein Ewing, 2017).

Around 10% of those initiating cannabis use become daily users (World Health Organization, 2016). The question of why some individuals escalate cannabis use is an intriguing but largely unanswered question. While substance use research has proposed many different factors, such as adolescent initiation, and aberrant cognitive control and reward processing (e.g., Lees et al., 2021), that could contribute to escalation of use, it is unclear to what extent these factors generalize over substances or whether substance-specific factors are at play. For example, positive cultural attitudes might increase one's chance of initiation and escalation (Holm et al., 2014, 2016), which, in combination with a social environment in which drug use is positively valued (Chabrol et al., 2006), might result in persistent use. Repeated use might also be more likely in those with limited behavioral control (Holmes et al., 2016), including adolescents, and those at risk through genetic predisposition (Agrawal et al., 2012). Also, individual reasons for use play a role, with individuals using to cope with the stress associated with traumatic events or mental health problems being at higher risk for escalation (e.g., Hyman & Sinha, 2009). Furthermore, men use cannabis about twice the rate women do (e.g., UNODC, 2019) and sex or gender difference might affect both the direct effects of cannabis and cannabis use trajectories (Khan et al., 2013). For example, women are more likely than men to use pipes or consume cannabis edibles, report a loss of appetite when high, and report nausea and anxiety when in withdrawal (Cuttler et al., 2016). Furthermore, women experience similar subjective high to men at lower THC doses (Matheson et al., 2020) and transition from daily use into dependence faster than men do (Khan et al., 2013).

Table 1. DSM-5 Criteria of Cannabis Use Disorder	
1	Cannabis is often taken in larger amounts or over a longer period than was intended
2	There is a persistent desire or unsuccessful efforts to cut down or control cannabis use
3	A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
4	Craving, or a strong desire or urge to use cannabis
5	Recurrent cannabis use resulting in a failure to fulfil major role obligations at work, school, or home
6	Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
7	Important social, occupational, or recreational activities are given up or reduced because of cannabis use
8	Recurrent cannabis use in situations in which it is physically hazardous
9	Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis
10	Tolerance: A need for markedly increased amounts of cannabis to achieve intoxication or desired effect
OR	Tolerance: A markedly diminished effect with continued use of the same amount of cannabis
11	Withdrawal: The characteristic withdrawal syndrome for cannabis
OR	Withdrawal: Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms
Note: DSM-5 (American Psychiatric Association, 2013a)	

From heavy use to dependence

More than one in three weekly-to-daily cannabis users will develop CUD (Leung et al., 2020). CUD is currently one of the most common substance use disorders and the most common reason for treatment entry after alcohol use (Degenhardt et al., 2018; Trimbos-instituut & WODC, 2021). Current efforts for treating CUD are often unsuccessful with six-month abstinence rates being less than 35% (Denis et al., 2006; Hoch et al., 2013). In the DSM-5 (American Psychiatric Association, 2013a), CUD is described as "problematic cannabis use leading to clinically significant impairments or distress". Individuals are diagnosed with CUD when they experienced more than 1 of the 11 defined diagnostic criteria (Table 1; 2-3 mild, 4-5 moderate, >5 severe) within the last year.

Different theories have been proposed to explain the development and maintenance of CUD (Bickel et al., 2018; Koob & Volkow, 2010; Robinson & Berridge, 2008). Cannabis affects the brain through the direct effects of THC on the endocannabinoid system, primarily through stimulation of cannabinoid 1 (CB1) receptors that can be found in brain regions including, but not limited to, the basal ganglia, hippocampus,

amygdala, and hypothalamus (Ferland & Hurd, 2020). Persistent cannabis use results in the downregulation of CB1 receptors in these regions known to play a crucial role in cognitive and emotional processes guiding our behavior. Cannabis cessation appears to upregulate CB1 receptors and restore at least part of its functioning within a month (D'Souza et al., 2016).

Similar to other substances, cannabis use also triggers the release of dopamine in the ventral tegmental area (VTA; Koob & Volkow, 2010). After persistent use, dopamine synthesis and release in the mesolimbic dopamine pathway (projecting from the VTA to striatal regions including the nucleus accumbens) will be downregulated. The resulting dopamine depletion (Volkow et al., 2014) is associated with increased motivation to use and indirectly limits control over this motivation, which can increase craving and result in higher problem severity. Glutamate levels are also affected by altered signaling of endocannabinoid system and, like dopamine, undergo dysregulation through the course of CUD development. Dysregulation in glutamate that occurs in a broad range of brain regions has been implicated in drug seeking behaviors in those with CUD (Colizzi et al., 2016).

Additionally, repeated experience of substance-related rewards will trigger associative learning processes attributing increased salience to those drugs and associated cues (Robinson & Berridge, 1993, 2008). Over time, the cues and the environment associated with drug use (e.g., smell or drug use paraphernalia) will trigger craving and compulsive use. At this stage, one has lost control over use and ceasing use will often result in cannabis withdrawal that includes physical (i.e., headaches, nausea etc. – dependent on the substance) and psychological (i.e. anxiety, altered mood, craving etc.) symptoms (Koob & Volkow, 2010; Robinson & Berridge, 1993). About 90% of those with CUD will experience withdrawal symptoms when ceasing use, with withdrawal symptoms peaking around day 4 after cessation (Bonnet & Preuss, 2017). Severity of withdrawal appears to depend on several factors including age (adults experiencing more severe withdrawal than adolescents), heaviness of use (heavier users experience more severe withdrawal), context of cessation (in- or out-patient), co-use of alcohol or tobacco (worsening withdrawal symptoms), presence of comorbid mental disorders (higher likelihood of severe withdrawal), and gender (women reporting stronger withdrawal and more physical withdrawal symptoms; Bonnet & Preuss, 2017). The experience of withdrawal, in combination with high motivations to use and compromised behavioral control, make that over 65% of those with CUD can still be diagnosed with CUD 3-years later (Feingold, Fox et al., 2015).

While theories of addiction propose mechanisms through which repeated cannabis exposure affects brain processes underlying motivation and control, resulting in loss of control over use and the development of CUD, most daily cannabis users will not

develop CUD (Leung et al., 2020). Hence, we should not lose sight of those cannabis users that do not develop CUD but might still experience short- and long-term negative consequences of their heavy use.

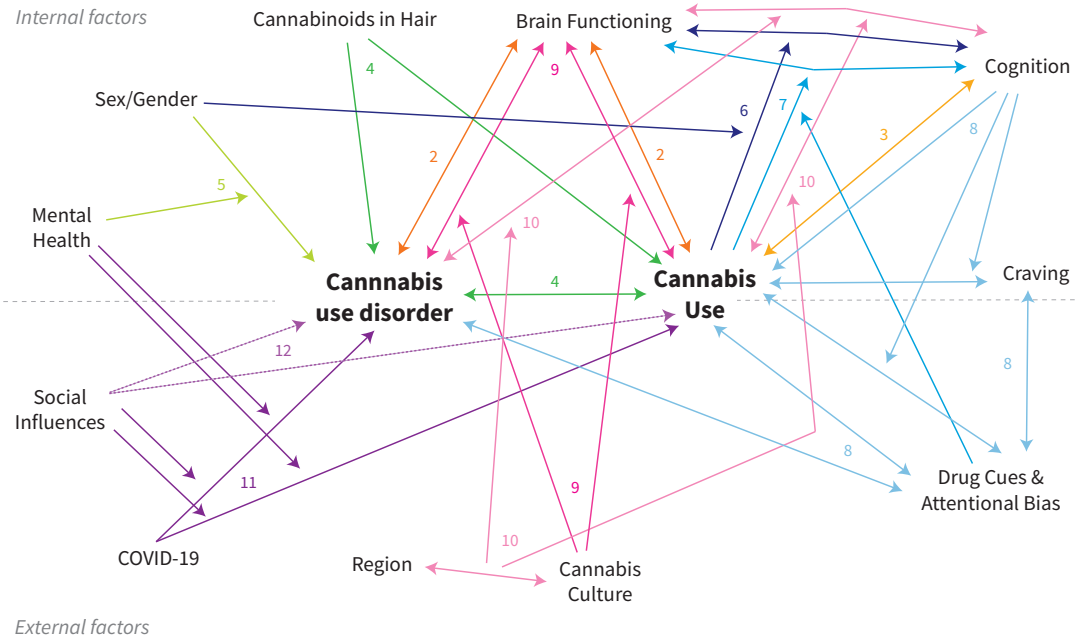

Figure 1. Overview of the most important direct associations and interactions between internal and external factors involved in cannabis use & cannabis use disorder as assessed in this thesis. Associations and interactions assessed and discussed in the following chapters in order to build towards a more complete neurocognitive model of cannabis use and cannabis use disorder. Chapters are colored and numbered.

Short- and long-term effects of cannabis use & dependence

Research efforts during the past two decades have steadily increased our knowledge on the effects of heavy cannabis use on the brain and associated behaviors. Acute cannabis intoxication reduces craving (e.g., Filbey et al., 2009) and negatively impacts cognitive functions such as attention (e.g., Ramaekers et al., 2009) and learning and memory (e.g., Ranganathan & D'Souza, 2006). These deficits persist with continued heavy use and dependence (e.g., Crane, Schuster, Fusar-Poli et al., 2013) and appear to be associated with altered brain processes underlying cognitive control (Blest-Hopley et al., 2020) and motivation (Cousijn et al., 2011). It is important to note, however,

that these association studies do not inform direction of effects, therefore, causality remains largely unclear. Furthermore, some of cannabis' effects on the brain and cognition have been found to subside with abstinence (Schreiner & Dunn, 2012).

Brain functioning appears to be affected by heavy use and dependence in multiple ways. Research has shown that, similar to other SUDs (DeWitt et al., 2015), individuals with CUD show increased functional connectivity within the default mode network and networks including the insula during rest. This suggests a role for interoceptive processes in CUD (Pujol et al., 2014) and potential problems with shifting from this default mode automated processing to enacting cognitive control through the executive control network (Utevsky et al., 2014; Vatansever et al., 2017). Furthermore, even when task performance remains similar to that of controls, individuals with CUD often show altered brain activation patterns in frontal, parietal, limbic, and cerebellar regions when performing tasks that require visual attention (Chang et al., 2006), interference control (Kober et al., 2014), and working memory (Sagar & Gruber, 2019). Although the lack of behavioral effects could be caused by methodological limitations (e.g., combination of small effect sizes and small sample sizes), these altered brain activation patterns could also reflect compensation mechanisms to support task performance (e.g., Sagar & Gruber, 2019).

Towards a more complete neurocognitive model of cannabis use & dependence

Existing theories of addiction and associated evidence through research has increased our understanding of the development of CUD – i.e., how heavy cannabis users and those with CUD differ from controls on a variety of neurocognitive measures and brain processes. However, we lack the understanding of the complex interactions between internal (i.e., brain functioning, cognition, motivation, sex/gender, mental health) and external (i.e., cultural attitudes, social influences, drug cues, negative life experiences) factors that are hypothesized to affect individuals' cannabis use trajectories and the potential negative consequences of heavy use. This knowledge is crucial to understand which heavy users are at high risk for dependence in order to prevent the transition into dependence, as well as to increase our understanding of individual risk factors for experiencing negative consequences of cannabis use on the brain and cognition. In this thesis, I will explore these interactions using a variety of methods to build towards a more complete neurocognitive model of cannabis use and dependence, focusing on brain functioning, cognition, motivation and the interactions sex/gender, mental health, drug cues and attentional bias, craving, region (e.g., country or state), cultural attitudes towards cannabis use, COVID-19, and social influences (Figure 1).

Chapter 2 and 3 will provide a literature overview of the evidence for the impact of cannabis use on the brain and related behaviors. Specifically, **chapter 2** discusses the short-term and long-term effects of heavy cannabis use and CUD on the brain, the potential mechanisms underlying these effects, and the current treatment options. In **chapter 3**, the scope narrows towards the effect of cannabis use on cognitive functioning.

Chapter 4 and 5 will discuss the measurement of cannabis use and CUD symptoms. **Chapter 4** discusses the associations of hair-derived cannabinoid concentrations with different self-report measures of cannabis use in individuals with CUD. **Chapter 5** will then use a network modelling approach to assess more complex associations between CUD symptoms in weekly cannabis users and how gender and mental health problems might affect those associations.

From there, **chapter 6, 7 and 8** will assess cognitive control and the underlying brain processes in heavy and dependent cannabis users, systematically investigating the role of different internal (i.e., gender/sex, craving) and external (i.e., cannabis cue exposure) factors in the associations of cognitive control and control related brain activity with cannabis use and CUD. **Chapter 6** discusses the potential role of gender in the association between measures of cannabis use and the brain processes associated with cognitive control, assessed using an N-back working memory task performed inside an MRI scanner. In **chapter 7**, an adapted N-back working memory task – including task-irrelevant cannabis cues – was used to assess whether the presence of external cannabis cues might hamper cognitive control and negatively affect the brain processes involved. **Chapter 8** assesses how a behavioral measure of control (interference control) affects the association between both explicit (craving) and implicit (attentional bias) motivation to use cannabis. Furthermore, it assesses whether cannabis users with variable heaviness of use and CUD show an attentional bias towards cannabis.

Chapter 9 and 10 explore cross-cultural differences in attitudes towards cannabis and how this affects brain processes underlying CUD. Attitudes towards cannabis are assessed in both Dutch and US cannabis users and controls, focusing on personal attitudes, perceived friends' and families' attitudes and the perceived attitude towards cannabis in ones' country (NL) or state (US-TX). **Chapter 9** explores whether these cultural attitudes are associated with resting state functional connectivity within and between brain networks associated with dependence. **Chapter 10** focusses on the role of these cultural attitudes in cognitive control related brain processes in individuals with CUD.

Finally, **chapter 11 and 12** will focus on other external factors that might be affect cannabis use: isolation due to COVID-19 pandemic and an individual's tendency to

socially attune to one's peers. **Chapter 11** will discuss the impact of the COVID-19 pandemic on cannabis users and how changes in mental health, social contact, and feelings of loneliness affected heaviness of cannabis use and dependence pre-to-post pandemic onset. **Chapter 12** zooms out towards the developmental trajectories of substance use disorders. It discusses the development and validation of the social attunement questionnaire, developed to assess the tendency of the individual to attune to their social environment in a variety of situations, including substance use. Furthermore, it explores how high social attunement tendencies might result in both increased chance for escalation of use as well as increased resilience to persistent heavy use, depending on the social environment, using adolescent and young adult alcohol use as an example.

Chapter 13 provides a summary and integration of the results, indicating highlights and challenges for future research before presenting our initial neurocognitive model of cannabis use and CUD and providing a research checklist for future cannabis research.

Chapter 2

Heavy cannabis use, dependence and the brain: a clinical perspective

This chapter is based on:
Kroon, E., Kuhns, L., Hoch, E., & Cousijn, J. (2020). Heavy cannabis use, dependence and the brain: a clinical perspective. *Addiction. 115*(3), 559-572. https://doi.org/10.1111/add.14776

Abstract

Aims. This narrative review aims to summarize and evaluate our knowledge of the relation between heavy cannabis use, Cannabis Use Disorder (CUD), and the brain. Epidemiology, clinical representations, potential causal mechanisms, assessments, treatment and prognosis are discussed.

Methods. Relevant literature was identified through existing systematic reviews, meta-analyses, and a PubMed search.

Results. Although causality is unclear, heavy and dependent cannabis use is consistently associated with a high prevalence of comorbid psychiatric disorders and learning and memory impairments that seem to recover after abstinence. Evidence regarding other cognitive domains and neurological consequences including cerebrovascular events is limited and inconsistent. Abstinence after treatment is achieved by a minority but treatment targeted at reductions in use appears to be more successful. Potential moderators of the impact of CUD on the brain include age of onset, heaviness of use, CUD severity, the ratio of Δ9-tetrahydrocannabinol to cannabidiol, and severity of comorbid disorders.

Conclusions. Despite the growing societal burden, our knowledge of long-term effects of daily cannabis use and CUD on brain-related outcomes is very limited. Mechanisms and causality remain to be established and increasing treatment demand calls for more collaboration between scientists and clinicians to align assessments and improve treatment options and outcomes.

Introduction

This narrative review summarizes our knowledge of the relation between heavy cannabis use (defined as (near) daily use), Cannabis Use Disorder (CUD) and the brain. Cannabis contains over a hundred different cannabinoids (Chandra et al., 2019), of which Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied. THC is the main psychoactive cannabinoid responsible for the cannabis 'high' and addictive potential. CBD has been suggested to ameliorate THC effects while having little psychoactive effect on its own (Niesink & van Laar, 2013). Aside from plant-based cannabis products, synthetic cannabinoids mimic the effects of THC. Given the scope of this review, the limited evidence on the effects of synthetic cannabinoids, and the chemical differences between plant-based and synthetic cannabinoids, we will only discuss the effects of plant-based cannabis products unless otherwise specified.

Although CUD is one of the most common Substance Use Disorders (SUDs), effects of CUD on the brain are still rarely studied. Daily cannabis use has been established as one of the best predictors of CUD. As such, findings from heavy users and, where possible, individuals with a diagnosed CUD will be evaluated. After a brief epidemiological overview, clinical representations, potential causal mechanisms, assessments, treatment and prognosis will be discussed. Table 1 provides a summary of the acute and long-term effects of heavy cannabis use and CUD on brain structure, cognition, psychiatric comorbidities, and neurological disorders.

Epidemiology

Cannabis is the most used drug worldwide with an estimated 188 million recreational users in 2017 (approximately 3.8% of the world population, UNODC, 2019). Paralleling population increases, the number of cannabis users has increased 16% between 2006 and 2016 (UNODC, 2018b). There are large continental and regional differences in cannabis use (UNODC, 2018b). Globally, the potency of cannabis (%THC) is increasing. Data from the United States (8.9% in 2008 to 17.1% in 2017) and Europe (herbal cannabis: 5.0% (2006) to 10.2% (2016), cannabis resin: 8.1% (2006) to 17.2% (2016)) indicate over a two-fold increase in potency within the last decade, with the THC:CBD ratio also rising (Chandra et al., 2019). Past year use among individuals older than 15 is currently stable at around 7.4% (EMCDDA, 2019; UNODC, 2019) in Europe, decreasing in Australia (from 12.6 % in 2001 to 10.4% in 2016, AIHW, 2017), but increasing in Canada (from 9.1% in 2011 to 14.7% in 2015, UNODC, 2019) and the United States (from 13.5% in 2015 to 13.9% in 2016, UNODC, 2018b). These increases are suggested to parallel trends in legalization and decreases in risk perception (SAMHSA, 2018). Cannabis use appears less common in Africa, Asia, and South and Central America (UNODC, 2018a). Nonetheless, the limited data available suggest that

Table 1. Summary of Current Evidence for the Effects of Cannabis on the Brain

	Short-term effects	Long-term effects		Suggested Reading
		Heavy Cannabis Use	Cannabis Use Disorder	
Brain Structure	**No evidence** to support or refute effects.	**Limited** evidence reduction hippocampal and prefrontal cortex volume. Inconsistent evidence for other brain structures. **Potential moderators:** heavy history ↑, CUD severity ↑, early onset ↑, sex.	**Limited** evidence structural alterations.	Lorenzetti et al., 2019
Cognition				
Learning & Memory	**Sufficient** evidence THC/cannabis impairs (non)-verbal learning and episodic memory. **Limited** evidence impairments other types of learning and memory. **Potential moderators:** dose ↑, early onset ↑, heavy history ↓, low THC:CBD ratio ↓	**Sufficient** evidence impairments in current heavy users. **Insufficient** evidence for lasting effects after abstinence. Evidence for (partial) recovery. **Potential moderators:** sub-acute THC/cannabis effects ↑, early onset ↑, heavy history ↑, comorbid psychopathology ↑	**Limited** evidence impairments in current CUD and lasting effects after abstinence. Preliminary evidence for (partial) recovery. **Potential moderators:** sub-acute THC/cannabis effects ↑, early onset ↑, heavy history ↑, CUD severity ↑, comorbid psychopathology ↑	Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013
Craving	**Sufficient** evidence THC/cannabis reduces craving. **Potential moderators:** age ↓, heavy history & CUD ↑	**Sufficient** evidence increased craving, **limited** evidence increased brain activity reward-related areas after exposure to cannabis-related stimuli. **Potential moderators:** heavy history ↑, CUD severity ↑	**Sufficient** evidence increased craving, **limited** evidence increased brain activity reward-related areas after exposure to cannabis-related stimuli. **Potential moderators:** heavy history ↑, CUD severity ↑	Cousijn, Goudriaan, et al., 2013; Cousijn & van Duijvenvoorde, 2018; Henry et al., 2014; Mokrysz, Freeman, et al., 2016; Treloar Padovano & Miranda, 2018; Vingerhoets et al., 2016
Cognitive Biases	**Limited** evidence cannabis related approach bias and attentional bias.	**Sufficient** evidence attentional bias **insufficient** evidence approach bias in current users. **No evidence** to support or refute lasting effects after abstinence. **Potential moderators:** heavy history ↑, CUD severity ↑, THC ↑, craving ↑	**Limited** evidence attentional bias **no evidence** to support or refute approach bias in current CUD. **No evidence** to support or refute lasting effects after abstinence. **Potential moderators:** heavy history ↑, CUD severity ↑, THC ↑, craving ↑	Zhang et al., 2018
Emotion Processing	Consistent, but **limited** evidence THC/cannabis impairs emotion recognition, particularly negative emotions. **Potential moderators:** low THC:CBD ratio ↓	**Limited** evidence impaired emotion identification/recognition and reduced activity in CB1 rich brain areas during emotional processing in current users. **No evidence** to support or refute lasting effects after abstinence.	**Limited** evidence impaired emotion identification/recognition and reduced activity in CB1 rich brain areas during emotional processing in current CUD. **No evidence** to support or refute lasting effects after abstinence.	Bayrakçı et al., 2015; Bossong, van Hell et al., 2013; Fusar-Poli et al., 2009; Gruber et al., 2009; Hindocha et al., 2015
Attentional Control	**Sufficient** evidence THC/cannabis impairs attentional control. **Potential moderators:** dose ↑, heavy history ↓	**Sufficient** evidence impairments sustained and divided attention in current heavy users. Insufficient evidence for lasting effects after abstinence. Evidence for (partial) recovery. **Potential moderators:** sub-acute THC/cannabis effects ↑, early onset ↑, heavy history ↑	**No evidence** to support or refute lasting effects.	Broyd et al., 2016; Crane, Schuster, Fusar-Poli, et al., 2013; Crean et al., 2011
Working Memory	**Inconsistent** evidence THC/Cannabis impairs working memory.	There is **inconsistent** evidence for long-term working memory deficits in heavy users. **Limited** evidence for recovery in heavy users. **Potential moderators:** sub-acute THC/cannabis effects ↑, heavy history ↑, early onset ↑, task complexity ↑	**No evidence** to support or refute lasting effects.	Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013
Motor Inhibition	**Sufficient** evidence THC/Cannabis impairs inhibition ongoing responses (stop-signal task). Inconsistent results with other inhibition tasks. **Potential moderators:** dose ↑	**Limited** and inconsistent evidence for impairments.	**Limited** and inconsistent evidence for impairments.	Broyd et al., 2016; Crane, Schuster, Fusar-Poli, et al., 2013; Crean et al., 2011
Decision Making	**Insufficient** evidence THC/Cannabis impairs decision-making.	**Insufficient** and inconsistent evidence for impairments. **Potential moderators**: cognitive subdomain.	**Limited** and inconsistent evidence for impairments. **Potential moderators:** CUD severity ↑	Broyd et al., 2016; Crane, Schuster, Fusar-Poli, et al., 2013; Crean et al., 2011
Intelligence	**No evidence** to support or refute effects.	There is **insufficient** and limited evidence for reduced intelligence.	There is **insufficient** and limited evidence for reduced intelligence. **Potential moderators:** CUD duration ↑	Fried et al., 2002; Meier et al., 2012; Mokrysz, Landy, et al., 2016; Rogeberg, 2013
Psychiatric Comorbidity				
Depression	**No evidence** to support or refute effects.	**Sufficient** evidence statistical association. Causality unclear. **Potential moderators:** early onset ↑, CUD severity ↑	**Sufficient** evidence statistical association. Causality unclear. **Potential moderators:** early onset ↑, CUD severity ↑	Feingold, Weiser et al., 2015; Schoeler et al., 2018
Bipolar Disorder	**No evidence** to support or refute effects.	**Sufficient** evidence statistical association. Causality unclear.	**Sufficient** evidence statistical association. Causality unclear.	Feingold, Weiser et al., 2015; Lev-Ran et al., 2013
Anxiety	**Sufficient** evidence THC/Cannabis increases risk anxiety and panic attacks. **Potential moderators:** dose ↑, low THC:CBD ratio ↓	**Sufficient** evidence statistical association. Causality unclear.	**Sufficient** evidence statistical association. Causality unclear.	Crippa et al., 2009; Kedzior & Laeber, 2014
PTSD	**No evidence** to support or refute effects.	**Sufficient** evidence statistical association. Causality unclear.	**Sufficient** evidence statistical association. Causality unclear.	Bonn-Miller et al., 2014
Psychosis & Schizophrenia	**Sufficient** evidence THC/cannabis increases risk transient positive symptoms. **Limited evidence** THC/cannabis increase risk negative symptoms. **Potential moderators**: dose ↑, low THC:CBD ratio ↓, Schizophrenia diagnosis ↑	**Sufficient** evidence association psychosis and cannabis use. Causality unclear. **Potential moderators:** heavy history ↑, low THC:CBD ratio ↓, early onset ↑	**Sufficient** evidence statistical association. Causality unclear. Potential moderators: heavy history ↑, low THC:CBD ratio ↓, early onset ↑	di Forti et al., 2019; Marconi et al., 2016; Myles et al., 2016)
Other Substance Use Disorders	--	**Sufficient** evidence statistical association. Causality unclear. **Limited** and inconsistent evidence for gateway to illicit, alcohol and cigarette use.	**Sufficient** evidence statistical association. Causality unclear.	Kandel & Kandel, 2015; Lynskey & Agrawal, 2018
Neurological Disorders				
Cerebrovascular Accidents	**Limited evidence** THC/Cannabis increases the risk cerebrovascular accidents. **Potential moderators:** heavy history ↑, synthetic cannabinoids ↑, comorbidity ↑, other drug use ↑	**No evidence** to support or refute effects.	**No evidence** to support or refute effects.	Hackam, 2015; Rezkalla & Kloner, 2018
Brain Tumors	--	**No evidence** to support or refute effects.	**No evidence** to support or refute effects.	Huang et al., 2015

the annual prevalence is also increasing in these regions (UNODC, 2018a).

Prevalence of use is highest for young adults (UNODC, 2019) and men (EMCDDA, 2019; UNODC, 2015). Around 10% of users become daily users (World Health Organization, 2016). Daily use is one of the best predictors of CUD, with around one in three developing dependence (Van der Pol, Liebregts, de Graaf, Korf et al., 2013).

Worldwide, CUD is amongst the most common SUDs (Degenhardt et al., 2018). An estimated 22.1 million people suffer from CUD, off which two-third are male (Degenhardt et al., 2018). Most CUDs remain untreated (EMCDDA, 2015; UNODC, 2019) but among those seeking treatment, demands are higher for adolescents and young adults (World Health Organization, 2016). Among those not seeking treatment, the annual remission rate is around 17% (Calabria et al., 2010). Genetic vulnerability, early life trauma, mental health problems, tobacco use, high potency cannabis, early onset, and intensity of use are suggested to play an important role in the development and severity of CUD (Agrawal, Lynskey, Bucholz, Martin et al., 2007; Freeman & Winstock, 2015; von Sydow et al., 2002).

Clinical representation

Cannabis use disorder as a brain disease

CUD is defined as problematic cannabis use leading to clinically significant impairments or distress (American Psychiatric Association, 2013a). Although still debated, SUDs including CUD are increasingly referred to as a brain disease. Supporting this, SUDs are associated with changes in brain structure and function that potentially impede recovery (Volkow et al., 2016). THC binds to the endocannabinoid 1 (CB1) receptor which is densely present in brain areas involved in learning, memory, reward, motivation, and control-processes crucial to SUD development, maintenance and recovery. The few existing studies that investigated brain mechanisms underlying CUD suggest that abnormal functioning of CB1 rich brain areas is common (e.g., Charboneau et al., 2013; Vingerhoets et al., 2016) and linked to increased cannabis use (Cousijn, Wiers, et al., 2014), (future) cannabis use problems (Vingerhoets et al., 2016), and craving (Charboneau et al., 2013). Studies investigating brain structure in cannabis users also point towards alterations in CB1 rich brain areas. While results are generally inconsistent, reductions in volume have been most consistently reported in the hippocampus and prefrontal cortex, including the orbitofrontal cortex (Lorenzetti et al., 2019). Studies in CUD specifically are missing; however, hippocampal volume appears to be smaller with increasing CUD severity (Chye et al., 2019). Additionally, the role of endocannabinoids in cerebral autoregulation and vascular tone, together with acute transient vascular effects of THC (e.g. hypertension), have been proposed as a mechanism for vascular-event-related brain damage in cannabis users (e.g., Esse et al., 2011).

Cognition

Cognition refers to all mental processes that support behavior and thoughts. Cognition can be subdivided into behaviorally distinct processes with partially

overlapping brain mechanisms and encompasses complex cognitive functions such as decision making that rely on the integrity of many lower level functions like attention, reward processing, and memory. The results of research into cannabis's effects on cognition is shaped by impairments of motivation and control-related cognitive functions, known to be impaired in other SUDs (Broyd et al., 2016; Crean et al., 2011), and clear impairments of learning and memory during cannabis intoxication (Ranganathan & D'Souza, 2006, Schoeler et al., 2016). SUDs are characterized by extremely strong motivations to use and loss of control over use (Uhl et al., 2019). Repeated cannabis use is thought to sensitize and condition users to the positively-experienced effects of use (Robinson, 1993). This will subsequently manifest in increased positive affect and reward attribution, craving, and cannabis-oriented cognitive biases (e.g., attentional bias, approach bias) in response to cannabis-related stimuli. Impaired control over these motivational processes would be reflected in compromised attentional control, working memory, inhibition and decision making. Therefore, besides potential short-term and long-term effects on learning and memory, evidence for the relation between cannabis use and motivation and control-related cognitive functions will be discussed.

Learning & memory

Cannabis intoxication impairs learning and memory. Episodic memory (autobiographical events) impairments are most prominent (Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013). Impairments may depend on THC dose and heavy cannabis users are generally only affected at higher dosages (Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013). Long-term effects are less clear. Impairments are most often found up to a few weeks after cessation (e.g., Ford et al., 2018; Thames et al., 2014). Although few studies focused on heavy use and CUD specifically, more severe users may experience larger deficits (Solowij et al., 2011; Thames et al., 2014) and less recovery of cognitive functions after abstinence (Bolla et al., 2002). Longer lasting sub-acute effects in heavier users and early onset use have both been linked to poorer recovery (Bosker et al., 2013; Hooper et al., 2014), but other factors such as high THC:CBD ratios (Morgan et al., 2018), sex (Crane, Schuster, & Gonzalez, 2013) and comorbid psychopathology (Schoeler et al., 2016) may also play a role.

Motivation & control-related cognitive functions

Craving. Heavy and dependent cannabis users display craving and increased brain activity in reward-related brain areas after exposure to cannabis-related stimuli (Cousijn, Goudriaan, et al., 2013; Filbey et al., 2009). Craving is stronger in more severe users (Henry et al., 2014), and has been found to predict CUD problem severity

(Vingerhoets et al., 2016), treatment outcome (Cousijn et al., 2015), and withdrawal severity (Cousijn & van Duijvenvoorde, 2018) in heavy users. Craving generally goes down during intoxication (Treloar Padovano & Miranda, 2018), but adolescents may be less prone to these satiation-induced decreases in craving (Mokrysz, Freeman, et al., 2016).

Cognitive biases. Although research is limited and replication is warranted, heavy and dependent users consistently show an attentional bias (i.e., fast attentional orientation and maintenance of attention) towards cannabis-related stimuli (Zhang et al., 2018). Attentional bias is weakly associated with craving (Field et al., 2004) and may be higher with increasing CUD severity (Cousijn, Watson, et al., 2013) and use of cannabis with high THC:CBD ratios (Morgan et al., 2010). Approach bias (i.e., relative automatic approach action tendencies) towards cannabis-related stimuli may also be predictive of cannabis use (Cousijn et al., 2011) and has been found to be stronger in intoxicated heavy users (Cousijn, Snoek, et al., 2013). Moreover, higher activity in cognitive control-related brain areas during an approach-avoidance task has been shown to predict reductions in problem severity (Cousijn et al., 2012).

Emotion processing. Cannabis intoxication consistently impairs emotion recognition (Hindocha et al., 2015). This effect is attributed to THC, while CBD partially attenuates the effect (Fusar-Poli et al., 2009). Effects may be larger for negative emotions as the use of THC has been found to selectively impair the normative attentional bias for negative but not positive faces. This impairment was accompanied by reduced activity for negative faces in reward, learning, and cognitive control-related brain areas (Bossong, van Hell et al., 2013). Heavy and dependent cannabis use have also been associated with emotion identification and discrimination deficits (e.g., Bayrakçı et al., 2015). Impairments may mostly be guided by misinterpretation of negative faces (Bayrakçı et al., 2015). However, both negative and positive emotional stimuli have been linked to reduced brain activity in CB1 rich brain areas like the anterior cingulate cortex and amygdala in heavy users (Gruber et al., 2009).

Attentional control. Attention refers to the capacity to direct attention towards relevant information and can be measured in a drug relevant (e.g., attentional bias discussed above) or irrelevant context. Cannabis intoxication consistently impairs attention in a dose-related manner and heavy cannabis users seem less affected due to tolerance (e.g., Ramaekers et al., 2009; Theunissen et al., 2012). Current evidence suggests long-term impairment of attention in tasks that require focus on a single (e.g., maintenance) or multiple processes (e.g., disengagement & orientation) in heavy cannabis users that resolve after abstinence (Bosker et al., 2013; Crane, Schuster, Fusar-Poli, et al., 2013). Moreover, earlier onset has been related to stronger impairments (Bosker et al., 2013; Hooper et al., 2014).

Working memory. Findings on the effects of cannabis intoxication (e.g., Schoeler et al., 2016; Weinstein et al., 2008) and long-term effects of heavy and dependent use (e.g., Harvey et al., 2007) on working memory (i.e., temporary memory storage crucial to use, update and manipulate information needed for daily life decision-making) are less consistent than effects on learning, memory, and attention. Heavier use (e.g., Crane, Schuster, & Gonzalez, 2013; Thames et al., 2014) and increasing task complexity (Crane, Schuster, Fusar-Poli, et al., 2013) may relate to stronger deficits, but comparability between studies is low. Age may also play a role, with spatial working memory deficits found in adolescents (Harvey et al., 2007) but not adults (Grant et al., 2012).

Inhibition and decision making. Inhibition refers to the capacity to override a prepotent response or stop the execution of a response when behavioral goals change (Swick et al., 2011). Inhibition is multifaceted, referring to fast forms of motor inhibition as well as slower decision-making related forms of inhibition (e.g., delayed gratification and decision making; Caswell et al., 2013). Regarding motor inhibition, cannabis intoxication consistently and dose-dependently decreases the ability to stop behavior (e.g., Metrik et al., 2012; Ramaekers et al., 2009). However, these effects may be partially driven by cannabis's motoric effects. Regarding decision-making related inhibition, results are inconsistent with some studies reporting increased impulsive decision making (e.g., Rogers et al., 2007; Weinstein et al., 2008), while others do not (e.g., Metrik et al., 2012; Ramaekers, Kauert et al., 2006), or only find effects on reaction times (Vadhan et al., 2007). Long-term effects on inhibition and decision-making are unclear due to the mixed results of a limited number of studies with variable research designs (Broyd et al., 2016). Nonetheless, decision-making deficits may be more pronounced in more dependent users (Gonzalez et al., 2012) and insensitivity to negative information (e.g., monetary loss) may increase risky decision making in cannabis users (e.g., Fridberg et al., 2010).

Intelligence

Several longitudinal studies suggest that heavy cannabis use is related to a decline in IQ (Fried et al., 2002; Meier et al., 2012). However, more recent studies suggest that this decline is more likely explained by other confounding variables (e.g., SES, Mokrysz, Landy, et al., 2016; Rogeberg, 2013) and sub-acute effects of cannabis intoxication (Fried et al., 2002).

Psychiatric comorbidities

US surveys estimate substantial comorbidity of CUDs with mood (39.6%), anxiety (30.5%), and personality (35.9%) disorders (Stinson et al., 2006). Most evidence points

towards a bidirectional relationship, where CUD increases the odds and symptom severity of other psychiatric disorders and vice versa (Richardson, 2010). For example, there is substantial evidence that cannabis use negatively impacts the development of manic symptoms in bipolar disorder (e.g., Lev-Ran et al., 2013) and CUD is associated with higher risks for comorbid depression (e.g., Chen et al., 2002). In turn, depression may increase CUD risk (Feingold, Weiser et al., 2015). Self-medication may play an important role in explaining these relationships. Although cannabis's therapeutic effects remain to be confirmed, reduction of anxiety or PTSD-related sleep problems are commonly reported motives of use (Bonn-Miller et al., 2014; Walsh et al., 2017). However, cannabis intoxication may also trigger anxiety attacks, especially at higher doses (Crippa et al., 2009; Fusar-Poli et al., 2009), and increase the risk for an anxiety disorder (Crippa et al., 2009; Kedzior & Laeber, 2014).

Although evidence is mixed (Gobbi et al., 2019; Hosseini & Oremus, 2019), earlier onset and heavier patterns of use may increase risks for comorbid psychiatric disorders. For example, adolescent-onset relative to adult-onset cannabis users had an increased risk of developing depression in mid-life (Schoeler et al., 2018). Early onset has also been associated with an increased likelihood of attempting suicide (e.g., Silins et al., 2014).

The relationship between cannabis and psychosis and schizophrenia is among the most investigated topics in the cannabis literature (di Forti et al., 2019; Marconi et al., 2016; Myles et al., 2016). Intoxication studies show a time-bound, dose-dependent effect of cannabis on positive psychotic symptoms (e.g., paranoia, delusions, and fragmented thinking; Murray et al., 2017). THC is responsible for these transient effects, which CBD may attenuate (e.g., Bhattacharyya et al., 2010). Studies investigating negative psychotic symptoms are scarce, but there are indications of THC-induced blunted affect, psychomotor problems, and emotional withdrawal (e.g., D'Souza et al., 2004). For individuals with schizophrenia, cannabis use can aggravate symptoms (e.g., D'Souza et al., 2005). Age of onset, heavy use and using high-potency cannabis increases the risk for psychosis and schizophrenia (Myles et al., 2016). However, more longitudinal studies are needed to establish causality and exclude the possibility of other explanations, such as shared (genetic) risk factors or self-medication of premorbid symptoms.

Other substance use disorders

Co-use of tobacco, alcohol and/or cannabis is common and individuals with more psychological problems are more likely to be polysubstance users (Connor et al., 2014). Regarding brain effects, it is likely that polysubstance use has cumulative or synergistic effects (Licata & Renshaw, 2010). Cannabis has been proposed as a gateway to harder illicit drugs like cocaine and opiates and has indeed been linked to an elevated risk of

cocaine and opiate use initiation (e.g., Kandel & Kandel, 2015). However, it remains questionable whether cannabis itself, and not social or genetic factors that cause shared liability, explains this sequence of transition (Degenhardt et al., 2010; Lynskey & Agrawal, 2018). In addition, a reverse gateway effect from cannabis to tobacco use has also been reported (e.g., Agrawal et al., 2010).

Neurological disorders

Cerebrovascular accidents

As the endocannabinoid system plays a role in cardiovascular regulation, it is suggested that cannabis use might result in cardiovascular problems that lead to cerebrovascular accidents (Alfulaij et al., 2018). Although there are only a handful of reports of hemorrhagic stroke after cannabis use, there have been multiple reported cases of ischemic strokes and transient ischemic attacks that were retrospectively associated with cannabis use (Hackam, 2015). In multiple cases of cannabis-associated ischemic stroke, re-exposure to cannabis resulted in a new ischemic stroke (Hackam, 2015). Recent reviews indicate a temporal link between cannabis use and ischemic stroke/transient ischemic attacks, but most studies fail to control for important confounding variables such as tobacco use (Ravi et al., 2018; Rezkalla & Kloner, 2018). Further research is needed to establish a causal relationship (Esse et al., 2011). Current evidence indicates that amount of use, the use of synthetic cannabis, age, gender, comorbidities, and other drug use may moderate this relationship (e.g., Esse et al., 2011; Ravi et al., 2018).

Brain tumors

There is currently insufficient proof of a relationship between heavy cannabis use/CUD and brain cancer (Huang et al., 2015). There are no studies investigating heavy users/CUD specifically and most studies in cannabis users suffer from low power and poor control over tobacco smoking (Huang et al., 2015). However, one study in a small sample of monthly cannabis users (Efird et al., 2004) indicated an increased risk for malignant primary adult-onset glioma, warranting further research.

Causal mechanisms

The causal mechanisms are largely unknown. Most evidence is correlational and based on indirect measures of brain structure and function. Longitudinal studies crucial to evaluate causality are limited. Cognitive deficits and co-morbid psychopathology could be pre-existing or driven by a third shared causal factor. Nevertheless, animal and human pharmacological studies provide insights into the potential working mechanisms.

THC resembles the naturally occurring agonist anandamide in its properties as a partial CB1 and CB2 (though with lower binding affinity) agonist (Pertwee, 2008). THC can thereby mediate dopaminergic and serotonergic neurotransmission, including dopamine release in the striatum and ventral tegmental area (Bossong et al., 2009), areas crucial for salience and reward processing. THC-induced striatal dopamine release appears blunted in dependent users (Bloomfield et al., 2014). THC-mediated alterations in salience processing may underpin cognitive and psychopathological deficits associated with cannabis use (Bhattacharyya, 2012). CBD may play an attenuating role by eliciting effects opposing those of THC in brain areas involved in reward processing and cognitive control (Bhattacharyya, 2012).

In rodents, chronic THC exposure causes a reduction in the number and signaling efficiency of CB1 receptors (e.g., Gonzalez et al., 2005; Sim-Selley, 2003). This downregulation has been related to withdrawal (Curran et al., 2016). Abstinence may restore CB1 density, with more rapid reversal in the striatum and midbrain than in cortical regions (Hirvonen et al., 2012). A more recent study has also found reversible and regionally selective downregulation of brain CB1 receptors in human heavy cannabis users (Hirvonen et al., 2012).

Furthermore, heavy cannabis use has been associated with dysregulation of the hypothalamus–pituitary–adrenal-axis (HPA-axis), which is involved in natural stress responses. Dysregulation of the HPA-axis may cause the blunted stress response to negative emotional stimuli (Somaini et al., 2012) and stress-related withdrawal symptoms such as dysphoria, anxiety, and irritability (Somaini et al., 2012; Volkow et al., 2016) observed in CUD.

Route of administration also influences the effects of cannabis. When inhaled (e.g., smoking, vaping, or dabbing), cannabinoids quickly travel via the lungs into the bloodstream towards the brain. In contrast, cannabinoids in edibles take longer to reach the bloodstream via the digestive system and bind to peripheral cannabinoid receptors (e.g., in the liver) before reaching the brain. THC reaches high levels in plasma very fast but is also a lipophilic substance easily absorbed by fat (Sharma et al., 2012). Although plasma is generally cleared of THC and its metabolites within a week (Karschner et al., 2009; Sharma et al., 2012), THC is still slowly released by fat into the bloodstream (Karschner et al., 2009). In line with this, heavy compared to occasional users exhibit slower blood clearance of THC, potentially causing longer lasting sub-acute effects (Sharma et al., 2012).

Assessments in clinical practice

The DSM and ICD are the golden standards for diagnosing CUD and other psychiatric disorders. According to the DSM-5, CUD can be defined as problematic

cannabis use leading to clinically significant impairments or distress (American Psychiatric Association, 2013a). While the ICD-10 (World Health Organization, 1993) and old DSM-4 (American Psychiatric Association, 2012) still differentiated between abuse and dependence, the DSM-5 classifies CUDs as mild (2-3 criteria), moderate (4-5 criteria), or severe (6 or more criteria) depending on the presence of any of eleven diagnostic criteria over a period of 12 months (American Psychiatric Association, 2013a). The diagnostic criteria pertain to loss of control, social problems, use in risky situations, and physical dependence. In addition, the DSM-5 includes craving and cannabis withdrawal syndrome as novel diagnostic criteria. Withdrawal symptoms include nausea, headaches, mood changes, aggression, appetite changes, and craving. These symptoms normally peak within the first week of abstinence and severity has been associated with heaviness of cannabis use (Levin et al., 2010).

Reliable and commonly used DSM- and ICD-based structured interviews to diagnose and assess the severity of CUD include the SCID, MINI, PRISM and WHM-CIDI. Although mostly used in academic settings, multiple brief questionnaires have been developed to assess and screen the severity of use-related problems (e.g., CUDIT-R, Adamson et al., 2010; CUPIT, Bashford et al., 2010; SDS, Martin et al., 2006) and quantity of use (e.g., TLFB, Hjorthøj, Hjorthøj et al., 2012). These measures have good psychometric properties and are time efficient, making them a valuable addition in clinical practice to gather helpful information about quantity and patterns of use (López-Pelayo et al. 2015).

Cognitive assessments can be very informative in clinical practice. At early stages of treatment, patients may experience cognitive impairments that can result in poorer understanding of therapeutic interventions and materials, hampering learning and change processes. Computerised cognitive assessments and training programs can be helpful although they are rarely used and evaluated. The Montreal Cognitive Assessment (MoCa, Nasreddine et al., 2005) is a short, 10-minute, cognitive battery that can be used to identify mild cognitive impairment in individuals with SUDs (Copersino et al., 2009). Clinicians are also advised to adapt communication to the individual patient's cognitive capacities. Repetition of information may be helpful until the patient attains abstinence and cognition improves. Treatment manuals (e.g., Hoch et al., 2017) describe such therapeutic procedures. Similar to cognition, comorbid psychopathology has been shown to affect treatment retention, efficacy, and prognosis (see section Prognosis), warranting assessment in early stages of treatment. In research, a large variety of cognitive tests and psychopathology assessments are used, with choices often guided by the available time and relevance to the subject of investigation. To improve our current knowledge base and clinical practice, more efforts should be made to align and standardize clinical and research assessments.

Treatment: current practice and new developments

Cannabis has become the primary reason for first-time treatment entry across all illicit drugs worldwide (UNODC, 2018a), with a 75% increase in Europe over the past 10 years (UNODC, 2019). Possible explanations for this rise in treatment demands include increasing CUD prevalence, changes in risk perception, increasing cannabis potency, changes in referral practices, and increasing availability and accessibility of treatment services (Montanari et al., 2017). In Europe, 5-10% of daily and near-daily users are currently in outpatient treatment – indicating a large treatment gap (EMCDDA, 2015). Despite high treatment demands, the number of clinical trials testing mental and psychosocial interventions for CUD specifically is still small (Gates et al., 2016).

Psychosocial interventions

Evidence supports the effectiveness of combinations of cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and Contingency Management (CM) or Psychosocial Problem Solving (PPS; EMCDDA, 2015; Gates et al., 2016). These interventions are usually short (1 to 12 sessions) and compared to inactive rather than active control groups (Davis et al., 2015). In children and adolescents, family therapy interventions are promising too (Bender et al., 2011; EMCDDA, 2015). Most clinical trials assess cessation or a reduction of use as primary outcomes. Rates of cannabis abstinence are low and unstable (Gates et al., 2016), but comparable to treatments for other SUDs. Interventions aimed to reduce frequency and intensity of consumption appear more successful in reducing CUD severity and cannabis-related psychosocial problems in addition to use (Gates et al., 2016).

Pharmacotherapy

No medications are yet licensed for CUD treatment. A systematic review (Nielsen et al., 2019) indicated that SSRI antidepressants, mixed action antidepressants, bupropion, buspirone, and atomoxetine are likely of little value in the treatment of cannabis dependence. The evidence base for the anticonvulsant gabapentin, oxytocin, and N-acetylcysteine is weak. Another systematic review (Hoch et al., 2019) found mixed effects of THC preparations for the reduction of cannabis withdrawal symptoms and treatment retention. A recent RCT (D'Souza et al., 2019) tested the efficacy and safety of the FAAH-inhibitor PF-04457845 in male daily cannabis users and found that those who received the drug, compared to placebo, had fewer withdrawal symptoms, and used less cannabis 4 weeks later. More clinical studies are needed to examine the benefits and safety of drugs for the treatment of CUDs.

New developments and future direction

Reaching and motivating youth with CUD is hard, but targeted digital media interventions are beginning to show some benefits in clinical settings (Tait & Christensen, 2010) and beyond (Hoch et al., 2016). Cognitive remediation as an adjunct to CBT and MET may also be promising. Little previous research has examined the neuropsychological factors that affect individuals with CUD ability to learn new skills in CBT, but there is initial evidence that lower scores on neuropsychological tests increase the chance of treatment dropout (Aharonovich et al., 2008). Exercise during an early treatment phase may accelerate the return of cognitive functioning and have a direct effect on whether patients find treatment useful and complete it (Sofuoglu et al., 2013). Moreover, add-on training to improve working-memory (Sweeney et al., 2018) or reduce cognitive biases (Jacobus et al., 2018) may also increase treatment success. While the causal neurobiological mechanisms underlying CUD will need to be unraveled, pharmacotherapy (Nielsen et al., 2019b) and neurostimulation (e.g., Transcranial Magnetic or Direct Current stimulation) aimed to enhance cognition (Salling & Martinez, 2016) have shown initial success in other SUDs. Considering the heterogeneity of CUD and high comorbidity rates, the potential benefits of individualized treatment options should also be addressed in future research.

Prognosis

Despite the unclear and highly variable long-lasting effects of heavy cannabis use and CUD, prognosis can be assumed to be worse for cannabis users with higher CUD severity. Since evidence-based CUD treatments are limited and abstinence rates are low (6-month follow up: 24%-35%, Denis et al., 2006; Hoch et al., 2014), prevention is pivotal. Heavy users in contact with health professionals should therefore always be encouraged to stop or reduce use to prevent further escalation. Among those that seek treatment, cognitive deficits may reduce treatment attendance (Copersino et al., 2012). While some cognitive deficits may precede CUD, cognitive deficits do appear to recover for those maintaining abstinence (Ganzer et al., 2016; Schreiner & Dunn, 2012).

Although more studies are needed to confirm this and study its mechanisms, odds for long-term abstinence (with or without treatment) and cognitive recovery may be negatively influenced by withdrawal severity (Budney et al., 2008; Levin et al., 2010), use of cannabis with high THC:CBD ratios (Ganzer et al., 2016), age of onset (Ganzer et al., 2016), CUD severity (Hooper et al., 2014) and comorbid mental disorders (Ganzer et al., 2016). Although increased risk of developing a CUD is highly undesirable, self-medication for anxiety, PTSD, depression, and psychosis related symptoms should be taken into account (Richardson, 2010).

While reducing cannabis use might improve treatment for comorbid psychiatric disorders, aggravation of symptoms combined with craving and withdrawal after reducing cannabis use may also cause setbacks in treatment. Importantly, effective pharmacotherapy for comorbid psychiatric disorders may reduce cannabis use as a consequence (Baker et al., 2010).

To date, no strong causal relationship between cannabis use and neurological disorders, such as brain cancer and stroke, has been established. The effect of continued cannabis use or abstinence on the prognosis of neurological disorders is therefore unclear.

Conclusions, limitations, and future directions

Despite the growing societal burden, our knowledge of the long-term effects of heavy cannabis use and CUD on brain-related outcomes is very limited. Heavy and dependent cannabis use is consistently associated with a high prevalence of comorbid psychiatric disorders and with learning and memory impairments that seem to recover after abstinence. Evidence regarding other cognitive domains and neurological consequences including cerebrovascular events is limited and inconsistent. Potential moderators of the impact of heavy cannabis use and CUD on the brain include age of onset, heaviness of use, CUD severity, THC:CBD ratio, and severity of comorbid disorders. The causal direction of the relationship between heavy cannabis use and CUD on cognitive, psychiatric, and physical health outcomes remains to be established. The current knowledge base is limited by the use of inconsistent terminology, varying research designs and paradigms causing low comparability across studies, as well as insufficient control of potential confounding factors (e.g., tobacco use). Future studies on individuals diagnosed with CUD are crucial to distinguish between dependence specific effects and effects of frequency of use. Furthermore, longitudinal studies are needed to unravel the underlying mechanisms and parse the role of shared risk factors (e.g., genetics) and pre-existing cognitive deficits and psychiatric symptoms to establish causality. There is a high need for more effective treatments as abstinence after treatment is achieved by a minority. Currently, treatment targeted at reductions in use appears most successful. To improve our current knowledge base, more efforts should be made to align and standardize clinical and research assessments.

Chapter 3

The short-term and long-term effects of cannabis on cognition: recent advances in the field

This chapter is based on:
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Abstract

The aim of this review is to discuss the most recent evidence for the short-term and long-term effects of cannabis on cognition. The evidence that cannabis intoxication is associated with short-term impairment across several basal cognitive domains, including learning and (episodic) memory, attentional control, and motor inhibition is increasing. However, evidence regarding the effects of long-term heavy cannabis use on cognition remains equivocal. Cannabis research suffers from difficulties in measuring cannabis exposure history, poor control over potential sub-acute effects, and heterogeneity in cognitive measures and sample composition. Multidisciplinary collaborations and investment in studies that help overcome these difficulties should be prioritized.

Introduction

Recent global changes in cannabis legislation parallel increases in use and decreases in harm perception (SAMHSA, 2018; UNODC, 2019). Yet, there is still little conclusive evidence on the effects of cannabis use. This review specifically focuses on the effects of cannabis use on cognition. Cognition encompasses our thoughts and shapes our behavior and refers to distinct but partially overlapping processes such as learning, memory, attention, inhibition, decision-making, and emotion regulation. Cannabis contains over a hundred different cannabinoids including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD, Chandra et al., 2019). Although the mechanisms are unclear, cannabinoids like THC and CBD potentially affect cognition through interactions with the endogenous cannabinoid system in the brain (Russo, 2016). This system in-turn regulates many other neurotransmitter systems including the dopamine system often implicated in substance use disorders (SUD, Covey et al., 2017). Moreover, like in other SUDs, the development of Cannabis Use Disorder (CUD) may also be related to pre-existing cognitive deficits (Bickel et al., 2018). Given the rapidly developing evidence base, we will discuss the most recent evidence for the effects of cannabis intoxication (short-term) and heavy cannabis use (almost daily use, long-term) on cognition (Table 1). We thereby start with basal cognitive functions, moving towards more complex cognitive functions and the role of affective processes therein.

Table 1. Summary of current evidence for short-term and long-term effects of cannabis on cognition
This table is an adaptation and update of the table presented in Kroon et al. (2019), focusing on the existing knowledge and most recent evidence for short-term and long-term effects of cannabis on cognition. The short-term effects column includes results from intoxication studies, while the long-term effects column includes evidence for the effects of longer periods of heavy (near daily) cannabis use on cognition.

	Short-term effects		Long-term effects		Suggested Reading	
Domain	**Evidence**	**Potential moderators**	**Evidence**	**Potential moderators**	**Reviews**	**Recent Evidence**
Learning & Memory	**Sufficient** evidence that THC/cannabis impairs (non)-verbal learning and episodic memory. **Limited** evidence for impairment of other types of learning and memory.	Dose ↑ Early onset ↑ Heavy history ↓ Low THC:CBD ratio ↓	**Sufficient** evidence for impairments in current heavy users. **Insufficient** evidence for lasting effects after abstinence. Indications of (partial) recovery.	Sub-acute THC/cannabis effects ↑ Early onset ↑ Heavy history ↑ Comorbid mental health issues↑	Schoeler & Bjattacharyya, 2013; Ranganathan & D'Souza, 2006; Blest-Hopley et al., 2020; Prini et al., 2020	Duperrouzel et al., 2019; Blest-Hopley et al., 2019; Aloi et al., 2020; Kloft et al., 2020; Cuttler et al., 2019; Miranda et al., 2019
Working Memory	**Inconsistent** evidence that THC/cannabis impairs working memory.	-	**Inconsistent** evidence for long-term working memory deficits in current heavy users. **Limited** evidence for recovery after abstinence.	Sub-acute THC/cannabis effects ↑ Heavy history ↑ Early onset ↑ Task complexity ↑	Schoeler & Bjattacharyya, 2013; Ranganathan & D'Souza, 2006; Blest-Hopley et al., 2020	Owens et al., 2019
Attentional Control	**Sufficient** evidence that THC/cannabis impairs attentional control.	Dose ↑ Heavy history ↓	**Sufficient** evidence for impairments in sustained and divided attention in current heavy users. **Insufficient** evidence for lasting effects after abstinence. Indications of (partial) recovery.	Sub-acute THC/cannabis effects ↑ Early onset ↑ Heavy history ↑	Broyd et al., 2016; Figueirdo et al., 2020; Crean et al., 2011	Petker et al., 2019
Motor Inhibition	**Sufficient** evidence that THC/cannabis impairs inhibition of ongoing responses (stop-signal task). **Inconsistent** results with other inhibition tasks.	Dose ↑	**Limited** and **inconsistent** evidence for impairments in current heavy users.	-	Broyd et al., 2016; Figueirdo et al., 2020; Crean et al., 2011	Petker et al., 2019
Cognitive Biases	**Limited** evidence for cannabis-related approach bias and attentional bias.	-	**Sufficient** evidence for attentional bias, but **insufficient** evidence for approach bias in current heavy users. **No evidence** to support or refute lasting effects after abstinence.	Heavy history ↑ CUD severity ↑ THC ↑ Craving ↑	O'Neill et al., 2020; Zhang et al., 2018	Alcorn et al., 2019; Van Kampen et al., 2020; Ruglass et al., 2019
Emotion Processing	**Consistent**, but **limited** evidence that THC/cannabis impairs emotion recognition, particularly for negative emotions.	Low THC:CBD ratio ↓	**Limited** evidence for impaired emotion identification/recognition in current heavy users. **No evidence** to support or refute lasting effects after abstinence.	-	-	Troup et al., 2019
Decision Making	**Insufficient** evidence that THC/cannabis impairs decision-making.	-	**Insufficient** and **inconsistent** evidence for impairments in current heavy users.	Cognitive subdomain	Broyd et al., 2016; Fatima et al., 2019; Zhang et al., 2018	Duperrouzel et al., 2019

THC = Δ9-tetrahydrocannabinol; CBD = cannabidiol

Cannabis and cognition: current knowledge and recent advances

Learning and memory

Cannabis intoxication impairs learning and memory in a dose-dependent manner, although significant individual differences exist (Petker et al., 2019; Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013). Studies in heavy cannabis users are less consistent, but learning and immediate recall deficits are most commonly reported in active cannabis users (Blest-Hopley et al., 2020). A recent longitudinal study (Duperrouzel et al., 2019) in adolescent cannabis users suggests a causal link between cannabis exposure and immediate, but not delayed recall in an episodic memory task. Furthermore, another recent study showed that trial-by-trial verbal learning rates were slower in cannabis users compared to controls, and that these learning rates were associated with altered functionality of the parahippocampal gyrus, thalamus, and midbrain regions (Blest-Hopley et al., 2019). While altered feedback processing may play a role in learning deficits observed in alcohol and other substance users, this may not necessarily be the case in cannabis users (Aloi et al., 2020). Furthermore, impairments may not be relegated to only memory of real experiences. Kloft et al. showed that cannabis intoxication increased susceptibility to false memory, an effect that appeared most prominent at immediate compared to delayed recall (Kloft et al., 2020).

Subacute intoxication effects likely contribute to the described effects in cannabis users. The effects of cannabis on memory performance and related alterations in brain activity fade with abstinence (Blest-Hopley et al., 2020). In line with this, working memory performance and functionality of the underlying brain network was only found to be impaired in individuals with a positive urine screen for THC (Owens et al., 2019). Despite the heterogeneous and potential timebound nature of the observed deficits, cannabis use-related learning and memory problems could seriously impact daily functioning of heavy cannabis users, including performance in school or at work. A combination of psychological, neurological, and neurobiological research (Prini et al., 2020) is crucial to further elucidate the apparent complexity of mechanisms underlying the effects of cannabis on memory.

Attention

Similar to learning and memory, cannabis intoxication consistently results in a THC-dose-dependent reduction of the capacity to orient attention towards task-relevant stimuli (D'Souza et al., 2008; Ramaekers et al., 2009; Theunissen et al., 2012). In heavy compared to occasional cannabis users, tolerance to the acute effect of cannabis on attentional control was related to reduced responsiveness of the reward system after intoxication (Mason et al., 2019). This may relate to the general tolerance to cognitive

impairments by cannabis intoxication often observed in heavy users (Ramaekers et al., 2009; Ranganathan & D'Souza, 2006; Schoeler & Bhattacharyya, 2013; Schwope et al., 2012; Theunissen et al., 2012). Heavy cannabis users also develop an attentional bias towards cannabis and related objects that may interfere with other attentional processes (e.g. Alcorn et al., 2019; but see Van Kampen et al., 2020). Although effect sizes were small, a recent meta-analysis showed evidence for an attentional bias towards cannabis-related words and pictures in heavy cannabis users (O'Neill et al., 2020). Attentional bias has been linked to the severity of CUD (Cousijn, Watson et al., 2013) and might reflect an involuntary early perceptual bias, supported by increased amplitude and earlier peak of the N1 component in response to distracting cannabis stimuli (Ruglass et al., 2019).

Inhibition

Cannabis use, and drug use in general, has often been associated with poor inhibitory control. With regards to motor inhibition, cannabis intoxication consistently and dose dependently reduces the ability to inhibit an ongoing motor response, as measured with the stop-signal task (e.g., McDonald et al., 2003; Metrik et al., 2012). In contrast, inhibition before a response is initiated, as measured with the go/no-go task, may not be impaired by intoxication (McDonald et al., 2003). Findings on the effects of heavy cannabis use on motor inhibition are less consistent (Broyd et al., 2016).

However, aside from potential problems caused by impairments in motor control due to cannabis intoxication (Boggs et al., 2018), motor inhibition might not well-reflect the daily life inhibition problems present in most substance users. Indeed, slower proactive inhibitory control-related processes, such as those measured with the classical Stroop were found to relate to cannabis craving (Van Kampen et al., 2020).

Decision-making

More complex cognitive functions such as decision-making heavily rely on the integrity of the basal cognitive functions discussed above and deficits in any of those might in turn result in risky decisions like substance use. The complexity of the processes involved may explain the inconsistent findings on the effects of cannabis intoxication and heavy use on decision-making (Broyd et al., 2016; Kroon et al., 2020). Nonetheless, progress has been made and recent studies provide new insight into how heavy cannabis use and the context in which decisions are made affect risky decision-making. For example, a recent study on financial delay discounting (preferring immediate small rewards over delayed bigger rewards) observed a positive relationship between increased delay discounting and frequency of cannabis use (Sofis et al., 2020). Interestingly, Gilman at al. found that heavy cannabis using adolescents

compared to controls differed on risk taking in the social, safety, and ethical domains, but not the financial domain (Gilman et al., 2015). In general, risky decision-making in heavy cannabis users seemed associated with increased sensitivity to immediate gain accompanied by decreased loss sensitivity (Fridberg et al., 2010; Wesley et al., 2011).

The importance of context and emotion

The previously discussed findings highlight the need for a more fine-grained investigation of cognitive subprocesses and their interactions, as well as the importance of the context in which cognition is measured. While cannabis use by a popular peer may bias decision-making in an occasional user, for individuals with a CUD, decision-making may be particularly compromised when confronted with cannabis-related cues. As with attentional bias, cannabis-related cues may also activate an approach bias towards cannabis in heavy cannabis users (Cousijn, Watson et al., 2013). Moreover, acute stress may influence cognitive performance. For example, acute stress affects prospective memory performance in both heavy cannabis users and controls, but the effects are larger in heavy cannabis users (Cuttler et al., 2019). On the other hand, increased working memory capacity seems to protect heavy cannabis users from craving under stressful circumstances (Miranda et al., 2019). Taken together, potential cognitive deficits in heavy cannabis users may manifest themselves depending on contextual factors.

The impact of cannabis use on emotion processing is an important factor to consider herein. Although data is limited, cannabis intoxication may negatively affect emotion recognition (Hindocha et al., 2015). This seems to be most apparent for negative emotions and appears to be related to reduced brain activity in reward and cognitive control related brain areas when presented with negative faces (Bossong, van Hell et al., 2013; Fusar-Poli et al., 2009). A recent study focusing on gender differences identified complex interactions between gender and cannabis use patterns in relation to the early processing of emotional stimuli (EEG, ERP: P1 and P3, Troup et al., 2019). This highlights the general importance of assessing gender differences in the effects of cannabis use. This is a particularly relevant issue in the domain of emotion processing research because of the high rates of comorbidity between cannabis use and disorders associated with emotion processing (e.g., anxiety) and the commonly reported gender difference in the prevalence of these disorders.

Field wide difficulties and future directions

Aside from the classic confounders such as polysubstance use and comorbid mental health problems, as well as a lack of longitudinal data limiting our understanding of the causal relationship between cannabis and cognition, cannabis research is facing

significant difficulties which have been brought to attention by the majority of recent reviews on the topic (Blest-Hopley et al., 2020; Fatima et al., 2019; Figueiredo et al., 2020; O'Neill et al., 2020). While overcoming these difficulties is of utmost importance, clear solutions are still lacking.

First, the vast majority of studies on the long-term effects of heavy cannabis use on cognition share one confounding factor: the abstinence period. Studies show that THC metabolites are detectable in the plasma of heavy cannabis users for over a week (Karschner et al., 2009) and even longer detectability is possible due to THC's lipophilic characteristics (Sharma et al., 2012). In line with this, cannabis-use-dependent neurocognitive impairments can be detected for as long as 28 days after cessation (Bolla et al., 2002). Hence, studies in current heavy cannabis users struggle to differentiate sub-acute from long-term effects. Although this confound should be acknowledged and more wide-spread assessment of THC metabolites is warranted, sub-acute effects should not always be seen as a problem in itself. After all, the mix of acute, sub-acute, and long-term effects represent what a current heavy cannabis user is dealing with in daily life. Nevertheless, more knowledge of the potential for recovery after abstinence and the role of CUD severity in recovery is needed.

Second, problems with quantifying use are often reported and pose a true problem for comparability across studies. Variable definitions of heavy cannabis use and the lack of standard cannabis units are recurrent problems. While both problems might reflect semantics, and defining categories for frequency and heaviness of use might indeed primarily require discussion, developing a standard unit is extremely complicated. Recently, attempts were made to develop a standard unit of cannabis (Kögel et al., 2017; Freeman & Lorenzetti, 2019), but the complexity and variability in cannabis products and routes of administration hampers practicality. Cannabis contains over a hundred different types of cannabinoids and the THC:CBD ratio differs significantly between region and even between batches (UNODC, 2018b). Poor knowledge about exposure history in most studies complicates research even further. To improve our knowledge base, accessible and more reliable methods to quantify cannabis use are needed. However, even then, research in most countries heavily relies on changes in local legislation to allow for these methods to be used.

Third, there are methodological problems that plague comparability in systematic reviews and meta-analyses. While increasing the amount of research will increase the power of these types of reviews, studies are rarely replicated and the variability between measures to assess the same cognitive construct remains a problem (Fatima et al., 2019; Figueiredo et al., 2020; O'Neill et al., 2020). An increase in power will not reflect an increase in knowledge when this heterogeneity problem is not solved. In line with this, it remains important to be aware of the risks of assuming that similar tasks

measure the same construct as is often done when aggregating results from stop-signal and go/no-go tasks (Littman & Takács, 2017).

Finally, it may be that the effects of heavy cannabis use on cognition are indeed mixed. The same dose of THC may result in impairments in some, while leading to improvement in others (Cousijn, Núñez et al., 2018). These individual differences are likely to depend on a large variety of moderating factors including THC:CBD ratio, differences in THC metabolization, poly-substance use, severity of cannabis dependence, age of onset, gender, and mental health. In turn, the combined effects of these factors might vary with the context under which cannabis is consumed and cognition is assessed.

Conclusion

The rapid increase of research into cannabis and its effects on cognition has provided us with answers as well as questions. While there is increasing evidence that cannabis intoxication negatively affects basal cognitive functions like episodic memory, attentional control, and motor inhibition, results on the long-term effects of heavy cannabis use, and potential recovery after abstinence, remain equivocal for most cognitive domains. Despite a slow start, cannabis research is breaking ground. Nevertheless, field-wide difficulties in quantification, methods of measuring cognitive constructs, and the influence of sub-acute effects seriously hamper the road ahead and require attention now. Multidisciplinary collaboration and investment in studies that solve these problems should be prioritized.

Chapter 4

Associations between hair-derived cannabinoid levels, self-reported use, and cannabis-related problems

This chapter is based on the following preprint:
Kroon, E., Cousijn, J., Filbey, F., Binz, T.M., & Kuhns, L.N. (n.d.). Associations between hair-derived cannabinoid levels, self-reported use, and cannabis-related problems. https://doi.org/10.31234/osf.io/s6rn2

Abstract

Background. As cannabis potency and cannabis use are increasing in newly legalized markets, it is increasingly important to measure and examine the effects of cannabinoid exposure.

Aims. The current study aims to assess how hair-derived cannabinoid concentrations – offering insight into three-month cumulative exposure – are associated with common self-report measures of cannabis use and cannabis use-related problems.

Methods. 74 near-daily dependent cannabis users self-reported their quantity of cannabis use, cannabis use-related problems, and estimated cannabis potency. Hair samples were provided to quantify 9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) using a liquid chromatography atmospheric pressure chemical ionization-tandem mass spectrometry method.

Results. Cannabinoids were detectable in 95.95% of the hair samples from individuals who tested positive on a urine screen for cannabis. Δ9-THC concentrations were positively associated with measures of self-reported potency (relative potency, potency category, and perceived 'high'), but Δ9-THC, CBD, CBN concentrations and THC/CBD ratio were not associated with self-reported quantity of use. Self-reported potency, but not hair-derived concentrations, were associated with withdrawal and craving. Self-reported quantity of cannabis use, but not cannabinoid concentrations, were associated with cannabis use-related problems.

Conclusions. The use of hair-derived cannabinoid quantification is supported for detecting cannabis use in near-daily users, but the lack of associations between hair-derived cannabinoid concentrations and self-report measures of use does not support the use of hair analyses alone for quantification of cannabinoid exposure. Further research comparing hair-derived cannabinoid concentrations with other biological matrices (e.g., plasma) and self-report is necessary to further evaluate the validity of hair analyses for this purpose.

Introduction

Cannabis is the most widely used drug with more than 209 million past year users (United Nations Office on Drugs and Crime, 2021). Given the evidence of increasing use in newly legalized markets (Hall & Lynskey, 2020) and parallel increases in cannabis potency (United Nations Office on Drugs and Crime, 2022), it is critical to examine the effects of cannabis use on health. Measuring cannabinoid exposure presents a uniquely complicated challenge, given the variation in the cannabinoid content of products and differences in bioavailability depending on route of administration. Hair analysis may provide a relatively accessible non-invasive method to complement self-reports to investigate the effects of cannabinoid exposure on health. However, it is currently unclear how suitable hair analysis is for quantifying cumulative cannabinoid exposure in frequent users. The aim of the current study was to examine the associations between different self-reported measures of cannabis use and hair-derived analysis of cumulative cannabinoid exposure with measures of cannabis-related problems to guide the selection of measures in future cannabis research.

The iCannToolkit was recently proposed by a consensus of international cannabis experts to standardize the measurement of cannabis use (Lorenzetti et al., 2021). The framework consists of three layers of assessment that differ in their accessibility and level of detail. The universal base layer is suitable for quick assessment in population-based surveys and emergency service settings and proposes using three self-report items to assess ever use, last use, and days of cannabis use in the past month. The mid layer is suitable for in-depth research on the effects of cannabis use on health and proposes detailed self-report assessment using the timeline followback methodology (TLFB; Sobell & Sobell, 1992) to assess the quantity of use per day over a specific period of time (i.e., past week, past month). However, inherent difficulties in accurately measuring cannabis and cannabinoid exposure emerge in this layer. There is substantial variation both within and across individuals in the types of cannabis products used, the method of administration, and the potency of products, which limits the ability to understand the effects associated with the main compounds in cannabis, particularly psychoactive Δ9-THC and non-psychoactive CBD. Experimental evidence suggests a dose-response relationship between THC exposure and related harms (Hines et al., 2020; Kroon et al., 2020), but detailed investigation of the effects of cannabis exposure in observational research requires the development of more accurate quantification methods. Because of this, the top-layer of the iCannToolkit includes biological measures to quantify cannabinoids or their metabolites in urine, saliva, plasma, or in the cannabis product itself. Several studies found strong correlations between TLFB-reported recent cannabis use and THC and metabolite concentration in urine and plasma (Barguil et al., 2022; Hjorthøj, Fohlmann et al., 2012). However, these methods

are challenging to use for many researchers and clinicians due to invasiveness and lack of accessibility (e.g., storage requirements). For example, cannabinoid metabolites lack stability in both urine and plasma samples when stored at room temperature even for short periods of time, resulting in metabolite degradation and inaccurate measurement (Dugan et al., 1994; Fraga et al., 1998; Skopp & Pötsch, 2002). Furthermore, urine and plasma analysis only detect cannabinoid concentrations within a narrow window of time, typically no more than 7 days. Cumulative exposure to cannabinoids over longer periods of time may be more informative regarding the effects of cannabis use on well-being, which develop over longer periods of time. While testing cannabis products would be valuable, it is complicated by differences in legal status across jurisdictions and product variability.

Analysis of cannabinoid metabolites in hair samples may be a viable alternative to measure cumulative exposure over longer periods of time (1 cm hair translates to 1 month), while reducing invasiveness and allowing for storage at room temperatures (Musshoff & Madea, 2006). This can be beneficial for investigating whether greater cumulative cannabinoid exposure, including THC and other compounds such as cannabinol (CBN), in chronic heavy users translates to increased harm and whether CBD may have protective effects. The state-of-the-art methods to quantify cannabinoid concentrations in hair have developed substantially over time and the preparation and analysis methods used influence the validity of the quantification (Shah et al., 2019). Liquid chromatography-mass spectrometry (LC-MS) is a gold standard method for detection of drugs of abuse, including THC (Shah et al., 2019). In a study of cannabis using psychiatric patients, LC-MS derived THC concentration and THC/CBD ratio were identified as potential markers for acute and chronic psychosis (Barguil et al., 2022).

To our knowledge, no studies have yet investigated the associations between TLFB reported recent cannabis use (the mid-layer of the iCannToolkit), cannabis use related problems, self-reported potency of typically used products, and hair-derived measures using liquid chromatography- tandem mass spectrometry (LC-MS/MS). Therefore, we aimed to assess how self-report measures of cannabis use, use-related problems, and potency are associated with each other and with hair-derived THC, CBD, CBN, and THC/CBD concentrations from the previous three months.

Methods and materials

Participants

Seventy-four cannabis users completed the included assessments as part of a larger fMRI project (Kroon et al., 2023). The study was approved by the ethics committee of the Department of Psychology of the University of Amsterdam (2018-DP-9616).

All participants were 18-31 years old, used cannabis 6-7 days per week on average for at least the previous year, had a mild-to-severe cannabis use disorder (MINI CUD score >1; Sheehan et al., 1997), did not seek treatment for their CUD, had no current psychological diagnoses other than anxiety, depression or ADHD/ADD, and did not use psychotropic medication.

Measures

Questionnaires

Participants reported their age and sex. Cannabis use related problems were assessed using the Marijuana Problem Scale (MPS; Hodgins & Stea, 2018), Cannabis Use Disorder Identification Test (CUDIT-R; Adamson et al., 2010), CUD semi-structured interview from the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1997), Marijuana Withdrawal Checklist (MWC; Budney et al., 1999), Marijuana Craving Questionnaire (MCQ; Heishman et al., 2009), and a craving Visual Analogue Scale (VAS; Mottola, 1993). Cannabis use was assessed using a one-month TLFB questionnaire (Robinson et al., 2014; Sobell & Sobell, 1992) and self-reported grams per week (days per week x grams per use day). Self-report measures of cannabis potency included price per gram, relative potency (scale 0-100), potency (category – very mild/mild/average/strong/very strong), perceived 'high' (scale 1-5), and THC percentage (categorical; see full questions in Appendix A - Figure S1). Participants also reported their preferred type of cannabis (flower/concentrate) and whether they regularly added tobacco to their cannabis (yes/no) when smoking it. Measures of other drug use included daily cigarette use (yes/no), the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993), and self-reported lifetime use of any drugs besides cannabis, alcohol, and tobacco.

Urine and hair samples

The presence (yes/no) of THC metabolites was assessed in urine (threshold 50 ng/mL THC-COOH). Hair was taken from the nape and sent to the Centre for Forensic Hair Analysis at the University of Zurich. A liquid chromatography atmospheric pressure chemical ionization-tandem mass spectrometry (LC-APCI-MS/MS) method was used for quantification of Δ9-THC, CBN and CBD in hair (pg/mg; Scholz et al., 2022). Δ9-THC and CBD concentrations were used to calculate THC/CBD ratio.

Data analysis

Non-parametric Kendall's tau correlations, fit for non-normal and ordinal data, were performed to assess the associations between 1) measures of cannabis-use related

problems, 2) self-reported cannabis use outcomes calculated from the TLFB (gram/day and days of use for 1 month, 14 days, and 7 days), and 3) hair-derived cannabinoid concentrations cumulated over the past three months. Due to the exploratory nature of this study, we did not correct for multiple comparisons and provided Bayes factors to be able to evaluate the strength of the evidence (Jeffreys, 1961) for the significant correlations (H_0: no correlation; Bayes Factor (BF_{10}) >100: extremely strong evidence for H_a, BF_{10} 30-100: very strong evidence for H_a, BF_{10} 10-30: strong evidence for H_a, BF_{10} 3-10: moderate evidence for H_a). Correlations were interpreted as significant if the Kendall's tau correlation was significant ($p < .05$) and there was at least moderate evidence for the correlation ($BF_{10} > 3.00$). Individuals that tested positive for THC on the urine screening but were negative for cannabinoids on the hair analyses were excluded from the analyses (N = 3). We conducted sensitivity analyses excluding cannabinoid concentration outliers (>2 SD above the mean: THC >2SD = 4, CBD >2SD = 5, CBN <2SD = 7). Additionally, we excluded values based on minimum thresholds used in legal proceedings in the detection of cannabis use (THC <50 = 33, CBD <50 = 46, CBD <50 = 35). We only reported effects that remained significant in these sensitivity analyses. Analyses were conducted using JASP version 0.16.4.0 (JASP Team, 2022).

Results

Sample characteristics

All 74 participants (66.22% male) tested positive for THC on the urine screening, with 71 participants (95.95%) also testing positive for THC in hair (Table 1). Participants used a median of 6 grams in an average week, reporting between 13 and 31 days of cannabis use (median = 30) and using a little less than 1 gram (median = .87) per day during the last month. CUDIT-R scores (median = 16) were indicative of problematic use (score >12; Adamson et al., 2010). The use of flower products (64.87%) was more common than the use of concentrates (35.13%), with no individuals reporting a preference for other products. Together, the self-report measures of potency were indicative of average-strong perceived potency and experienced 'high'. Half of the participants reported daily cigarette use, with variable levels of nicotine dependence (FTND range: 1-7, median = 5), and 93.06% reported regularly adding tobacco to their cannabis. In general, AUDIT scores (median = 5) were below at-risk alcohol use (score > 8), but 2.7% (N = 2) of participants reported potential hazardous use (score >12; Saunders et al., 1993).

Table 1. Sample characteristics				
Scale and ordinal outcomes	**Description**	**Median (MAD)**	**Range**	**N**
General				
Age	years	21 (2)	18-31	74
Cannabis use				
Average cannabis use	Gram/week	6 (3.2)	.28-21.00	71
Cannabis use days (TLFB)	Last month	30 (1)	13-31	70
	Last 14 days	13 (1)	6-14	69
	Last 7 days	6 (1)	2-7	70
Cannabis gram/day (TLFB)	Last month	.87 (.32)	.07-3.00	70
	Last 14 days	89 (.38)	.03-3.00	70
	Last 7 days	.85 (.44)	.05-2.86	70
Cannabis use age of onset	years	15 (1)	12-19	72
Cannabis use related problems				
Cannabis Use Disorder symptoms	MINI CUD score	5 (1)	2-10	74
Cannabis use problems	MPS score	6.5 (3.5)	0-32	74
Cannabis use and related problems	CUDIT-R score	16 (5.0)	6-32	74
Withdrawal	MWQ score	8 (3)	1-25	74
Craving	MCQ score	40.5 (9.5)	16-76	74
	VAS score	5.5 (1.5)	0-9.6	74
Other drug use				
Alcohol use and related problems	AUDIT score	5 (2)	1-14	73
Nicotine dependence	FTND score	5 (1)	1-7	37
Cigarette use	Cigarettes/day	7 (3)	2-21	37
Other drug use	Lifetime	13.5 (13.5)	0-352	74
Self-reported potency estimates				
Self-reported relative potency	Scale 0-100	65 (15)	0-100	74
Self-reported 'high'	Scale 1-5	4 (1)	1-5	74
Self-reported price per gram	Euro	9.5 (1.5)	3-15	73
Cannabinoids in hair				
THC	pg/mg	62.00 (45.00)	6-3200	71
CBD	pg/mg	38.00 (22.00)	10-1900	71
CBN	pg/mg	56.00 (31.00)	11-1800	71
THC/CBD	pg/mg	1.33 (1.25)	.03-36.36	71
Nominal outcomes	**Description**	**Percentage**		**N**
Gender	F/M	33.78/66.22		74
Urine screening THC	Positive/negative	100.00/0.00		74
Daily cigarette use	yes/no	50.00/50.00		74
Preferred cannabis type	concentrate/flower	35.13/64.87		74
Tobacco added to cannabis	yes/no	93.06/6.94		72
Self-reported potency	very light/light/average/strong/very strong	0.00/1.35/50.00/36.49/12.16		74
Self-reported THC percentage	<5/5-10/10-15/15-20/20-25/25-30/>30	0.00/5.41/20.27/40.54/28.38/4.05/1.35		74

Note. TLFB: timeline follow back; THC: delta-9-tetrahydrocannabinol; CBD: cannabidiol; CBN; cannabinol; MINI CUD: mini international neuropsychiatric interview, cannabis use disorder; MPS: marijuana problem scale; CUDIT-R: cannabis use disorder identification test; MWQ: marijuana withdrawal questionnaire; MCQ: marijuana craving questionnaire; VAS: visual analogue scale; AUDIT: alcohol use disorder identification test; FTND; Fagerström test for nicotine dependence; pg/mg: picogram per milligram; ms: milliseconds.

Table 2. Correlations between measures of cannabinoids, cannabis use, cannabis use related problems and self-reported measures of potency

Measure			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	THC	Kendall's τ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	CBD	Kendall's τ	.160	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	1.050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	CBN	Kendall's τ	**.508*** **	**.488*** **	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	**>100**	**>100**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	THC/CBD	Kendall's τ	**.539*** **	**-.309*** **	.130	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	**>100**	**>100**	.546	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	CUD score	Kendall's τ	.045	-.013	.026	.062	-	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	.180	.157	.162	.206	-	-	-	-	-	-	-	-	-	-	-	-	-
6	MPS	Kendall's τ	.092	-.038	.028	.080	**.422*** **	-	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	.290	.172	.164	.250	**>100**	-	-	-	-	-	-	-	-	-	-	-	-
7	CUDIT-R	Kendall's τ	.078	-.043	.034	.117	**.543*** **	**.433*** **	-	-	-	-	-	-	-	-	-	-	-
		BF_{10}	.245	.177	.169	.432	**>100**	**>100**	-	-	-	-	-	-	-	-	-	-	-
8	Gram/Week	Kendall's τ	.046	.065	.168*	-.016	**.235** **	**.211***	**.236** **	-	-	-	-	-	-	-	-	-	-
		BF_{10}	.183	.213	1.224	.160	**9.581**	**4.297**	**10.069**	-	-	-	-	-	-	-	-	-	-
9	Gram/Day	Kendall's τ	.065	.019	.119	.024	**.217***	.200*	.181*	**.688*** **	-	-	-	-	-	-	-	-	-
		BF_{10}	.213	.162	.435	.164	**4.787**	2.846	1.674	**>100**	-	-	-	-	-	-	-	-	-
10	Relative potency	Kendall's τ	**.200***	-.022	.143	.155	.004	.057	.113	.160	.027	-	-	-	-	-	-	-	-
		BF_{10}	**3.055**	.160	.719	.936	.152	.195	.412	1.056	.165	-	-	-	-	-	-	-	-
11	%THC category	Kendall's τ	.148	.056	.154	.080	.098	.168	.186*	**.297** **	.150	**.252** **	-	-	-	-	-	-	-
		BF_{10}	.798	.195	.911	.250	.319	1.363	2.269	**>100**	.804	**21.738**	-	-	-	-	-	-	-
12	'High' category	Kendall's τ	**.203***	.035	.198*	.140	-.033	.002	.064	.100	.044	**.363*** **	.029	-	-	-	-	-	-
		BF_{10}	**3.378**	.170	2.903	.665	.165	.152	.209	.325	.180	**>100**	.161	-	-	-	-	-	-
13	Potency category	Kendall's τ	**.243***	.093	**.265** **	.143	**.226***	.106	**.231***	**.359*** **	**.262** **	**.636*** **	**.304** **	**.434*** **	-	-	-	-	-
		BF_{10}	**12.756**	.294	**29.467**	.715	**8.104**	.367	**9.857**	**>100**	**22.606**	**>100**	**>100**	**>100**	-	-	-	-	-
14	Price/gram	Kendall's τ	.005	-.008	-.023	.038	.090	.069	.067	-.065	-.102	.107	.153	.067	.081	-	-	-	-
		BF_{10}	.156	.156	.162	.174	.284	.220	.215	.213	.331	.366	.920	.216	.254	-	-	-	-
15	Withdrawal	Kendall's τ	.037	.045	.060	.017	**.422*** **	**.447*** **	**.352*** **	.164	.085	.083	**.250** **	.007	.164	.064	-	-	-
		BF_{10}	.172	.180	.203	.158	**>100**	**>100**	**>100**	1.160	.266	.260	**20.262**	.152	1.234	.209	-	-	-
16	Craving MCQ	Kendall's τ	.096	.041	.120	.052	**.350*** **	**.287** **	**.215** **	**.276** **	**.282*** **	.049	.134	-.079	.160	.050	**.242** **	-	-
		BF_{10}	.306	.176	.452	.189	**>100**	**95.488**	**5.697**	**46.231**	**49.988**	.183	.616	.246	1.114	.185	**14.979**	-	-
17	Craving VAS	Kendall's τ	.083	.026	.097	.041	**.275** **	**.207***	.124	**.229** **	.115	.120	.176*	-.103	**.235***	.110	**.212** **	**.539*** **	-
		BF_{10}	.260	.162	.311	.175	**57.264**	**4.390**	.509	**7.974**	.408	.467	1.722	.345	**11.298**	.389	**5.104**	**>100**	-

Note. H_0: no correlation; BF_{10} >100: extremely strong evidence for H_A, BF_{10} 30-100: very strong evidence for H_A, BF_{10} 10-30: strong evidence for H_A, BF_{10} 3-10: moderate evidence for H_A, BF_{10} 1-3: anecdotal evidence for H_A, BF_{10} .30-1.00: anecdotal evidence for H_0, BF_{10} .10-.30 (moderate evidence for H_0). BF_{10} >3 are colored in shades of grey with darker colors representing stronger evidence for H_A; Significance levels: * p <.05, ** p < .01, ***, p < .001; Correlations considered significant based on p < .05 and BF_{10} > 3 are presented in bold.

Measures of cannabis use, cannabis use related problems, and potency

There was decisive evidence for a positive correlation of THC and CBD concentrations with hair CBN, but no evidence for a correlation between THC and CBD concentrations or between THC/CBD ratio and CBN (Table 2). Furthermore, there was moderate to strong evidence for a positive correlation between THC concentrations and self-reported relative potency, perceived 'high', and potency (category) with strong evidence for a similar correlation between CBN concentrations and potency (category). Cannabinoid concentrations were not associated with other measures of cannabis use and related problems.

Self-reported relative potency and THC percentage (category) were positively correlated with cannabis use in gram/week (decisive evidence), with only relative potency showing a similar correlation with gram/day in the last month (strong evidence). There was moderate evidence for a positive correlation between potency (category) and CUDIT-R score, whereas no correlations between other measures of cannabis use related problems and self-reported potency were observed. There were several positive correlations among the different self-report measures of potency (Table 2), but no correlations with price per gram were observed. Furthermore, there was strong positive correlation between self-reported THC percentage (category) and withdrawal, as well as craving (VAS) and self-reported potency (category).

There was decisive evidence for a positive correlation between CUD, MPS and CUDIT-R scores, and moderate to strong evidence for a positive correlation of those measures with cannabis use in gram/week. The measure of gram/day based on last month TLFB assessment only showed anecdotal to moderate positive correlations with CUD, MPS and CUDIT scores. There was decisive evidence for a positive correlation of CUD, MPS, and CUDIT-R scores with withdrawal, whereas evidence for positive correlations with craving (MCQ and VAS) was mixed depending on the measure of cannabis use related problems (Table 2). However, while there was no evidence for a correlation between withdrawal and measures of cannabis use (gram/week or gram/day), there was decisive evidence for a positive correlation of those measures with craving (MCQ). Furthermore, there was decisive evidence for a positive correlation between both measures of craving, and moderate to strong evidence for positive correlations between those measures and withdrawal.

Table 3. Self-reported cannabis use and timeline follow back assessments of use

Measure			1	2	3	4	5	6	7
1	Gram/Week	Kendall's τ	-	-	-	-	-	-	-
		BF_{10}	-	-	-	-	-	-	-
2	Cannabis use days Last month	Kendall's τ	**.293****	-	-	-	-	-	-
		BF_{10}	**81.024**	-	-	-	-	-	-
3	Cannabis use days Last 14 days	Kendall's τ	**.381*****	**.808*****	-	-	-	-	-
		BF_{10}	**>100**	**>100**	-	-	-	-	-
4	Cannabis use days Last 7 days	Kendall's τ	**.439*****	**.696*****	**.865*****	-	-	-	-
		BF_{10}	**>100**	**>100**	**>100**	-	-	-	-
5	Cannabis gram/day Last month	Kendall's τ	**.688*****	**.277****	**.313*****	**.341*****	-	-	-
		BF_{10}	**>100**	**40.414**	**>100**	**>100**	-	-	-
6	Cannabis gram/day Last 14 days	Kendall's τ	**.750*****	**.305*****	**.395*****	**.423*****	**.838*****	-	-
		BF_{10}	**>100**	**>100**	**>100**	**>100**	**>100**	-	-
7	Cannabis gram/day Last 7 days	Kendall's τ	**.719*****	**.310*****	**.405*****	**.471*****	**.781*****	**.906*****	-
		BF_{10}	**>100**	**>100**	**>100**	**>100**	**>100**	**>100**	-

Note. H_0: no correlation; BF_{10} >100: extremely strong evidence for H_a, BF_{10} 30-100: very strong evidence for H_a, BF_{10} 10-30: strong evidence for H_a, BF_{10} 3-10: moderate evidence for H_a, BF_{10} 1-3: anecdotal evidence for H_a, BF_{10} .30-1.00: anecdotal evidence for H_0, BF_{10} .10-.30 (moderate evidence for H_0). BF_{10} >3 are colored in shades of grey with darker colors representing stronger evidence for H_a; Significance levels: * p <.05, ** p < .01, ***, p < .001. Correlations considered significant based on p < .05 and BF_{10} > 3 are presented in bold.

Looking at the correlations between different outcomes calculated from the last month TLFB and self-reported gram/week (Table 3), there was very strong to decisive evidence for positive correlations between all measures, regardless of timeline (1 month, 14 days, 7 days) and unit (number of days, gram/day).

Discussion

The aim of this study was to examine how self-report measures of cannabis use and potency and hair-derived quantifications of cumulative cannabinoid exposure in individuals with CUD relate to each other and self-reported measures of use and use-related problems to guide recommendations for cannabis and cannabinoid measures in future research. While self-reported quantity of use was not associated with cannabinoid concentrations, some measures of self-reported perceived potency were positively associated with hair-derived THC and CBN concentrations. The lack of associations between cannabinoid concentrations and TLFB self-reported use and cannabis-related problems does not provide support for the use of hair analysis for quantification of cumulative cannabis exposure in near-daily users.

Hair-derived cannabinoids were detected in 95.95% of cannabis users who met the diagnostic criteria for CUD and tested positive for cannabis in a urine sample, indicating the utility of hair analysis for yes/no detection of cannabis use in heavy users, aligning with Steinhoff and colleague's findings indicating high agreement between self-report weekly or daily use with detection in hair (Steinhoff et al., 2023). Cannabinoid concentrations were not related to measures of cannabis-related problems or grams per day as measured by the TLFB or self-reported grams per week. While variability in product potency could weaken correlations between self-reported cannabis use and cannabinoid exposure, the previously observed strong correlations between blood plasma-derived cannabinoids and self-reports (Barguil et al., 2022; Hjorthøj, Fohlmann et al., 2012) suggest that limitations related to hair analysis should also be considered. Factors such as environmental contamination (i.e., smoke, transfer from other via sebum/sweat; Berthet et al., 2016; Moosmann et al., 2015) likely introduce noise into the data which may obscure associations and different cannabinoid extraction methods might affect comparability across studies. Quantification of THC metabolites instead of cannabinoids themselves would circumvent the issue of environmental contamination but is practically and technically challenging (Moosmann et al., 2015). Furthermore, individual factors can influence the bioavailability and metabolism of cannabinoids, including but not limited to sex, frequency of use, and route of administration further obscuring potential associations. However, we did observe moderate to strong evidence of weak associations of both THC and CBN concentrations with self-reported perceived potency of cannabis products. While this suggests there is an observable signal in the hair of near-daily cannabis users, it does not justify its use for cannabinoid quantification given the described drawbacks.

Importantly, TLFB-derived grams per day based on either a 7-, 14-, or 31-day period were highly associated and showed similar associations with other measures. While additional studies are needed to draw strong conclusions about the validity of different

time frames, the results suggest that even the 7-day TLFB is a valuable measure of cannabis use that can be administered quickly in line with the mid-layer of the iCannToolkit. Grams per week, calculated based on the two-item self-report of typical days of use per week and typical grams per day, was more strongly and consistently related to cannabis-use related problems than the TLFB-derived grams per day measures. Given the short length, the validity and reliability of this measure should be further investigated as it may be flexibly implemented in large scale epidemiological studies of the effects of cannabis use on physical and mental health.

A few limitations are important to discuss. First, these findings are specific to a sample of Dutch individuals who meet the diagnostic criteria for CUD. Suitability of hair-derived cannabinoid quantification may differ depending on severity of use, with detection potentially more difficult in more occasional users (e.g., Taylor et al., 2017). Additionally, the included sample consisted only of individuals who use cannabis flower or concentrates. While the specificity of the sample removed noise that would be introduced via different cannabis products and methods of administration, it also limits the generalizability of the findings. Finally, the absence of other biospecimens to compare to the hair-derived cannabinoid concentrations limits the strength of the conclusions we can draw about both the suitability of the method and the validity of the associations between self-report use measures, and potency. Future studies including the iCannToolkit proposed plasma, urine, saliva, and cannabis products themselves in addition to hair are crucial for a clear determination of the value of hair analysis and the reliability of biospecimen analyses generally.

In conclusion, the use of hair-derived cannabinoid quantification is supported for detecting cannabis use in heavy, near-daily users, with a 95.95% overlap with cannabis use detection in urine. However, the lack of correlations between cannabinoid concentrations and self-reported use and problems suggests it is not currently a suitable method for quantifying the level of cumulative cannabis exposure in the previous three months.

Chapter 5

Gender differences in cannabis use disorder symptoms: a network analysis

This chapter is based on:
Kroon, E., Mansueto, A., Kuhns, L., Filbey, F., Wiers, R., & Cousijn, J. (2023). Gender differences in cannabis use disorder symptoms: a network analysis. *Drug and Alcohol Dependence,* 243, 109733. https://doi.org/10.1016/j.drugalcdep.2022.109733

Abstract

Background. While cannabis use in women is increasing worldwide, research into gender differences in cannabis use disorder (CUD) symptomology is lacking. In response to limited effectiveness of addiction treatment, research focus has been shifting from clinical diagnoses towards interactions between symptoms, as patterns of symptoms and their interactions could be crucial in understanding etiological mechanisms in addiction. The aim of this study was to evaluate the CUD symptom network and assess whether there are gender differences therein.

Methods. A total of 1257 Dutch individuals reporting weekly cannabis use, including 745 men and 512 women, completed online questionnaires assessing DSM-5 CUD symptoms and additional items on plans to quit or reduce use, cigarette use, and the presence of psychological diagnoses. Gender differences were assessed for all variables and an Ising model estimation method was used to estimate CUD symptom networks in men and women using network comparison tests to assess differences.

Results. There were gender differences in the prevalence of 6 of the 11 symptoms, but symptom networks did not differ between men and women. Cigarette use appeared to only be connected to the network through withdrawal, indicating a potential role of cigarette smoking in enhancing cannabis withdrawal symptoms. Furthermore, there were gender differences in the network associations of mood and anxiety disorders with CUD symptoms.

Conclusion. The association between smoking and withdrawal as well as gender differences in the role of comorbidities in the CUD network highlight the value of using network models to understand CUD and how symptom interactions might affect treatment.

Introduction

Men compared to women use cannabis at almost double the rate (UNODC, 2019). However, cannabis use in women is increasing (Colell et al., 2013), paralleling the increasing legalization of cannabis use in multiple countries and US states (SAMHSA, 2018; UNODC, 2019). Studies are suggestive of gender differences in both the acute effects of cannabis (Fogel et al., 2017; Matheson et al., 2020; Sholler et al., 2020) – with women usually showing larger subjective responses to similar doses of THC – and the withdrawal symptoms when ceasing cannabis use (Cuttler et al., 2016; Schlienz et al., 2017) – with women reporting more nausea and anxiety and men reporting more sleep-related withdrawal symptoms (Bassir Nia et al., 2018; Khan et al., 2013). Also, while psychiatric comorbidities are highly prevalent (>90%) in men and women (Khan et al., 2013), women are more likely to report comorbid anxiety and mood disorders, specifically. Furthermore, women appear to transition more quickly from first use to cannabis use disorder (CUD; Khan et al., 2013). Taken together, these differences could affect prevention and treatment efforts and highlights the importance of research into gender differences in cannabis use and CUD.

CUD is responsible for the most treatment entries for illicit Substance Use Disorders (SUDs) worldwide (UNODC, 2018a). While CUD treatment efforts are unsuccessful for most, research into evidence-based CUD treatment is still limited (Gates et al., 2016). In response to the limited effective treatment for mental health problems including CUD (24-35% abstinence after 6 months; Denis et al., 2006; Hoch et al., 2013), research interest has been shifting towards a symptom network approach. Rather than focusing on a general clinical diagnosis, the network theory of mental disorders (Borsboom, 2017) proposes that individual symptoms and their interaction are crucial components in understanding the development and maintenance of mental disorders. Instead of viewing all symptoms as originating from a common cause, the mental disorder, symptoms should be studied as entities that interact with each other in causal ways giving rise to mental health problems. These interactions between symptoms can be seen as a network in which the nodes represent the symptoms, and the edges represent the association between pairs of symptoms (accounting for the presence of all other symptoms). The structure of the network as well as the weight of the connections between symptoms could provide valuable insights into the development of mental disorders, how they can effectively be treated, and even how treatment could be tailored to an individual using idiographic network models (e.g., Howe et al., 2020).

This theoretical transition from diagnosis to symptoms is also reflected in the increasing number of studies using network models to assess mental disorders, such as depression (Hoorelbeke et al., 2016), psychosis (van Rooijen et al., 2017),

and common comorbidities between psychopathologies (Fried et al., 2017; Isvoranu et al., 2021). However, while rapidly increasing, the number of studies assessing the symptom networks in SUDs is currently limited and the evidence base is too small to inform treatment. Rhemtulla et al. (2016) applied network models to substance abuse and dependence symptoms of a variety of substances, including cannabis, in a large sample of adult twins that used at least one illicit substance a minimum of six times in their life (Rhemtulla et al., 2016). Across substances, *using more than planned* was the most central symptom, also showing a strong association with *tolerance*. However, there were substantial differences between substances in both edge weight between symptoms and centrality of specific symptoms in the network. Looking at cannabis, there was a strong association between *inappropriate timing of use, the time it takes to use and recover from it,* and *the interference of use with work and other obligations*. While this study showed the feasibility of using a network approach in assessing CUD symptoms, replication using the most recent DSM-5 CUD symptoms as well as the assessment of the potentially crucial role of gender is needed. With the previous differentiation between cannabis abuse and dependence symptoms in the DSM-IV, men reported more symptoms of abuse than women, but no differences emerged in symptoms of dependence (Khan et al., 2013). Now that the DSM-5 forgoes the differentiation between abuse and dependence, it is important to assess whether gender differences in CUD symptoms are still present.

The current study aimed to explore gender differences in CUD symptoms using a network approach in Dutch individuals that used cannabis at least once per week during the last year. First, we constructed a network including the 11 items of the Mini International Neuropsychiatric Interview (MINI) DSM-5 interview to assess the interaction between symptoms of CUD. Second, we assessed whether men and women differed in the prevalence of specific symptoms. Third, we assessed potential gender differences in the symptom networks as well as differences in pairwise symptom associations and measures of centrality. Fourth, analyses were run to assess the role of plans to quit or reduce cannabis use, daily cigarette use (particularly common in Dutch individuals that use cannabis; e.g., van Laar et al., 2020), and comorbid mental health problems in the CUD symptom networks in both men and women. As most previous studies were conducted in dissimilar samples (e.g., in countries with cannabis legislation incomparable with Dutch legislation), using different measures (e.g., DSM-IV instead of DSM-5), and not assessing the complex associations between CUD symptoms, cigarette use, and mental health problems in both men and women, all aims of this study were treated as exploratory.

Methods

Sample

Data was collected online as part of the screening process for an MRI study on CUD. All procedures were approved by the ethics committee of the department of psychology of the University of Amsterdam (2018-DP-9616). The Dutch-speaking participants, all between 18-30 years old and living in the Netherlands at the moment of assessment, were only included if they consented to the storage and use of the screening data, indicated using cannabis at least once a week during the last year, and identified as either man or woman. A total of 1257 individuals (59.3% men) met these inclusion criteria.

Table 1

DSM-5 MINI Cannabis Use Disorder (CUD) Symptoms

Label	Description	Item
UseMore	Use more	During times when you use the drug, did you end up using more cannabis than you planned when you started?
RedQuit	Reduce or quit attempt	Did you repeatedly want to reduce or control your cannabis use? OR* Did you try to cut down or control your cannabis use but failed?
Time	Time investment	On the days that you used cannabis, did you spend substantial time obtaining cannabis, using it, or recovering from its effects?
Crave	Craving	Did you crave or have a strong desired or urge to use cannabis?
Respon.	Responsibilities	Did you spend less time meeting your responsibilities at work, at school or at home, because of your repeated cannabis use?
Social	Social effects	If your cannabis use caused problems with your family or other people, did you still keep on using it?
Risky	Risky use	Did you use cannabis more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?
Health	Health effects	Did you continue to use cannabis, even though it was clear that the cannabis has caused or worsened psychological or physical problems?
Activ.	Less activities	Did you reduce or give up important work, social or recreational activities because of your cannabis use?
Toler.	Tolerance	Did you need to use cannabis a lot more in order to get the same effect that you got when you first started using it or did you get much less effect with continues use of the same amount?
Withd.	Withdrawal	When you cut down on heavy or prolonged use of the drug, did you have any of the following withdrawal symptoms?

Note: * Both questions were asked as separate items and later score according to the scoring guidelines.

Measures

Qualtrics online questionnaire software was used. Age and gender ('What is your gender?'; answers: man, woman, other (non-binary, not further specified)) were assessed and a digitalized Dutch version of the DSM-5 CUD section of the MINI 7.0.2 (American Psychiatric Association, 2013a; Sheehan et al., 1997) was administered to

assess 11 CUD symptoms (Table 1). Participants also reported the average number of days per week they used cannabis over the last year, whether they had plans to either quit or reduce cannabis use, and whether they used cigarettes on a daily basis (yes/no). To assess additional substance use for descriptive purposes, participants completed the alcohol use disorder identification test (AUDIT; Saunders et al., 1993), and self-reported their lifetime use of any other substance (excluding alcohol, cigarettes and cannabis). To assess history of mental health problems, participants reported lifetime diagnoses of any psychological disorder. Disorders that fit within the categories of mood disorder (dysthymia, depression & bipolar disorder), anxiety disorder (social anxiety, generalized anxiety disorder, OCD & PTSD) or externalizing disorder (ODD, ADHD & ADD) were included in the analysis.

Data analysis

Gender differences on all measures were assessed using Mann-Whitney U tests (violation of normality assumption) or chi-square tests (categorical variables) using JASP 0.14.1.0 (JASP Team, 2020). All other analyses were performed with R version 4.0.2 and 4.2.0 (R Core Team, 2020). Network analysis was performed for the full sample and separately for men and women with the eLasso method and the Ising model using the R package Bootnet (Epskamp et al., 2018; default = "IsingFit"). Model selection was based on the Extended Bayesian Information Criterion (EBIC) with gamma = 0.25 and the AND-rule. Strength centrality was estimated with the R package qgraph (Epskamp et al., 2012). Bootstrapped confidence intervals (1000 bootstraps) were used to investigate accuracy of edge-weights (Appendix B - Figures S2-S7), case-dropping bootstraps (1000 bootstraps) were used to investigate the stability of strength centrality (Appendix B - Figures S8-S10), and bootstrapped difference tests (1000 bootstraps) were used to test for significant differences between edges within the same network (Appendix B - Figure S11; Epskamp et al., 2018). To test for gender differences in the network structure, global strength, strength of all nodes, and weight of all edges, we performed a network comparison test with the R package NetworkComparisonTest (van Borkulo et al., 2017; 1000 iterations, gamma = 0.25, AND-rule). Two participants with missing data on the variables "plan to reduce" and "plan to quit" were excluded from the network analyses including these variables. All analyses should be considered exploratory in nature.

Table 2. Sample Characteristics

Measure		Women (N = 512)		Men (N = 745)		Total (N = 1257)		
		M (SD)	Mdn	M (SD)	Mdn	M (SD)	Mdn	Comparison test
General	Age	21.8 (3.2)	21	21.6 (3.1)	21	21.7 (3.1)	21	U = 184529.50, p = .32
Cannabis use	CUD severity score	4.7 (2.9)	4	5.2 (3.0)	5	5.0 (3.0)	5	U = 209065.50, p = .004
	Last year days per week	5.1 (2.1)	6	5.5 (1.8)	6	5.3 (1.9)	6	U = 210461.50, p < .001
	Plans to reduce	N = 270 (52.7%)		N = 409 (54.9%)		N = 679 (54.0%)		X^2(1, N = 1255) = .65, p = .42
	Plans to quit	N = 59 (11.5%)		N = 114 (15.3%)		N = 173 (13.8%)		X^2(1, N = 1255) = 3.72. p = .05
Other substance use	Daily cigarette use	N = 317 (61.9%)		N = 472 (63.4%)		N = 789 (62.8%)		X^2(1, N = 1257) = .27, p = .60
	AUDIT score	7.2 (4.9)	6	8.4 (5.7)	7	7.9 (5.4)	7	U = 211899.50, p < .001
	Other substance use	76.3 (204.1)	20	112.9 (573.8)	22	98.0 (460.8)	21	U = 201795.00, p = .08
Mental Health	Mood disorder	N = 143 (27.9%)		N = 96 (12.9%)		N = 239 (19.0%)		X^2(1, N = 1257) = 44.60, p <.001
	Anxiety disorder	N = 97 (19.9%)		N = 30 (4.0%)		N = 127 (10.1%)		X^2(1, N = 1257) = 74.36, p < .001
	Externalizing disorder	N = 95 (18.6%)		N = 159 (21.3%)		N = 254 (20.2%)		X^2(1, N = 1257) = 1.46, p = .23

Note: AUDIT = alcohol use disorder identification test; CUD = cannabis use disorder; M = mean; Mdn = median; SD = standard deviation

Results

Sample characteristics

On average, participants used cannabis 5.3 days per week (SD = 1.9; Table 2). Their average CUD severity score was 5.0 (SD = 3.0), indicative of moderate CUD. Men scored higher on CUD severity, cannabis use days per week, and alcohol use and related problems (AUDIT). Women were more likely to have self-reported diagnoses of mood and anxiety disorders (Table 2).

CUD symptom network

Figure 1A represents the full sample symptom network in which the nodes represent all MINI CUD symptoms and edges represent partial associations (controlled for all other associations) between those symptoms. The network was dense (mean weight = .37), with 43 non-zero edges over 55 possible edges. As can be seen from the edges, *craving* was associated with several other symptoms including *unsuccessful quit attempts*, *withdrawal*, *tolerance*, *time spent on use* and *social effects*. Furthermore, there was an association between *using more than planned* and having experienced *unsuccessful quit attempts*. While most symptoms were closely interconnected and similarly central based on strength, *tolerance* and *risky use* were less interconnected. *Risky use* was connected to the rest of the network solely through *social effects*, *health effects* and *responsibilities*, while *tolerance* had the strongest direct relationship with *craving*. This was also reflected in the lower strength of *tolerance* and *risky use* (Appendix B - Figure S1A).

Table 3

Gender Differences in Reported Cannabis Use Disorder Symptoms

Symptom		Women (N = 512)	Men (N = 745)	Comparison test	Result	Total (N = 1257)
		N (%)	N (%)			N (%)
1	Use more	273 (53.3%)	385 (52.2%)	χ^2 = (1, N = 1257) = 0.15, p = .74	M ≈ W	662 (52.7%)
2	**Reduce or quit**	**270 (52.7%)**	**437 (58.6%)**	**χ^2 = (1, N = 1257) = 4.33, p = .04**	**M > W**	707 (56.2%)
3	**Time investment**	**194 (37.9%)**	**333 (44.7%)**	**χ^2 = (1, N = 1257) = 5.78, p = .02**	**M > W**	527 (41.9%)
4	Craving	340 (66.4%)	512 (68.7%)	χ^2 = (1, N = 1257) = 0.75, p = .39	M ≈ W	852 (67.8%)
5	**Responsibilities**	**201 (39.3%)**	**369 (49.5%)**	**χ^2 = (1, N = 1257) = 12.92, p < .001**	**M > W**	570 (45.3%)
6	**Social effects**	**126 (24.6%)**	**244 (32.8%)**	**χ^2 = (1, N = 1257) = 9.69, p = .002**	**M > W**	370 (29.4%)
7	**Risky use**	**56 (10.9%)**	**154 (20.7%)**	**χ^2 = (1, N = 1257) = 20.66, p < .001**	**M > W**	210 (16.7%)
8	Health effects	230 (44.9%)	320 (43.0%)	χ^2 = (1, N = 1257) = 0.48, p = .49	M ≈ W	550 (43.8%)
9	Less activities	114 (22.3%)	174 (23.4%)	χ^2 = (1, N = 1257) = 0.20, p = .65	M ≈ W	288 (22.9%)
10	**Tolerance**	**331 (64.6%)**	**559 (75.0%)**	**χ^2 = (1, N = 1257) = 15.83, p < .001**	**M > W**	890 (70.8%)
11	Withdrawal	263 (51.4%)	367 (49.3%)	χ^2 = (1, N = 1257) = 0.54, p = .46	M ≈ W	630 (50.1%)

Note: N and percentages reflect the number and the percentage of individuals that reported experiencing the presented symptom; Bold text reflects the symptoms with significant gender differences; M = Men, W = Women.

CUD symptoms in men and women

Men and women were equally likely to report *using more than planned* (1), *reducing or giving up activities* (9), and *experiencing craving* (4), *health problems* (8), or *withdrawal symptoms* (11; Table 3). However, men more often reported *unsuccessful attempts to reduce or quit use* (2), *a substantial time investment* (3), *less time spend on responsibilities* (5), *social effects* (6), *risky use* (7), and *tolerance* (10).

Gender differences in CUD symptom networks

Estimated CUD symptom networks of men (Figure 1D) and women (Figure 1C) were similar; they did not differ in structure (M = 0.60, p = .94), global strength (S = 0.11, p = .97) or centrality (strength: lowest p-value = .19; Appendix B - Figure S1B & S1C). Like the network including the full sample, the networks were dense (men: mean weight = 0.34, 38 non-zero edges over 55 possible edges; women: mean weight = 0.34, 37 non-zero edges over 55 possible edges; all edge weights presented in Appendix B - Table S1). Most associations appeared similar between genders, except for *tolerance*; for men *tolerance* was connected through *craving, time investment* and *responsibilities*, while in women *tolerance* was connected through *using more than expected, less activities,* and *craving*. When comparing specific edges between genders, there only appeared to be one significant difference in the association between *time investment* and *tolerance* (p = .02); while there was a direct association between *tolerance* and *time investment* in men, even after controlling for the presence of all other associations, this association was not observed in women.

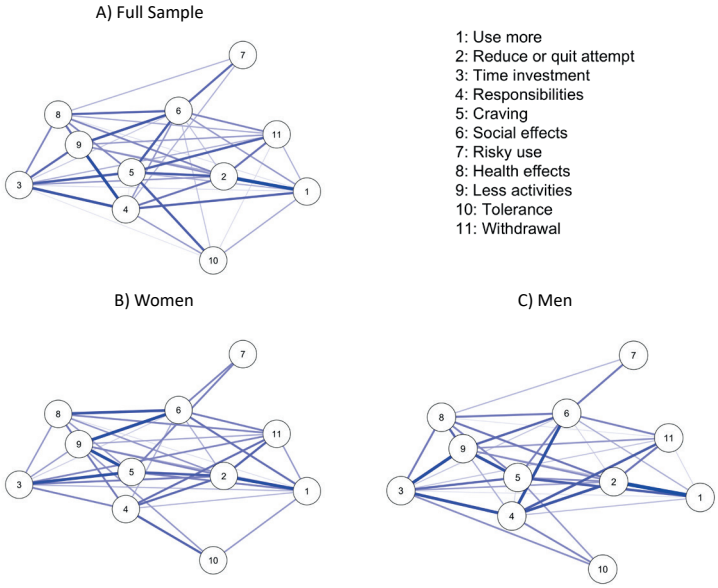


Figure 1. Cannabis use disorder (CUD) symptom networks. Nodes represent the eleven MINI CUD symptoms. The edges represent their positive associations, controlled for all other associations. Edge width and saturation reflect edge weight. To improve comparability, edge width and saturation were scaled to the largest edge weight across the three networks (edge weight = 1.141). The average of the Spring layout of the men and women networks were used to plot all networks to improve network comparability and visibility. N = 1257.

CUD symptoms, comorbidity, and plans to reduce or quit networks: gender differences

Network analyses showed that *cigarette use* was associated with the CUD symptom network through *withdrawal* and *time investment*, a potential effect of the co-occurrence of nicotine dependence in these individuals (Figure 2A). *Plans to quit* and *plans to reduce* were related to each other but differentially connected to symptoms. *Plans to reduce* were primarily related to previous *unsuccessful attempts to reduce or quit*, while *plans to quit* were more consistently associated with real-life outcomes of heavy use, such as *health problems, less activities, social effects,* and effects on *responsibilities*. The presence of *externalizing disorders* was not connected to the network. The presence of *mood disorders* was connected primarily through *withdrawal* and was connected to the presence of *anxiety disorders*, which in turn was only connected to the CUD network through *mood disorders*.

Comparing these networks across genders (Figure 2B-2C), while *daily smoking* was only connected to the network in men, this did not constitute a significant difference between genders ($p = .77$). The connection of *anxiety* and *mood disorders* with the network

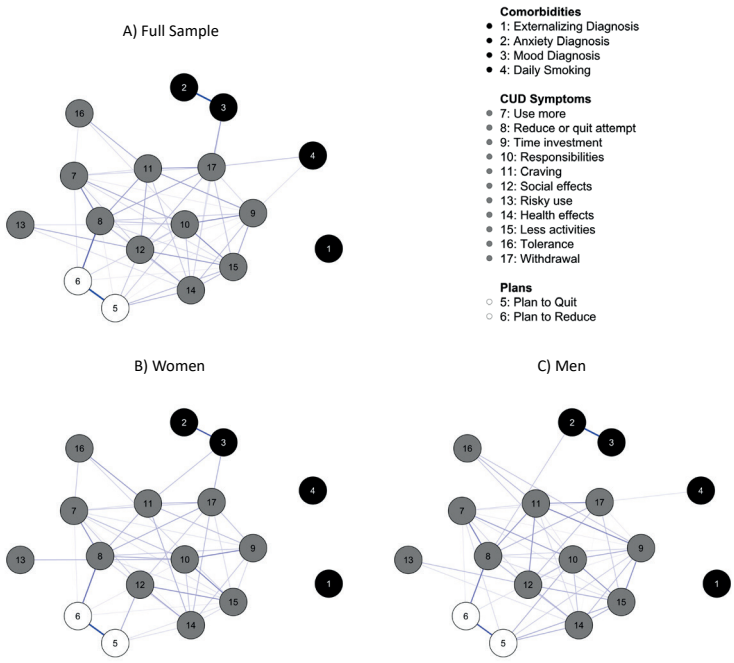


Figure 2. Cannabis use disorder (CUD) symptom networks including exploratory variables. Nodes represent the eleven MINI CUD symptoms and additional exploratory variables. The edges represent their positive associations, controlled for all other associations. Edge width and saturation reflect edge weight. To improve comparability, edge width and saturation were scaled to the largest edge weight across the three networks (edge weight = 2.039). Different node colors represent different groups of variables (CUD symptoms, comorbidities, and plans). The average of the Spring layout of the men and women networks was used to plot all networks to improve network comparability and visibility. N = 1255.

did differ between men and women. In men, *anxiety* was connected to *unsuccessful reduce or quit attempts* while this was not the case in women (significant difference, p = .004). Also, in men, *mood disorders* were only connected to CUD symptoms through their association with *anxiety*, while the reverse was true for women, in which *anxiety* was only related to CUD symptoms through its association with *mood disorders*. *Mood disorders* in women connected to the rest of the network differently than anxiety did in men. The direct associations were with *craving* (significant difference, p = .03) and *withdrawal* (no significant difference, p = .23). In these models, the difference in the association between *time investment* and *tolerance* was still significant (p = .006). Additional differences were observed in the associations between *responsibilities* and *risky use* (p = .04) and between *less activities* and *tolerance* (p = .03), which were only present in women, and in the association between *craving* and *social effects* (p = .04), which was only present in men. When correcting results for multiple comparisons

with the Holm–Bonferroni method, the gender difference in the relationship between *anxiety* and *unsuccessful reduce or quit attempts* remained significant (all edge weights presented in Appendix B - Table S2).

Discussion

We evaluated the associations between DSM-5 CUD symptoms in individuals reporting weekly cannabis use using a network approach, with a specific focus on gender differences. While several symptoms were more commonly reported by men than women, the pattern and strength of the associations between symptoms appeared similar between genders. However, exploratory analyses assessing the association of comorbid mental health problems with CUD symptoms did reveal gender differences; while the presence of *anxiety* and *mood disorders* were associated with each other in both men and women, the way they connected to the CUD symptom network was different.

The estimated CUD symptom network was dense, in line with a previous study assessing the DSM-IV CUD symptom network (Rhemtulla et al., 2016), and consistent between men and women. This density might theoretically affect the developmental trajectory of CUD; in denser networks, when one symptom occurs (e.g., *craving*) the pathology can more easily spread (i.e., other symptoms develop) through the network because the initial symptom is connected to many other symptoms (e.g., Borsboom & Cramer, 2013). Centrality was similar for most symptoms, except *risky use* and *tolerance*. *Tolerance* was primarily associated with other symptoms through *craving*, which could indicate that while there are reciprocal connections between *craving* and *tolerance*, *tolerance* mainly affects other symptoms through *craving*. *Risky use*, a former DSM-IV criteria of abuse rather than dependence, was only connected to the rest of the network through *responsibility*, *social effects*, and *health effects*. Consequently, individuals reporting risky cannabis use could represent a clinically relevant sub-group. Of note, only 16.7% reported *risky use* (Table 3). Dutch young adults (mean age = 21.7) may encounter limited situations in which *risky use* would occur (e.g., due to lack of car ownership), warranting replication in other countries, including samples with a wider age range.

Men over-reported six out of eleven MINI CUD symptoms compared to women, while total CUD scores differed less than one point on average (Table 2). Interestingly, while symptom prevalence differed, symptom networks did not; when present, the symptoms interacted in the same way in men and women. So, while this could indicate that the CUD symptom network is activated through different symptoms, and that different symptoms might pose early warning signs for CUD in men and women, symptoms appear to interact in similar ways. As the network is dense and interconnected in both men and women, targeting treatment to those symptoms that

are central and pose the biggest daily life problem for a specific individual will likely also help diminish other symptoms (e.g., Borsboom & Cramer, 2013).

Plans to reduce or *quit*, which might trigger seeking treatment, were related to each other. Having *plans to reduce*, was associated to the network through *unsuccessful attempts to quit* – potentially indicative of a lack of self-efficacy in quitting, but a persistent willingness to reduce use. *Plans to quit* were associated with the network through several symptoms that are indicative of daily life negative effects (i.e., *social effects, health effects, less activities,* and affected *responsibilities*) – potentially initiating the desire to quit (e.g., Copersino et al., 2006; Terry-McElrath et al., 2008).

Given the high co-occurrence in individuals that use cannabis (Connor et al., 2013), we assessed how daily cigarette smoking and the presence of mood disorders, anxiety disorders, and externalizing disorders were associated with CUD symptoms. *Cigarette* use was primarily related to the network through *withdrawal*, an association that might arise from associated nicotine withdrawal. While further investigation into different types of withdrawal symptoms and how they associate with CUD symptoms in individuals that also report using cigarettes is crucial, our results highlight the importance of considering cigarette smoking in treatment for CUD to potentially prevent withdrawal-related return to use. Further research is needed to assess whether simultaneous cessation negatively affects the chance one returns to use (e.g., Vandrey et al., 2008) or not (e.g., Apollonio et al., 2016). Notably, when looking at both men and women separately, *daily smoking* was connected to *withdrawal* only in men, but gender differences were not significant.

Looking at comorbidities, *externalizing disorders* were very prevalent (20.2%) but did not relate to the CUD symptom network. This indicates that individuals reporting weekly cannabis use who have an externalizing disorder are not more or less likely to report one or more CUD symptoms compared to other individuals reporting weekly cannabis use. While having an externalizing disorder might be a risk factor for heavy cannabis use and CUD (e.g., Farmer et al., 2015), within a group of individuals reporting weekly cannabis use, externalizing disorder presence may not influence CUD symptoms.

The prevalence of both *mood* (women: 27.9%; men: 12.9%) and *anxiety disorders* (women: 19.9%; men: 4.0%) was higher in women than men. Depression and anxiety were related to each other in both genders, but the way they were associated with the CUD symptoms differed. In men, *anxiety disorders* were related to CUD symptoms through unsuccessful attempts to reduce or quit, which could increase anxiety but could also be increased by anxiety (i.e., possible feedback loop). *Mood disorders* were only related to CUD symptoms through anxiety disorders in men. In contrast, in women, depression was associated with CUD symptoms through *craving* and *withdrawal*, while

anxiety only related to the rest of the network through *mood disorders*. This could indicate potential gender-specific self-medication mechanisms (e.g., Levin et al., 2010). Since using to reduce anxiety or depressive feelings is part of the withdrawal spectrum, these associations could be indicative of a self-medication feedback loop between mood disorders/anxiety and using to feel better, which in turn also affects craving and additional CUD symptoms. Nevertheless, research into specific withdrawal symptoms is crucial to unravel these mechanisms.

Some limitations should be noted. First, the MINI DSM-5 CUD semi-structured interview (Sheehan et al., 1997) is not validated for use as an online self-report. While this warrants clinical validation, assessment of the DSM-5 CUD symptoms through online self-report can be highly informative as large-scale data collection is not feasible in in-person interview settings. Second, the current sample is a convenience sample and large samples based on set criteria that ensure matching on most variables are needed to confirm our results. Third, splitting the data by gender did affect our sample size, which resulted in two smaller groups of unequal size. However, sample size differences were not large enough to justify concerns with regards to the network comparison test results. Furthermore, we identified stable edges in women that were not present in men (Appendix B - Figures S2-S7), making it unlikely that sample size affected our outcomes. Nevertheless, the relatively small sample size of the subgroups made it unfeasible to test more complex models in which continuous levels of other drug use and AUDIT scores could be added. Future studies with sufficient power should assess how CUD symptoms are associated with a wider range of substances, including more detailed assessments of substance use and related problems. Fourth, individual time series data is needed to further assess and confirm the proposed development of symptomology based on current results. Finally, while our results can be important to guide future hypotheses, our study was exploratory, and the findings should be treated as such.

Conclusions

Our study shows that CUD symptoms are highly interconnected and that while there are gender differences in prevalence of symptoms, the symptoms interact with each other in similar ways in men and women. However, gender differences in how comorbidities are associated with CUD symptoms as well as the association between cigarette use and withdrawal symptoms highlight the importance of further research into complex associations between these factors to inform clinical practice.

Chapter 6

The role of sex in the association between cannabis use and working memory related brain activity

This chapter is based on:
Kroon, E., Kuhns, L. N., Kaag, A. M., Filbey, F., & Cousijn, J. (2022). The role of sex in the association between cannabis use and working memory related brain activity. *Journal of Neuroscience Research, 100*(6), 1347-1358. https://doi.org/10.1002/jnr.25041

Abstract

Although cannabis use patterns differ between men and women, studies on sex differences in the effects of cannabis on the brain and cognitive control are largely lacking. Working memory (WM) is a component of cognitive control believed to be involved in the development and maintenance of addiction. In this study, we evaluated the association between cannabis use and WM-(load)-related brain activity in a large sample, enabling us to assess sex effects in this association. The brain activity of 104 frequent cannabis users (63% men) and 85 controls (53% men) was recorded during an N-back WM task. Behavioral results showed a significant interaction between WM-load and group for both accuracy and reaction time, with cannabis users showing a relatively larger decrease in performance with increasing WM-load. Cannabis users compared to controls showed a relatively smaller reduction in WM(-load)-related activity in the precuneus and posterior cingulate cortex at higher WM-load. This WM(-load)-related activity was not associated with performance nor cannabis use and related problems. An exploratory analysis in the cannabis group showed higher WM-related activity in the superior frontal gyrus in men compared to women. While cannabis users showed higher WM-(load)-related activity in central nodes of the default mode network, this was not directly attributable to group specific worsening of performance under higher cognitive load. Further research is necessary to assess whether observed group differences increase with higher cognitive load, how group differences relate to measures of cannabis use, and how sex affects these group differences.

Introduction

Although gender and sex differences in cannabis use are well-documented with twice as many men using as women (UNODC, 2019), sex differences in the association between cannabis use and the brain are rarely investigated. Cannabis is the most used illicit drug worldwide with about 192 million users in 2018 (UNODC, 2020). Since both animal and human research is primarily conducted with male animals and men, we are largely uncertain about the effects of cannabis on the approximately 64 million women that use cannabis every year.

As cannabis use among women is increasing, it is crucial to look into potential sex differences in the effects of cannabis (Colell et al., 2013). Research shows sex differences in the preferred route of administration (Cuttler et al., 2016), physiological effects of THC (Sholler et al., 2020), self-reported intoxication (Cuttler et al., 2016; Fogel et al., 2017; Matheson et al., 2020), and type of withdrawal symptoms (Cuttler et al., 2016; Schlienz et al., 2017). Also, comorbidities in individuals with a cannabis use disorder (CUD) differ between men and women (Bassir Nia et al., 2018; Khan et al., 2013) and women transition from first use to CUD faster (Khan et al., 2013), which could warrant different prevention and treatment approaches.

Differences in the development of CUD may be partially guided by biological sex differences in the endocannabinoid system (Bassir Nia et al., 2018; Calakos et al., 2017; Laurikainen et al., 2019). Although the direction of the effect is inconsistent and highly dependent on study design, CB1 receptor density and availability differ between males and females. For example, Laurikainen et al. (2019) found higher CB1 receptor availability in males, with higher availability associated with lower visuospatial working memory (WM) performance in both males and females (Laurikainen et al., 2019). Nevertheless, studies on sex differences in the association between cannabis and cognition are sparse and a sample bias towards men remains prominent in brain research.

Theories of addiction highlight the importance of cognitive control, including WM, in the development and maintenance of substance use disorders (Bickel et al., 2018). WM is the short-term memory storage that enables us to flexibly use, update, and manipulate information needed to make decisions, and is reliant on fronto-parietal brain activation (Owen et al., 2005). The N-back task is commonly used to assess WM-related brain activity but results regarding the effects of cannabis therein are inconsistent. Hatchard et al. (2020) found increased activity in the right superior frontal gyrus (SFG) and temporal regions in cannabis users during a letter N-back task but found no behavioral differences in performance (Hatchard et al., 2020). On the other hand, Owen at al. (2020) found a positive urine test for THC to negatively relate to performance on the N-back task (using picture stimuli). Also, task-related brain

activation mediated the association between a positive test and task performance, while general measures of cannabis use were unrelated to performance and brain activity (Owens et al., 2019). These inconsistencies are also reflected in earlier research (Solowij & Battisti, 2008), in which some studies found associations between cannabis use and WM-related brain activity (Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2008) or connectivity (Ma et al., 2018), while others did not (Cousijn, Wiers et al., 2014; Jager et al., 2006). In studies that do find an association, increased activity in WM-related regions in cannabis users is often observed despite no performance difference (e.g., Cousijn, Wiers et al., 2014; Hatchard et al., 2020; Jager et al., 2006). This increase in activation is commonly interpreted as a compensation mechanism indicative of increased effort to maintain performance in cannabis users.

A primary concern with previous fMRI WM studies is small sample sizes, with most lacking balanced and sizable samples to assess sex differences, which could partly explain inconsistent finding between studies. To our knowledge, there are currently no studies that investigated the role of sex in WM performance and related brain activity in cannabis users, while sex differences in fronto-parietal functioning could play a considerable role in the faster transition from use to dependence in women (Calakos et al., 2017; Khan et al., 2013). A recent study did assess the role of sex in neuropsychological functioning in cannabis users, showing that sex differences could be domain specific with women outperforming men on visual recognition, but the reverse being true for attention and executive functions including spatial working memory (Savulich et al., 2021). Furthermore, a study in cocaine users examined the effect of sex on the association between use and WM performance and related activity in the prefrontal cortex (PFC; Cousijn et al., 2021). While they found no effect of sex or group on WM performance, both sex and group moderated PFC activity. Specifically, cocaine using women showed more WM-related middle frontal gyrus (MFG) activation than cocaine using men and non-drug using women showed less WM-related MFG activation than non-drug using men. Also, WM-related activity in multiple fronto-limbic areas was negatively associated with cocaine use in women only. These results are partially in line with an earlier neuroimaging meta-analysis suggesting women generally recruit more frontal and limbic structures during classic WM-tasks (Hill et al., 2014), providing evidence of sex-dependent PFC alterations in substance users.

In the current study, we combined three datasets with identical N-back tasks allowing us to evaluate the association between cannabis use and WM-related brain activity, with sufficient power to detect potential sex differences in this association. While we did not expect the employed N-Back task to reveal behavioral differences between the cannabis and control group, nor between men and women, we expected cannabis users to show increased WM-related activation in fronto-parietal regions

compared to controls. This hypothesis is in line with suggested compensatory mechanisms of increased effort in cannabis users. Expectations regarding the role of sex in the association between cannabis use and WM-related activity are highly speculative. Based on limited earlier research (Cousijn et al., 2021; Hill et al., 2014) we expected women to show increased WM-related activation in frontal regions with a more prominent effect in cannabis users.

Materials & methods

The current study combined data from three different fMRI studies using an identical letter N-back task to assess how cannabis use influences WM performance and related brain activity (see Appendix C - Figure S1 for additional study specific information). Procedures were approved by the medical ethical committee of the Academic Medical Centre of the University of Amsterdam (study 1, data also used in Cousijn, Wiers et al., 2014) and the ethical committee of the department of psychology of the University of Amsterdam (study 2: 2015-DP-6387, unpublished data; study 3: 2018-DP-9616, unpublished data). All participants provided informed consent before the start of the session and were financially compensated for their participation.

Participants

A total of 104 frequent cannabis users (63% men) and 85 never to sporadic using controls (53% men) were included. Cannabis users used 10-31 times per month for at least the previous year, while the controls used 0-50 times in their life with a maximum of 5 uses in the last year. Additional exclusion criteria were excessive other substance use, excessive alcohol use and a history of major psychological or medical problems (see Appendix C - Figure S1 for additional study specific exclusion criteria). Participants were requested to abstain from using drugs or alcohol 24 hours before the session. A urine screening was conducted to assess recent substance use and all who tested positive for a substance other than THC in the cannabis group were excluded.

Assessments

Cannabis use and cannabis use disorder severity

In all studies, severity of cannabis use was assessed using the cannabis use disorder identification test-revised (CUDIT-R; Adamson et al., 2010) and heaviness of use was assessed as grams of cannabis used per week. Furthermore, self-reported age of onset and last use were recorded. DSM-5 CUD severity was assessed in study 2 and 3 only, using the cannabis section of the Structured Clinical Interview for the DSM (First, 2015; study 2) or the CUD section of the Mini International Neuropsychiatric Interview 7.0.2 (Sheehan et al., 1997; study 3). As both measures reflect DSM-5 symptoms but are

not measured using the same methods and scale, scores will be analyzed separately for these studies.

Other substance use

In all studies, alcohol use and related problems were assessed with the alcohol use disorder identification test (AUDIT; Saunders et al., 1993). Average number of cigarettes per day was assessed and nicotine dependence was assessed using the Fagerström test for nicotine dependence (FTND; Heatherton et al., 1991). A substance use history questionnaire was used to measure self-reported lifetime use of other substances.

Sex

In study 1 and 2, sex was assessed with the question 'are you a man or a woman?' during a pre-inclusion phone screening. In study 3, participants were asked the following two questions: 'What is your gender?' (answers: man, woman, other) and 'What biological sex were you identified with at birth?' (answers: male, female, intersex/undetermined). Individuals with non-binary gender or a gender identification not matching their biological sex at birth were not included in any of the studies to clarify grouping criteria. As gender (identity) was not specifically assessed in all studies, the term *sex* will be used throughout this article. However, we must note that the reported difference between men and women may reflect biological as well as gender-related influences.

Other assessments

IQ was estimated using different methods: study 1 used the Dutch reading test for Adults (Schmand et al., 1991), study 2 used the matrix reasoning and similarities subscales of the fourth edition of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2012), and study 3 used the matrix reasoning and vocabulary subscale of the WAIS-IV. Scores were standardized before combining the data. The Beck's depression inventory (BDI-II; Beck et al., 1961) was used to assess depressive symptoms in all studies. Symptoms of trait and state anxiety were assessed using the State Trait Anxiety Inventory (STAI; Spielberger & Sydeman, 1994) in study 2 and 3 only.

N-back task

Blood oxygen level dependent (BOLD) signals were recorded during a letter N-back task. Blocks with three different N-back levels were included: 0-back (recognition), 1-back (low WM load) and 2-back (high WM load). During each trial, a capital letter was presented in the middle of the screen requiring a response: press the target

button when the letter is a target in the current block, otherwise press the non-target button. In the 0-back blocks, participants were instructed to press the target button when the letter 'X' was presented (recognition). In the 1-back blocks, participants were instructed to press the target button when the letter presented was the same as the letter in the last trial (low WM-load). In the 2-back blocks, participants were instructed to press the target button when the letter presented was the same as the letter presented before the previous trial (high WM-load). All blocks were repeated 4 times in a fixed order (2-back – 0-back – 1-back) resulting in a total of 12 blocks. Each block included 15 2-second trials (block duration 30 second) followed by a 5 second break with instructions for the next block (task duration 7 minutes). No feedback was provided during or after the task. The difference between 2-back trials and 0-back trials was used as a measure of the effect of WM and the difference between 2-back trials and 1-back trials was used as a measure of the effect of WM-load.

fMRI data acquisition

Study 1

Scanning was performed at the University Medical Center Amsterdam, using a 3T Intera MRI scanner (Philips Intera, Best, The Netherlands) with 8-channel SENSE head coil. High resolution structural scans were acquired for anatomical reference (T1 turbo field echo, TR = 9.60 s, TE = 4.60 ms, 182 slices, slice thickness = 1.20 mm, field of view (FOV) = 256 × 256 mm, voxel size = 1 × 1 mm, flip angle = 8°). During the N-back task, BOLD responses were recorded using a T2* single-shot echo-planar imaging (EPI) sequence (TR = 2.30 s, TE = 30 ms, 38 slices, slice thickness = 3 mm, inter slice gap = 0.30 mm, FOV = 220 x 220 mm, voxel size = 2.30 x 2.30 mm, flip angle = 80°).

Study 2

Scanning was performed at the Spinoza Centre for Neuroimaging at the University Medical Center Amsterdam, using a 3T Intera MRI scanner (Philips Intera, Best, The Netherlands) with 32-channel SENSE head coil. High resolution structural scans were acquired for anatomical reference (T1 turbo field echo, TR = 8.20 s, TE = 3.80 ms, 220 slices, slice thickness = 1 mm, FOV = 240 × 188 mm, voxel size = 1 × 1 mm, flip angle = 8°). During the N-back task, BOLD responses were recorded using a T2* single-shot EPI sequence (TR = 2 s, TE = 28 ms, 37 slices, slice thickness = 3 mm, inter slice gap = 0.30 mm, FOV = 240 x 240 mm, voxel size = 3 x 3 mm, flip angle = 76°).

Study 3

Scanning was performed at the Spinoza Centre for Neuroimaging at the University of Amsterdam, using a 3T Achieva MRI scanner (Philips Intera, Best, The Netherlands)

with 32-channel SENSE head coil. High resolution structural scans were acquired for anatomical reference (T1 fast field echo, TR = 8.20 s, TE = 3.70 ms, 220 slices, slice thickness = 1 mm, FOV = 240 × 188 mm, voxel size = 1 × 1 mm, flip angle = 8°). During the N-back task, BOLD responses were recorded using a T2* single-shot multiband accelerated (MB4) EPI sequence (TR = 0.55 s, TE = 30 ms, 36 slices, slice thickness = 3 mm, inter slice gap = 0.30 mm, FOV = 240 x 240 mm, voxel size = 3 x 3 mm, flip angle = 55°).

fMRI data preprocessing

Preprocessing was conducted using FSL FEAT (FMRIB's Software Library version 5.0.6, part of fMRI Expert Analysis Tool version 6.0) and non-brain tissue was removed using BET (Brain Extraction Tool). Preprocessing settings included regular-up slice timing correction, high-pass filtering (90s), MCFLIRT motion correction, spatial smoothing (5mm FWHM Gaussian kernel) and prewhitening. Functional scans were registered to the participants high resolution T1-weighted scan (BBR, 12DOF) and transformed to standard space (MNI-152) using FNIRT (FMRIB's non-linear registration tool). None of the participants showed excessive motion (max residual motion = 0.20 mm).

Data analysis

Sample characteristics

For all included questionnaire, means and standard deviations or medians (in case of violation of assumption of normality) per group and per sex within group were calculated using R (version 4.1.2; R Core Team, 2021) in RStudio (version 2021.9.2.382; RStudio Team, 2022). Chi-square tests (or Fisher's exact test when sample size was below five for any of the included cells) were used to compare group and sex differences in categorical variables. Additionally, the effect of group, sex, and their interaction on the included questionnaires with a continuous outcome was assessed using a linear mixed model approach with maximum likelihood estimation, random intercept and subject, sex and group as random variables to account for the grouping structure of the data.

N-back task performance

The effects of WM-load, group, sex, and their interactions on N-back task performance (accuracy (% correct) and reaction time (on accurate trials)) were assessed using a linear mixed model approach with maximum likelihood estimation, random intercept and subject and WM-load as random variables to incorporate repeated measures. All potential models (including at minimum WM-load, group, and

sex) were run and the model with the best fit was selected based on Akaike Information Criterion (AIC; lower AIC reflecting relatively better fit and ΔAIC > 2 (between models) indicating substantial support for relatively better fit; Burnham & Anderson, 2002).

fMRI data

As described in the preregistration (https://aspredicted.org/blind.php?x=uh4t82), first, a general linear model (GLM) analysis was conducted in FSL's FEAT adding the three different trial types, 0-back, 1-back, and 2-back, as regressors convolving them with a double gamma hemodynamic response function, which incorporates the undershoot before oxygen rich blood flow increases in a specific area into each regressor (Lindquist et al., 2009), and adding temporal derivates to improve model fit. The effect of WM (2back – 0-back) and the effect of WM-load (2back – 1back) on brain activity (BOLD response) were the primary contrasts of interest.

Second, whole brain mixed effects analyses (FLAME 1) were run in FSL FEAT, using cluster-wise multiple comparison correction ($Z > 3.10$, cluster-based $p < 0.05$) to assess the effects of group, sex, and their interaction on WM and WM-load related brain activity, while controlling for scanner/sequence differences by adding study as a regressor to the model.

Third, mean activations in significant clusters were extracted using FSL featquery to visualize the direction of the effects. Additionally, separate regression analyses were conducted to assess whether extracted activation within the significant clusters could be explained by accuracy (% correct) and reaction time (on accurate trials) on the N-back task or whether extracted activation (within the cannabis group) could be explained by severity or cannabis use (CUDIT-R score), heaviness of cannabis use (grams/week), or age of onset. Also, the moderating role of sex in these associations was assessed.

Results

Sample characteristics

Sex distribution ($\chi^2 = (2.14)$ ($N = 189$), $p = 0.14$) and handedness ($p = 0.41$; Table 1) did not differ between groups, but the cannabis group included more daily smokers than the control group ($\chi^2 = (13.19)$ ($N = 189$), $p < 0.001$; Table 1). The number of daily smokers ($\chi^2 = (0.04)$ ($N = 189$), $p = 0.84$) did not differ between men and women, but there were more left-handed women than men ($p = .04$).

Cannabis users scored higher than the controls on trait anxiety ($B = -4.87$, 95% CI = -9.29:-0.45, $p = 0.03$) and other substance use ($B = -21.63$, 95% CI = -39.29:-3.98, $p = 0.02$; Table 1). No other effects of group, sex, nor their interaction were observed for any of the outcomes (Appendix C - Table S1).

Table 1. Sample characteristics

Measures	Unit	Cannabis Group			Control Group		
		Total	Men	Women	Total	Men	Women
N (% of group)		104	66 (63%)	38 (37%)	85	45 (53%)	40 (47%)
Handedness	L/R	2/101	0/66	2/35[1]	4/81	1/44	3/37
Age	Median	22	22	21	22.50	22	22
Estimated IQ[2]	Mean (SD)	-0.16 (0.96)	-0.13 (0.95)	-0.21 (0.99)	0.19 (1.01)	0.30 (1.03)	0.06 (0.98)
Depression (BDI)	Med	6	6	6	4	4	4.50
State anxiety (STAI)[3]	Mean (SD)	33.44 (9.08)*	32.92 (9.43)	34.26 (8.59)	31.90 (6.31)*	31.10 (7.25)	32.73 (5.15)
Trait anxiety (STAI) [3]	Med	37	36	38	34	33	34
Alcohol use and related problems (AUDIT)	Med	6	6	5	5	6	3
Smoking	N(%)	54 (52%)	34 (52%)	20 (53%)	22 (26%)	10 (22%)	12 (30%)
Nicotine Dependence (FTND)	Med	2	2	2.50	0.50	0	1
Cigarettes/Day	Med	9	8	10	6	8	5
Other substance use	Med	12.50*	12.50	12.50	0*	0	0
Cannabis use and related problems (CUDIT-R)	Mean (SD)	13.56 (5.90)	13.48 (5.95)	13.68 (5.89)	-	-	-
CUD symptoms[4]							
Study 2	Mean (SD)	3.47 (1.60)	3.56 (1.65)	3.38 (1.59)	-	-	-
Study 3	Mean (SD)	5.27 (2.23)	5.10 (2.16)	5.60 (2.41)	-	-	-
Gram/Week	Med	3	3	2.5	-	-	-
Age of Onset	Median	15	15	15.5	-	-	-
Days since last use	Med	1	1	1	-	-	-

*Note: AUDIT: alcohol use disorder identification test; BDI: Beck's depression inventory; CUD: cannabis use disorder; CUDIT-R: cannabis use disorder identification test; FTND: Fagerström test for nicotine dependence; STAI: state trait anxiety inventory; [1] Missing handedness data for one participant; [2] Using standardized (Z) scores to compare studies; [3] STAI State & STAI Trait only assessed in study 2 and 3; [4] CUD scores separate for study 2 (SCID) and 3 (MINI) due to different measures used to assess DSM-5 CUD symptoms, study 1 did not assess CUD; Medians are reported when assumptions of normality were violated (as assessed using Shapiro-Wilk Normality tests); * p < 0.05.*

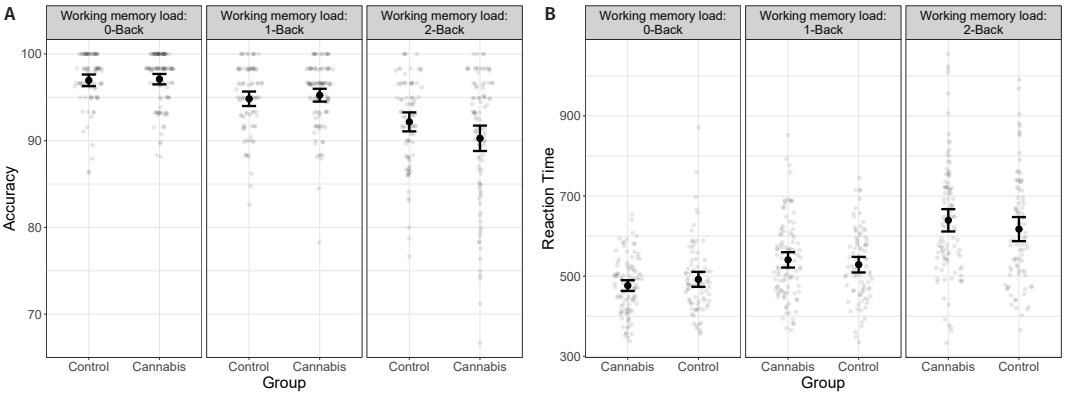


Figure 1. N-back task performance.

A) No group differences in mean accuracy on 0-back, 1-back and 2-back trials. Accuracy decreased with increasing working memory load and an interaction between group and working memory load was found.

B) No group differences in mean reaction times on 0-back, 1-back and 2-back trials. Reaction time increased with increasing working memory load and an interaction between group and working memory load was found. Error bars reflect standard error (SE) of the mean.

Table 2. Final models showing the effect of working memory (WM)-load on accuracy and reaction time during the N-back task

Model	Model coefficients					
	Fixed effects					Random effects
Accuracy	**B**	**95% CI (B)**	**SE (B)**	***t***	***p***	***SD***
(Intercept)	96.58	95.48 – 97.69	0.57	170.85	< 0.001	2.38
WM: 0-back - 1-back	-1.85	-2.95 – -0.75	0.56	-3.28	**0.00**	3.69
WM: 0-back - 2-back	-6.80	-7.90 – -5.70	0.56	-12.04	**< 0.001**	
Group	-0.05	-1.40 – 1.31	0.69	-0.07	0.95	
Sex	0.79	-0.19 – 1.78	0.50	1.58	0.12	
WM: 0-back - 1-back * Group	-0.28	-1.91 – 1.35	0.84	-0.34	0.74	
WM: 0-back - 2-back * Group	2.01	0.37 – 3.64	0.84	2.40	**0.02**	
Reaction Time	**B**	**95% CI (B)**	**SE (B)**	***t***	***P***	***SD***
(Intercept)	483.94	456.38 – 511.51	14.11	34.30	< 0.001	89.10
WM: 0-back - 1-back	61.94	44.78 – 79.11	8.78	7.05	**< 0.001**	56.78
WM: 0-back - 2-back	160.96	143.86 – 178.07	8.75	18.39	**< 0.001**	
Group	13.60	-17.89 – 45.10	16.07	0.85	0.40	
Sex	-10.49	-38.70 – 17.72	14.39	-0.73	0.47	
WM: 0-back - 1-back * Group	-22.35	-47.81 – 3.12	13.03	-1.71	0.09	
WM: 0-back - 2-back * Group	-32.55	-57.98 – -7.13	13.01	-2.50	**0.01**	

Mixed model results using random intercept and maximum likelihood estimation. WM: working memory; CI: Confidence Interval; SE: Standard Error; SD: Standard deviation; Other models ran as part of the model selection process can be found in Table S2 and Table S3. Accuracy: ΔAIC = 3.33; Reaction time: ΔAIC = 2.59.

Behavioral N-back results

As expected, accuracy decreased with increasing WM-load (Tukey post hoc: 0-back – 1-back: $p < 0.01$, 0-back – 2-back: $p < 0.001$, 1-back – 2-back: $p < 0.001$; Figure 1), but no main effect of group or sex was found (Table 2). However, there was a significant interaction between WM level and group (Table 2). Post hoc simple effects t-tests showed lower 2-back accuracy in cannabis users versus controls ($t(189) = -2.04$, $p = 0.04$). Adding the interactions of sex with WM-load and group, as well as the three-way interaction to the model did not reveal additional significant effects and did not improve model fit (Appendix C - Table S2).

Similar results were found for reaction time (RT) on accurate trials, where performance was found to be WM-load dependent with RT increasing with increasing difficulty (Tukey post hoc: 0-back – 1-back: $p < 0.01$, 0-back – 2-back: $p < 0.001$, 1-back – 2-back: $p < 0.001$; Figure 1; Table 2). No effect of sex or group was found, but there was an interaction between group and WM-load (Table 2). However, while the pattern was similar to the interaction effect found for accuracy, the post hoc simple effects t-tests showed that there were no significant group differences on any of the WM-levels (lowest p-value = 0.18). Adding the interactions of sex with WM-load and group as well as the three-way interaction to the model did not reveal additional significant effects and did not improve model fit (Appendix C - Table S3).

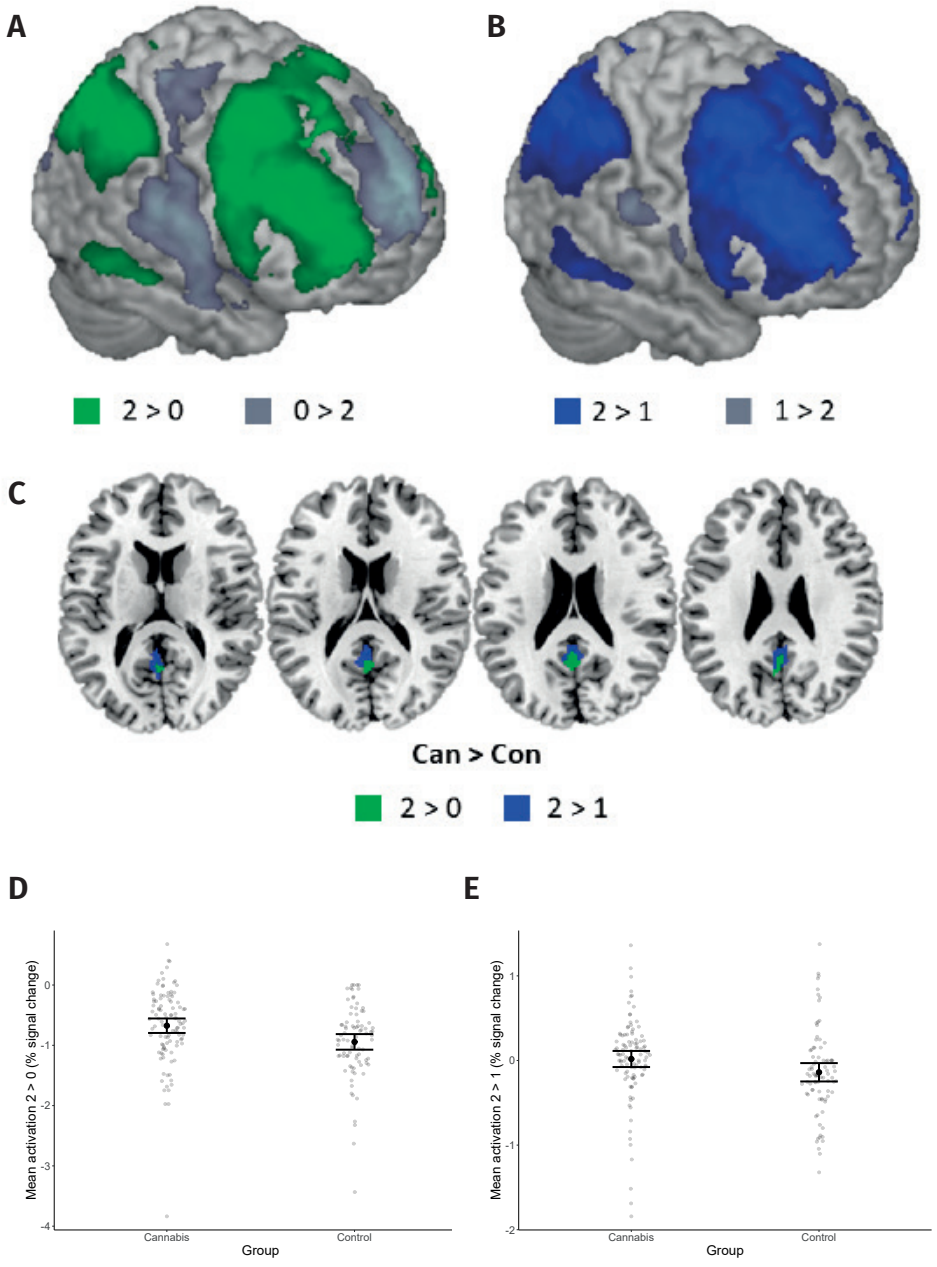


Figure 2. fMRI results. A) WM-related activation (2>0) across groups; B) WM-load-related activation (2>1) across groups; C) Group differences (Can > Con) in WM (2>0) and WM-load-related (2>1) activation. D) mean WM-related activation (2>0) extracted from the group difference cluster E) mean WM-load related activation (2>1) extracted from the group difference cluster. Error bars reflect standard error (SE) of the mean. WM: working memory; Can: cannabis group, Con: control group; 0: 0-back, 1: 1-back, 2: 2-back

fMRI N-back results: WM(-load) effects

Whole brain analysis revealed a clear pattern of WM (2>0 and 0>2; Figure 2A) and WM-load (2>1 and 1>2; Figure 2B) related activation. Higher WM load was associated with relatively higher activation in fronto-parietal regions known to be part of the central executive network and a relatively lower activation in default mode network regions including the precuneus and posterior cingulate cortex (PCC; Appendix C - Table S4).

Table 3. Group differences in WM and WM-load related activation

					MNI coordinates			
	Comparison	Cluster size (voxels)	Brain regions	Hemisphere	X	Y	Z	Zmax
WM effect								
2 > 0	Con > Can	ns	ns	ns	ns	ns	ns	ns
2 > 0	Can > Con	164	Precuneus	Mid	0	-60	16	4.18
			PCC	Left	-2	-50	24	4.09
WM-load effect								
2 > 1	Con > Can	ns	ns	ns	ns	ns	ns	ns
2 > 1	Can > Con	404	PCC	Mid	0	-50	22	4.75
			Precuneus	Left	-2	-58	14	4.53
			Lingual gyrus	Left	-4	-60	4	3.34

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 3.10$); WM: working memory; Can: cannabis group, Con: control group; 0: 0-back, 1: 1-back, 2: 2-back; PCC: posterior cingulate cortex.

fMRI N-back results: the effects of group, sex and their interaction

Cannabis users showed relatively higher WM-related and WM-load-related activity than controls in a cluster including the precuneus and PCC (Table 3; Figure 2C). Further inspection of the mean WM-related activation extracted from this cluster showed that while activation in these regions was lower during 2-back trials than 0-back trials in both groups, this difference was smaller in the cannabis group (Figure 2D). A similar but less pronounced pattern was observed for WM-load related activity, where the cannabis group showed similar activation for both trial types, but controls showed relatively lower activity in these regions on the more difficult 2-back trials compared to 1-back trials (Figure 2E). No effects of sex or the interaction between group and sex on WM(-load) related activation were found.

Within cannabis group association between measures of cannabis use and WM(-load) related activity

Mean WM(-load) related activation was not associated with cannabis use and related problems (CUDIT-R; WM: $R^2 = -0.00$, $F_{1,102} = 0.79$; N = 103, $\beta = -0.01$, p = 0.38; WM-load: $R^2 = -0.01$, $F_{1,102} = 0.01$; N = 103, $\beta < 0.001$, p = 0.92), grams of cannabis use per week (WM: $R^2 = -0.01$, $F_{1,101} = 0.58$; N = 102, $\beta = -0.01$, p = 0.58; WM-load: $R^2 = -0.01$, $F_{1,101}$

= 0.08; N = 102, β = 0.00, p = 0.78) or age of onset (WM: R^2 = 0.001, $F_{1,102}$ = 0.29, β = 0.04, p = 0.29; WM-load: R^2 = -0.01, $F_{1,101}$ = 0.26, β = 0.01, p = 0.61). Similarly, no association between activation and accuracy (WM, 2-0 accuracy: R^2 = 0.01, $F_{1,97}$ = 1.95; N = 98, β = -0.01, p = 0.17; WM-load, 2-1 accuracy: R^2 = 0.00, $F_{1,97}$ = 1.40; N = 98, β = -0.01, p = 0.24) or RT (WM, 2-0 RT: R^2 = -0.01, $F_{1,99}$ = 0.28; n = 100, β < 0.001, p = 0.60; WM-load, 2-1 RT: R^2 = 0.01, $F_{1,98}$ = 1.63; N = 99, β < 0.001, p = 0.21) on the N-back task was found in the cannabis group. In the control group, higher WM-related activation in these regions was associated with lower performance (WM, 2-0 accuracy: R^2 = 0.05, $F_{1,81}$ = 5.04; N = 82, β = -0.03, p = 0.03). However, these results were no longer significant (Table 1; (R^2 = 0.01, $F_{4,44}$ = 1.08; N = 48, β = -0.03, p = 0.05) after correcting for the variables that differed across groups (trait anxiety, smoking and other drug use). Additional analyses showed that sex did not moderate any of the associations between extracted activity and any of the cannabis or performance related variables (lowest uncorrected p-value = 0.11).

Table 4. Sex differences in WM and WM-load related activation in the cannabis group only

					MNI coordinates			
	Comparison	Cluster size (voxels)	Brain regions	Hemisphere	X	Y	Z	Zmax
WM effect								
2 > 0	Female > Male	ns	ns	ns	ns	ns	ns	ns
2 > 0	Male > Female	181	SFG	Right	26	2	64	4.00
WM-load effect								
2 > 1	Female > Male	ns	ns	ns	ns	ns	ns	ns
2 > 1	Male > Female	ns	ns	ns	ns	ns	ns	ns

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, Z > 3.10); Can = cannabis group, Con = control group; 0 = 0-back, 1 = 1-back, 2 = 2-back; SFG = superior frontal gyrus

fMRI N-back results: exploratory analysis of sex effects within the cannabis group

Non-planned exploratory whole brain analyses were performed to assess whether the effect of WM and WM-load related brain activity differed between men and women within the cannabis group. Analyses revealed that men (2>0; M = 0.74, SD = 0.53) show relatively higher WM related activation in the superior frontal gyrus (SFG) compared to women (2>0; M = 0.38, SD = 0.36), while there was no effect for WM-load related activation (Table 4). The increased activation could not be explained by cannabis use variables or performance (lowest uncorrected p-value = 0.25).

Discussion

The aim of the current study was to assess the effects of cannabis on WM and WM-load related brain activity and the potential role of sex in these effects. Results showed no sex effect on WM or WM-load related brain activity. However, cannabis users showed higher WM as well as WM-load related activity in the precuneus and PCC

compared to controls. This relative over recruitment of regions known to be central nodes of the default mode network could be indicative of a relatively smaller shift from default mode to executive control network activation with increasing difficulty (e.g., Bossong, Jansma et al., 2013; Danckert & Merrifield, 2018; Raichle, 2015).

Based on previous inconsistencies in the effect of cannabis use on WM performance, we hypothesized that there would be a general effect of WM-level but no effects of group on performance. Results showed a clear effect of WM-level with accuracy going down and reaction time going up with increasing difficulty. However, there was also an interaction between group and WM-level on performance, with more pronounced reduction in performance with increasing difficulty in cannabis users compared to controls. Although inconsistent with previous studies (e.g., Cousijn, Wiers et al., 2014; Hatchard et al., 2020), this is in line with the general expectation that current cannabis users experience problems with cognitive control related functions such as WM (e.g., Crean et al., 2011; Scott et al., 2018), which could be more pronounced when cognitive load increases. These results also indicate previous studies with smaller sample sizes (e.g., Hatchard et al., 2020; Jager et al., 2006; Kanayama et al., 2004) may have been underpowered to detect subtle 2-back group differences. As performance on 2-back trials is often close to ceiling, as can also be seen in the current study, it is also important to assess the effects of current cannabis use on performance under higher cognitive load.

The fMRI results showed a group difference in WM (2>0) and WM-load (2>1) related activation in the precuneus and PCC, with cannabis users showing relatively higher activation than controls. Both groups show higher activation in these regions on 0-back trials than on 2-back trials, but the relative reduction in activation as cognitive load increases is less pronounced in the cannabis group. The direction of the group difference was the same for WM-load related activity, but controls showed higher activation for 1-back than 2-back trials while activation was similar for both trial types in the cannabis group. While we expected relatively higher WM and WM-load related activation in the cannabis group, the specific regions in which these activation differences were found do not match our hypotheses. Cannabis users were expected to show increased fronto-parietal and not precuneus or PCC, activity as a compensatory mechanism to maintain performance (as proposed in e.g., Cousijn, Wiers et al., 2014; Hatchard et al., 2020; Jager et al., 2006). The precuneus and PCC are well-known nodes of the default mode network in which activity is expected to go down with increased cognitive effort (Raichle, 2015). Indeed, activity was relatively lower for 2-back than 0-back trials and also lower for 2-back trials than 1-back trials in controls. However, in the cannabis group, activity was comparable for 2-back and 1-back trials and the relative reduction in activity with increasing cognitive effort was

less pronounced. While higher default mode network activity during higher cognitive load could indicate reduced attention or effort (Danckert & Merrifield, 2018) and thereby potentially affect performance, activity was not predictive of performance in the cannabis group. Nevertheless, higher activity in these regions was associated with lower accuracy in the control group (before adding multiple control variables). This is in line with earlier results on executive functioning by Bossong, et al. (2013) in which task performance was negatively affected by THC and associated with reduced deactivation in regions of the default mode network (Bossong, Jansma et al., 2013). However, the THC induced reduction in performance was not associated with activation of fronto-parietal regions. Although results are not consistent across groups and findings should be treated with caution, it is worth investigating to what extent higher default mode network activation during cognitively demanding tasks, rather than altered fronto-parietal activation, affects performance.

No sex differences or interactions between sex and group in WM and WM-load related activation or performance were found. While using a different task, these results are in line with a recent study on response inhibition in cannabis users, where group differences in activity but no sex or group-sex interaction effects were found (Wallace et al., 2020). Although speculative, this lack of sex effects may indicate that the sex differences in cannabis use patterns and the development of CUD are not directly related to differences in cognitive control related processes. Nevertheless, evidence is limited, and research is warranted to replicate these findings and assess how sex differences in motivational processes rather than cognitive control related processes might relate to sex differences in cannabis use. However, it could also be the case that we were underpowered to detect more subtle interaction effects using a relatively strict whole-brain threshold. Hence, an additional whole brain analysis was conducted to assess sex differences within the cannabis group. Men showed higher WM-related activation than women in the SFG, a frontal region important in higher cognitive functions like WM (e.g., Ranganath et al., 2003; Rypma et al., 1999), while no sex difference was found for WM-load related activation. The direction of the observed effect is opposite from our expectations that WM-related frontal activation would be higher in women than men (Cousijn et al., 2021; Hill et al., 2014) and differences in activity did not relate to cannabis use or performance. These results should be treated with caution due to the exploratory nature of this analysis. While studies with sex comparisons in cannabis users focusing on cognitive control are largely lacking, activation in the SFG has regularly been found to differ between substance users and controls during cognitive tasks. For example, previous studies showed increased activation in the right SFG in cannabis users compared to controls during WM tasks (Kanayama et al. 2004; Hatchard et al. 2020), but another study found cannabis users

to display relatively lower activation in the SFG during learning (Nestor et al., 2008) and mixed directions of these effects have also been identified for other addictive behaviors (García-García et al., 2014; Hester & Garavan, 2004; Moreno-López et al., 2012). The SFG is apparently involved in cognitive functions including WM, but it is unclear in what way addictive behaviors, sex, and cognitive load affect its involvement.

While the sample size and mixed sex sample of this study are substantial advantages, there are several limitations that should be noted. First, cannabis users had higher anxiety scores than controls, but differences were relatively small and scores below clinical thresholds. Second, higher cigarette and substance use in the cannabis group could have affected the results; however, other drug use (Connor et al., 2014; UNODC, 2016) and mental health problems (e.g., Agosti et al., 2002) are more common among substance users than controls. Thus, a fully matched sample might not accurately reflect the cannabis using population. As there might also be substantial overlap in the underlying mechanisms and the causal effects of these substances on the brain, controlling for the existing differences in the analyses would also potentially obscure the effects of cannabis use. Third, while participants testing positive on other substances than cannabis were excluded, we were not able to verify the instructed 24h abstinence from alcohol and cannabis. Nevertheless, it seems unlikely that direct rather than indirect effects of cannabis would have affected the results as reaction times were similar between groups, which would not be expected in case of direct intoxication effects (Hartman & Huestis, 2013). Fourth, performance was relatively high on the most difficult 2-back trials and studies should be encouraged to increase WM-load to assess whether WM(-load) effects are more pronounced when cognitive demand increases. Fifth, in our study we were not able to differentiate between biological sex and gender effects. This is a clear limitation of most studies not initially designed for studying gender and sex effects and future studies should be specifically designed to make this differentiation. These studies should also aim to not exclude individuals with non-binary gender, but rather take gender into account as a more continuous measure (Heidari et al., 2016). Last, the design of our study is cross-sectional and longitudinal studies assessing the causal nature of the association between cannabis use and altered brain functioning are essential.

In conclusion, cannabis users showed poorer performance and a smaller reduction in activation in central nodes of the default mode network when cognitive load increased. Explorative analyses revealed higher WM-related SFG activity in cannabis-using men compared to women; however, sex effects were non-significant when the cannabis and control groups were both included. To further unravel the impact of cannabis use on brain and behavior, studies investigating tasks requiring higher cognitive demands, clinical populations, and longitudinal effects are needed.

Chapter 7

Context dependent differences in working memory related brain activity in heavy cannabis users

This chapter is based on:
Kroon, E., Kuhns, L., & Cousijn, J. (2022). Context dependent differences in working memory related brain activity in heavy cannabis users. *Psychopharmacology, 239*(5), 1373-1385. https://doi.org/10.1007/s00213-021-05956-y

Abstract

Rationale. Compromised cognitive control in cannabis use-tempting situations is thought to play a key role in the development of cannabis use disorders. However, little is known about how exposure to cannabis cues and contexts may influence cognitive control and the underlying neural mechanisms in cannabis users.

Objectives. Working memory (WM) is an attention reliant executive function central to cognitive control. In this study we investigated how distracting cannabis words affected WM load-dependent performance and related brain activity in near-daily cannabis users (N = 36) relative to controls (N = 33).

Methods. Brain activity was recorded during a novel N-back flanker WM task with neutral and cannabis flankers added as task-irrelevant distractors.

Results. On a behavioral level, WM performance did not differ between groups and the presence of cannabis flankers did not affect performance. However, in cannabis users compared to controls, the presence of cannabis flankers reduced WM load-related activity in multiple regions, including the insula, thalamus, superior parietal lobe, and supramarginal gyrus.

Conclusions. The group specificity of these effects suggest that cannabis users might differ from controls in the way they process cannabis related cues, and that cannabis cue exposure could interfere with other cognitive processes under cognitively demanding circumstances. Future studies should focus on the role of context in cognitive control related processes like WM and attention to further elucidate potential cognitive impairments in heavy cannabis users and how these relate to loss of control over drug seeking itself.

Introduction

Cognitive control deficits play an important role in substance use disorders (SUDs), including cannabis use disorders (CUDs); the inability to refrain from cannabis use in a tempting and arousing cannabis use related context is thought to support the development and maintenance of CUD (Goldstein & Volkow, 2011). Several studies indicated compromised cognitive control (Charles-Walsh et al., 2016; Cousijn, Watson, et al., 2013), hyperresponsivity to cannabis-related cues (e.g., Cousijn, Goudriaan, et al., 2013; Zhou et al., 2019), and altered functioning of the underlying brain areas (Kober et al., 2014) in cannabis users, however, relatively little is known about how these processes interact. The goal of this study was to investigate the influence of a distracting cannabis use related context on cognitive control in cannabis users.

Working memory (WM) is considered to be a central aspect of cognitive control and is essential for many higher-order cognitive processes (Unsworth & Engle, 2007). WM requires attention and involves the 'online' maintenance and manipulation of information. Multiple types of WM tasks have shown robust activation in a widespread network of frontal-parietal brain areas (Linden et al., 2003; Owen et al., 2005). While several studies have shown that cannabis intoxication and heavy cannabis use can impair WM performance, these impairments are not consistently found (Bossong et al., 2014; Schoeler & Bhattacharyya, 2013). Several functional magnetic resonance imaging (fMRI) studies have examined the relationship between heavy cannabis use and brain activity and connectivity during WM tasks. Although group differences in performance are rarely found, there is some evidence for differences in brain activity and WM network functioning (including primarily frontal and parietal regions; Owen et al., 2005). Multiple studies have found that, compared to controls, heavy cannabis users show increased activity in WM related areas (e.g., prefrontal cortex) and recruit additional areas that are not usually expected to play a crucial role in WM (e.g., subcortical areas involved in emotion and reward processes), without differences in WM performance (Kanayama et al., 2004; Smith et al., 2010). This over-recruitment is often interpreted as a compensation strategy needed in order to perform on a behaviorally similar level as controls (Bossong et al., 2014) and might be more prominent in early onset cannabis users (Becker et al., 2010). With regards to WM network functionality, stronger network response during an N-Back WM task is associated with an increase in cannabis use six months later (Cousijn, Wiers, et al., 2014), suggesting that individuals who require more network effort for accurate performance are more likely to escalate cannabis use over the following six months.

Based on most addiction theories (e.g., Koob & Volkow, 2010; Robinson & Berridge, 1993), strong fronto-limbic reward and emotion-related reactivity in response to cannabis cues and contexts in fronto-limbic brain areas would be expected to

interfere with fronto-parietal cognitive control related processes, biasing cognition towards cannabis use (e.g., craving, attentional bias, approach actions). Therefore, on a conceptual level, WM performance in tempting and challenging cannabis-related contexts may more closely relate to actual use and CUD severity than WM performance in a non-tempting neutral context. If this is the case, some specific cannabis-related deficits in WM may have been overlooked in previous studies using relatively neutral WM tasks. Indeed, multiple studies have shown that context-dependent emotional state affects performance as well as brain activity during cognitive control tasks (Erk et al., 2007; Iordan et al., 2013). For example, cannabis users show lower inhibition than control participants when the task requires inhibiting risky responses in the foresight of a potential reward, but not in a more classic rule-based task with inhibitory responses based on neutral stimuli (Griffith-Lendering et al., 2012). Similarly, weekly cannabis users performed worse than non-using controls on an adapted Stroop task including cannabis-related words, while performing similarly to controls when presented with neutral words (Cousijn, Watson, et al., 2013). This increased attentional bias for cannabis-related words was associated with severity of dependence (Cousijn, Watson, et al., 2013; Field, 2005). Aside from strong behavioral reactivity to cannabis-related cues, cannabis users also displayed relatively higher activity in reward related limbic regions compared to controls when presented with cannabis cues (e.g., Cousijn, Goudriaan, et al., 2013; Zhou et al., 2019). These findings support the idea that differences between cannabis users and non-users in attention reliant cognitive processes like WM may be more evident in a cannabis-related context than in a cannabis-unrelated or neutral context, however, research into this area is currently missing.

In this study we aimed to investigate the influence of a distracting cannabis related context on WM load-dependent performance and brain activity during a WM task in heavy cannabis users relative to controls. We developed an N-Back flanker task in which cannabis and neutral words flanked the standard letter N-back task (Mackworth, 1959). Previously, flankers have been used in a variety of cognitive tasks to induce a task-irrelevant component that distracts from the main goal of the task (e.g., Mclean et al., 2014; Trujillo et al., 2021). The cannabis-related words used in the current study have previously been shown to induce attentional bias in heavy cannabis users, interfering with the color naming of cannabis relative to the neutral words in a Stroop task (Cousijn, Watson, et al., 2013). While the flanker condition increases attentional task load, requiring participants to actively inhibit the flankers, the cannabis-related words add an additional attentional component for cannabis users specifically. Similar to previous studies with a standard N-back task, we expected performance to be WM-load dependent in both groups with lower accuracy and longer reaction times for high WM load (2-back trials) than for low WM load (1-back trials). However, we expected cannabis flankers to

increase task load (i.e., effort) in cannabis users only, such that performance would be lower but WM-related frontal-parietal brain activity would be higher in cannabis users compared to controls for cannabis flanker trials, but not for neutral flanker trials. To further explore the potential mechanisms underlying group differences in brain activity, we investigated whether individual's peak activity in significant clusters covaried with WM load-dependent performance and severity of cannabis use.

Materials and methods

The current study was part of a larger project that aimed to investigate neurocognitive processes involved in heavy cannabis use and CUD and will only describe the results of the participants that completed the N-back-flanker task. The ethical committee of the department of psychology of the University of Amsterdam approved the study (2015-DP-6387) and all participants were fully informed and provided informed consent before participation. All participants received monetary compensation for their participation.

Table 1. Sample characteristics

Measures	Cannabis Group	Control Group
N (% male)	36 (53)	33 (49)
Age, median	21	21
Estimated Intelligence, WAIS-IV matrix reasoning and similarities mean (SD)	21.03 (4.16)	22.00 (4.37)
Educational level, highest completed education, median	2	2
Impulsivity (BIS-11), mean (SD)	70.86 (6.89)	71.35 (5.70)
ADHD (CAARS), median	16	15
Depression (BDI), median	4	2
Trait Anxiety (STAI-Trait), median	33.5	34
State Anxiety (STAI-State), median	29.5	31
Alcohol use and related problems (AUDIT), median	6	5
Cigarette smoking, % cigarette smokers	47	42
Cigarettes per day (cigarette smoking), mean (SD)	9.74 (4.19)	9.75 (5.56)
Nicotine Dependence (FTND), mean (SD)	2.88 (1.96)	2.29 (1.64)
Lifetime other drugs use, median	12*	0*
Cannabis use and related problems (CUDIT-R), median	13*	0*
Cannabis use onset (age), mean (SD)	15.39 (1.92)	-
Cannabis use onset heavy use (age), mean (SD)	17.63 (1.96)	-
Cannabis gram per week, mean (SD)	2.74 (2.31)	-
Cannabis use days per week, mean (SD)	4.88 (1.67)	-
Cannabis Use Disorder (SCID DSM-5), mean (SD)	3.50 (1.63)	-
Self-reported cannabis abstinence (days), mean (SD)	1.28 (0.91)	-

* $p < .001$ for group comparison; Medians are reported in case of non-parametric assessment of group differences and for assessment of group differences based on count data with over 2 categories; SD, standard deviation; WAIS-IV, Wechsler Adult Intelligence Scale IV (Wechsler 2012); CAARS, Conners' Adult ADHD Rating Scales (Sandra Kooij et al. 2008); BDI, Beck Depression Inventory (Beck et al. 1961); STAI, State Trait Anxiety Inventory (Spielberger and Sydeman 1994); AUDIT, Alcohol Use Disorder Identification Test (Saunders et al. 1993); CUDIT-R, Cannabis Use Disorder Identification Test (Adamson et al. 2010); FTND, Fagerström Test for Nicotine Dependence (Heatherton et al. 1991); SCID-5, Structured clinical interview DSM-5 – Cannabis use disorder symptoms (First 2015).

Participants

A total of 38 heavy cannabis users and 34 healthy controls between 18 and 25 years old were recruited through online (e.g., social media) and offline (e.g., cannabis outlets) advertisements in the Amsterdam area. Potential participants were screened during a telephone interview before inclusion. Heavy cannabis users were required to use cannabis 10-30 times a month for at least two years, while control participants used cannabis at least once, but no more than 50 times during their life and not during the last year. General exclusion criteria were excessive alcohol use (Källmén et al., 2019; Alcohol Use Disorder Identification Task (AUDIT) score > 12; Saunders et al., 1993), smoking more than 20 cigarettes per day, the current use of prescription or illicit psychoactive drugs other than cannabis, substance use other than cannabis over a hundred times, previous or current serious physical (requiring regular visits to a specialists) or mental health (major axis-1 disorders) problems, leaving school before age 16, and previous or current treatment for CUD or plans to enter treatment. Groups were closely matched on age, sex, IQ, educational level, alcohol use, smoking, substance use other than cannabis, and mental health outcomes (Table 1).

Participants were instructed to refrain from using alcohol and drugs (except for nicotine and caffeine) 24 hours before the test session (See Table 1 for self-reported cannabis abstinence). During the test session, a urine drug test was performed to identify recent use of amphetamine, methamphetamine, benzodiazepines, cocaine, opiates, and cannabis (THC). Participants that tested positive (except for THC in the heavy cannabis use group) were excluded from the analysis.

Questionnaires

Cannabis use and related problems during the last six months were assessed using the Cannabis Use Disorder Identification test (CUDIT-R; Scores > 12 indicative of potential CUD; Adamson et al., 2010). Similarly, the AUDIT (Saunders et al., 1993) and Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) were used to identify last six months alcohol and cigarette use and related problems respectively. A substance use history questionnaire was used to assess frequency, quantity, and onset of alcohol use, cigarette use, cannabis use, as well as other illicit drug use. Additionally, a DSM-5 structured clinical interview for cannabis dependence (SCID DSM-5 CUD; score 2-3 = mild, score 4-5 = moderate, score >5 = severe; First, 2015) was administered to assess cannabis dependence. Severity of depression (Beck's Depression Inventory (BDI); Beck et al., 1961), anxiety (State-Trait Anxiety Inventory (STAI); Spielberger & Sydeman, 1994), and ADHD (Conners' Adult ADHD rating Scales (CAARS); Sandra Kooij et al., 2008) symptoms were assessed. Additionally, intelligence was estimated using the matrix reasoning and similarities subtests of the Wechsler Adult Intelligence

Scale IV (WAIS-IV; Wechsler, 2012) and educational level was classified with a single question assessing highest completed education (Dutch higher education levels; 1 = MBO (vocational education) or less, 2 = HBO (university of applied sciences), 3 = WO (university)).

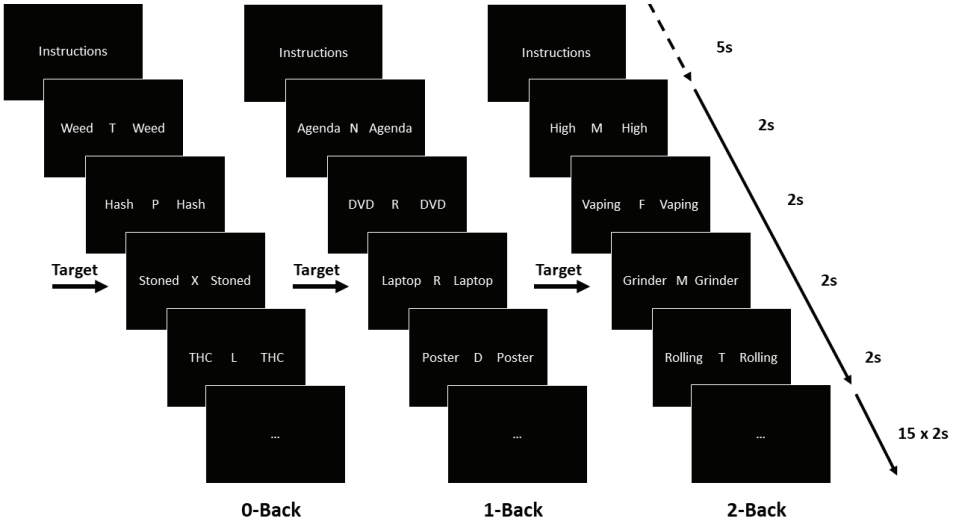


Figure 1. Task overview. Stimuli were similar to regular letter N-back stimuli, presenting a letter in the center of the screen during every trial. Cannabis (see 0-back and 2-back) or a neutral (see 1-back) words were simultaneous presented on both sides of this letter during the entire trial. Letters and words changed every trial, but the flanking words (cannabis or neutral) were consistent over each block of 15 trials. Before the start of the task, participants were given sufficient time to read instructions for the difference trial types. Block specific instructions were presented again for 5 seconds at the start of each block, followed by a block of 15 trials lasting 2 seconds each resulting in a total block length of 30 seconds.

N-back flanker task

The participants performed the adapted N-back-flanker task, developed using E-prime 2.0 software (Psychology Software Tools; Schneider et al., 2002), while fMRI blood-oxygen-level-dependent (BOLD) signals were recorded. The task included 6 different types of blocks including three WM loads (0-back (recognition), 1-back (low WM load), and 2-back (high WM load)) and two flanker types (neutral or cannabis; 3x2 factorial design). All block types were presented twice in a fixed order resulting in a total of 12 blocks of 15 trials. Each trial was presented for a fixed duration of 2 seconds, resulting in 30 seconds per block and a total task length of 7 minutes (including the 5 second instructions before the start of each block; Figure 1). During each trial a capital letter was presented with either a neutral or cannabis 'flanker' on the left and right side. Flankers were either cannabis related words (cannabis-context trials; e.g., 'joint' or

'high') or neutral stationary words (neutral-context trials; e.g., 'paperclip' or 'printer') and were matched on word length and number of syllabi. Substance related words and matched neutral words have been validated for use in designs assessing attentional bias in substance users (Ataya et al., 2012). The included neutral and cannabis words were previously used in an attentional bias study using the modified cannabis Stroop task (Cousijn, Watson, et al., 2013). The results of this study show that heavy cannabis users were slower naming the color in which cannabis words were printed than they were at naming the color in which neutral words were printed, indicating an attentional bias towards the cannabis relative to the neutral words. Before the 0-back (baseline recognition) blocks, participants were instructed to press the target button when a letter 'X' (the target) was presented. In the 1-back (low WM-load) blocks, participants were instructed to press the target button when the presented letter was identical to the letter presented during the previous trial. Similarly, in the 2-back (high WM-load) blocks, participants were instructed to press the target button when the presented letter was identical to the letter presented in the trial before the previous trial. During all non-target trials, participants pressed the non-target button. Each block of 15 trials included 5 target trials. No feedback on performance was provided during or at the end of the task.

Procedure

The consent procedure was followed by a first series of pen-and-paper questionnaires and the WAIS subscale assessments. The urine drug test was performed before practicing the scanner tasks. After MRI safety screening, participants completed a 50-minute scan session. After scanning, two series of pen-and-paper questionnaires and additional behavioral tasks were conducted.

Imaging parameters & preprocessing

A 3T Intera MRI scanner (Philips Intera, Best, the Netherlands) with a 32-channel SENSE head coil, located at the Spinoza Centre for Neuroimaging at the University Medical Center Amsterdam, was used for image acquisition. For each participant, a high-resolution structural scan was obtained for anatomical reference (T1 turbo field echo, TR = 8.2 s, TE = 3.8 ms, 220 slices, slice thickness = 1.0 mm, field of view (FOV) = 240 × 188 mm, voxel size = 1 × 1 mm, flip angle = 8°). BOLD responses were recorded during the N-back-flanker task using a T2* single-shot echo-planar imaging (EPI) sequence (TR = 2.0 s, TE = 28 ms, 37 slices, slice thickness = 3 mm, inter slice gap = .3 mm, FOV = 240 x 240 mm, voxel size = 3 x 3 mm, flip angle = 76°).

Preprocessing was conducted with FSL FEAT (FMRIB's Software Library version 5.0.6, part of fMRI Expert Analysis Tool version 6.0). Non-brain tissue and skull

were removed using BET (Brain Extraction Tool) where after regular-up slice time correction, high-pass filtering (sigma = 90), motion correction (using MCFLIRT), spatial smoothing (5mm full-with-half-maximum Gaussian kernel), and prewhitening were applied. The functional data was then registered to the participant's structural T1-weighted image and transformed to standard space (MNI-152) using FNIRT (FMRIB's non-linear registration tool).

Data analysis

Behavioral data analyses

Sample characteristics were compared over groups using either independent sample t-tests, Mann-Whitney U tests (in case of violation of assumptions) or chi-square tests (in case of categorical data) in RStudio (version 1.1.463; R Core Team, 2013). Trials without a response and those with a reaction time below 200ms were excluded. Then, a linear mixed effects model approach with maximum likelihood estimation and stepwise model selection was used to assess whether WM-load, flanker type, group or their interactions affected task performance measured as accuracy (percentage correct responses) and reaction time on accurate trials (RT). In all models the intercept was allowed to vary over participants (random intercept) while random slopes were included for WM-load and flanker type to account for repeated measures within participants. Model fit was assessed using Akaike's information criterion (AIC) to compare models.

fMRI analyses

A check for excessive motion did not result in the exclusion of any participants (max. motion = 2.36mm). A general linear model (GLM, ordinary least squares) analysis was conducted using FSL's FEAT. All 6 different trial types (WM load (3) x Flanker type (2)) were added as regressors and convolved with a double gamma hemodynamic response function. Temporal derivatives were added to the model to improve fit. Three contrasts were created to assess the main effect of flanker (Cannabis (c) > Neutral (n)), the main effect of WM (2-back (2) > 1-back (1)) and their interaction ((2c > 1c) > (2n > 1n)). Next, whole-brain mixed effects (FLAME1) group analyses with cluster-wise correction for multiple comparisons ($Z > 2.3$, cluster-based significance $p < .05$) were conducted, where independent sample t-tests were used to assess group differences (Control – Cannabis) on each of the three contrasts.

For descriptive purposes, we identified regions of maximal effect within the identified cluster by thresholding the contrast maps at $Z > 3.1$ (> 10 voxels per region) and extracted mean peak activation for each individual within these regions using FSL Featquery. This allowed for exploratory inspection of the direction of the effects

and how individual mean peak activation levels within these specific regions covary with heaviness of cannabis use (gram per week) and severity of cannabis use related problems (CUDIT-R; SCID DSM-5 CUD) within the group of cannabis users. Additional exploratory regression analyses were conducted to assess whether task performance was predictive of individual mean peak activation.

Results

Sample characteristics

Three participants were excluded for testing positive on a drug other than cannabis (1 cannabis group, 1 control group) during the test session or for not following task instructions (1 cannabis group). The final sample consisted of 36 heavy cannabis users and 33 controls. As can be seen in Table 1, groups did not differ on sex ($\chi^2(1, N = 69) = .13$, $p = .72$), age ($Z = -.03$, $p = .78$), estimated IQ ($t(65) = .95$, $p = .35$), educational level ($\chi^2(2, N = 69) = 4.86$, $p = .09$), impulsivity ($t(66) = .33$, $p = .74$), ADHD symptoms ($Z = -.57$, $p = .57$; CAARS), depression ($Z = -1.94$, $p = .052$; BDI), and trait ($Z = -.70$, $p = .49$) nor state ($Z = -.59$, $p = .56$) anxiety (STAI). With regards to substance use related measures, the groups did not differ on alcohol use and related problems ($Z = -.80$, $p = .42$; AUDIT), number of cigarette smokers ($\chi^2(1, N = 69) = .16$, $p = .69$), number of cigarettes per day ($t(23) = .008$, $p = .99$), or nicotine dependence ($t(28) = .92$, $p = .36$; FTND), but heavy cannabis users reported higher lifetime other substance use ($Z = -4.48$, $p < .001$) and higher cannabis use and related problems ($Z = -7.30$, $p < .001$; CUDIT) than control participants. Additional sample characteristics are reported in Table 1.

Table 2. Final selected models showing the effect of working memory (WM)-load on accuracy and reaction time during the N-back task

Model	**Model coefficients**					
	Fixed effects					**Random effects**
Accuracy	**B**	**95% CI (B)**	**SE (B)**	***t***	***p***	***SD***
(Intercept)	92.28	94.03 : 96.52	.63	150.83	<.001	3.03
WM-load: 1-back	-3.00	-4.43 : -1.57	.73	-4.12	<.001	2.95
WM-load: 2-back	-5.32	-6.75 : -3.88	.73	-7.31	<.001	
Flanker	-	-	-	-	-	4.04

Reaction Time	**B**	**95% CI (B)**	**SE (B)**	***t***	***P***	***SD***
(Intercept)	454.36	428.86 : 479.87	12.98	35.00	<.001	88.04
WM-load: 1-back	44.50	23.76 : 65.24	10.53	4.23	<.001	53.07
WM-load: 2-back	109.52	88.78 : 130.26	10.53	10.40	<.001	
Flanker	-	-	-	-	-	38.66

Mixed model results using random intercept and maximum likelihood estimation. CI: Confidence Interval; SE: Standard Error; SD: Standard deviation

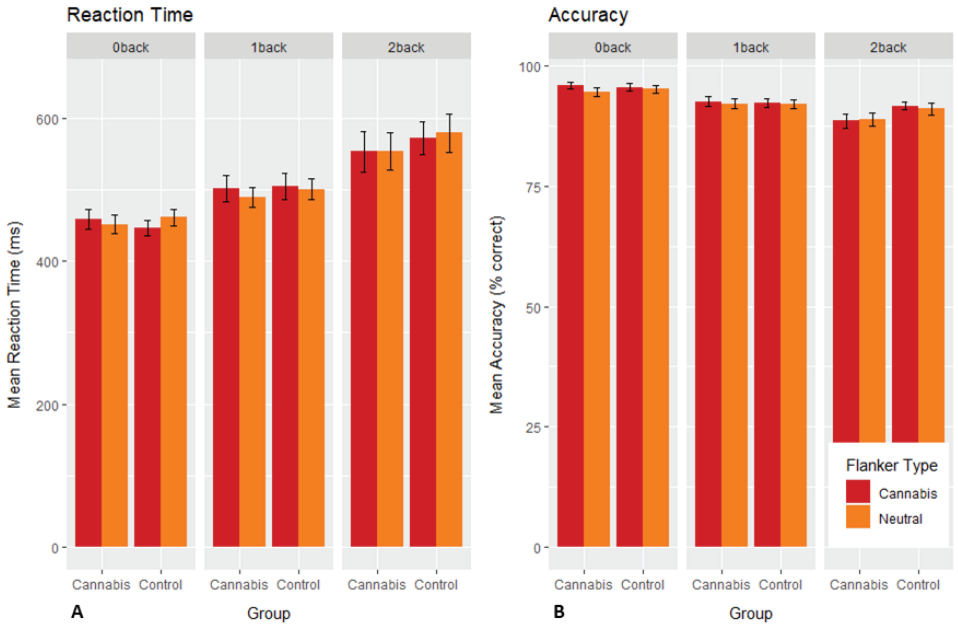


Figure 2. N-back Flanker performance.

A) Mean reaction times for 0-back, 1-back and 2-back per flanker type in cannabis users and controls. Reaction time increased with increasing working memory load, independently of group or flanker types (lowest p-value < .001).

B) Mean accuracy for 0-back, 1-back and 2-back per flanker type in cannabis users and controls. Accuracy decreased with increasing working memory load, independently of group or flanker types (lowest p-value = .004). Error bars reflect standard error (SE) of the mean.

N-back performance

The final model showed that increased WM-load negatively affected accuracy (0back-1back: B = -3.00, 95% CI = -4.43:-1.57, p < .001; 0back-2back: B = -5.32, 95% CI = -6.75:-3.88, p = < .001; Table 2) as well as reaction time (0back-1back: B = 44.50, 95% CI = 23.76:65.24, p < .001; 0back-2back: B = 109.52, 95% CI = 88.78:130.26, p < .001; Table 2; Figure 2). None of the assessed models revealed a significant effect of flanker type, group, or any of their interactions on accuracy or reaction time (see Appendix D - Table S1 for full model selection).

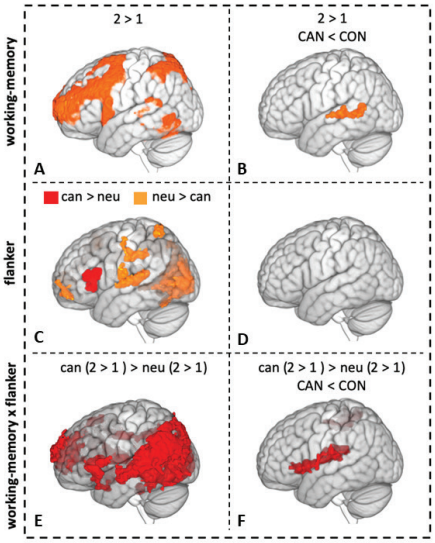


Figure 3. fMRI results.

A) 2 > 1 working memory related brain activity across groups;
B) Group difference (cannabis group < control group) in 2 > 1 working memory related brain activity;
C) Flanker related activation (cannabis > neutral) and deactivation (neutral > cannabis);
D) No group differences in flanker related activation;
E) Activity for the interaction between working memory load and flanker type;
F) Group differences (cannabis group < control group) in activity for the interaction between working memory load and flanker.

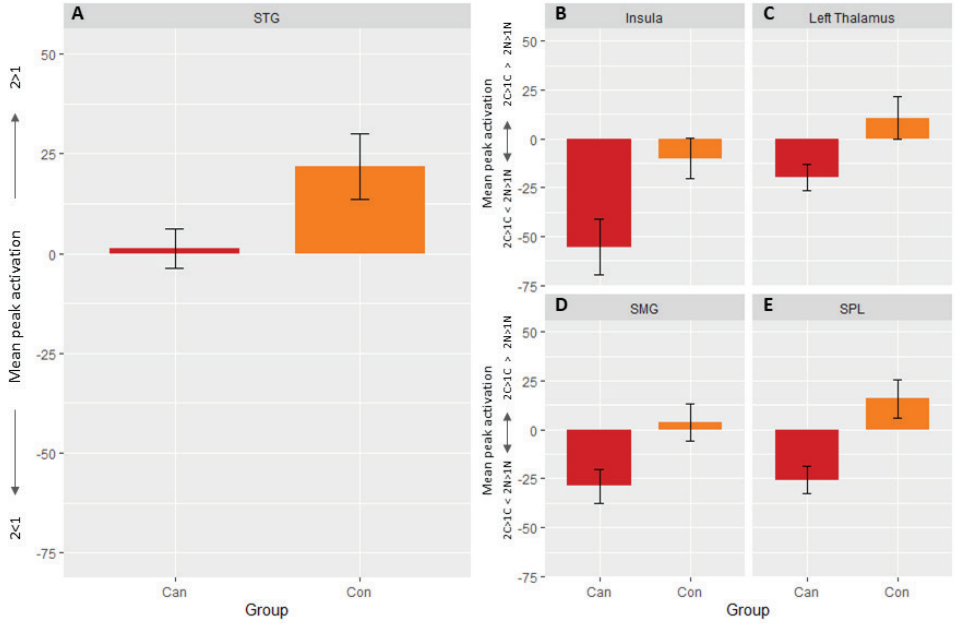


Figure 4. Group differences in mean peak activation in significant clusters found for the WM and interaction contrasts.

A) Group differences in mean working memory related (2>1) peak activation (unitless beta-estimates) of the superior temporal gyrus (STG) (MNI coordinates: X = -64, Y = -28, Z = 4). Group differences in mean interaction ((2c > 1c) > (2n > 1n)) related activation (unitless beta-estimates) of the
B) insula (MNI coordinates: X = -40, Y = 18, Z = -2),
C) left thalamus (MNI coordinates: X = -10, Y = -22, Z = 16),
D) Supramarginal gyrus (SMG; MNI coordinates: X = 44, Y = -38, Z = 48),
E) Superior parietal lobe (SPL; MNI coordinates: X = 18, Y = -50, Z = 60).

Figure A reflects differences in activation for 1-back and 2-back trials, with positive values being indicative of higher mean peak activation for 2-back trials compared to 1-back trials (2>1) and negative values reflecting the reverse (1>2);
Figure B-E reflect working memory related activity (2>1) where positive values reflect relatively higher working memory related activity for cannabis flankers (2C>1C > 2N>1N) and negative values reflect the reverse (2C>1C < 2N>1N). Error bars reflect standard error (SE) of the mean.

Table 3. Group differences in activation for the flanker, working memory, and interaction contrast

					MNI coordinates				
	Comparison	**Cluster size (voxels)**	**Brain regions**	**Hemisphere**	**X**	**Y**	**Z**	**Zmax**	f^2
Flanker Effect									
c > n	Can > Con	ns	ns	ns	ns	ns	ns	ns	ns
c > n	Con > Can	ns	ns	ns	ns	ns	ns	ns	ns
WM Effect									
2 > 1	Can > Con	ns	ns	ns	ns	ns	ns	ns	ns
2 > 1	Con > Can	420	STG	Left	-64	-28	4	3.35	0.20
			MTG	Left	-60	-52	6	3.20	0.18
			Angular Gyrus	Left	-54	-54	14	2.92	0.15
Flanker x WM interaction Effect									
(2c > 1c) > (2n > 1n)	Can > Con	ns	ns	ns	ns	ns	ns	ns	ns
(2c > 1c) > (2n > 1n)	Con > Can	1301	Thalamus	Left	-12	-20	16	3.35	0.20
			Operculum	Left	-48	-22	14	3.33	0.20
			Insula	Left	-40	8	4	3.26	0.19
		731	SPL	Right	18	-50	60	3.82	0.28
			SMG	Right	44	-38	48	3.56	0.23
			PCG	Right	46	-26	46	3.21	0.18

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 2.3$); c = cannabis flanker, n = neutral flanker; Can = cannabis group, Con = control group; 1 = 1-back, 2 = 2-back; STG = superior temporal gyrus; MTG = middle temporal gyrus; SPL: superior parietal lobe; SMG: supramarginal gyrus; PCG = postcentral gyrus; Effect size: $f^2 \geq 0.02$ = small, $f^2 \geq 0.15$ = medium, $f^2 \geq 0.35$ = large.

fMRI analysis

Increased WM load resulted in increased activity in a widespread network of frontoparietal regions known to be involved in WM performance (Figure 3A; full overview in Appendix D - Table S2; Owen et al., 2005). In a group comparison, controls showed significantly higher WM-related activation in the superior temporal gyrus (STG), middle temporal gyrus (MTG) and angular gyrus (Figure 3B; Table 3). Post-hoc analysis of extracted mean peak activity showed that these differences emerged from controls having increased WM-related brain activity in the STG when presented with more difficult WM trials, while there was close to no difference in activity between 2-back and 1-back trials in heavy cannabis users (Figure 4A).

Regardless of group or WM load, flanker-related activity was higher for neutral flankers in a widespread number of areas, while activity was higher for cannabis flankers in the inferior frontal gyrus (IFG) only (Figure 3C; full overview in Appendix D - Table S2). No group difference in flanker-related brain activity was found.

When looking at the interaction between WM load and flanker type, controls showed higher activation in the thalamus, operculum, insula, superior parietal lobe (SPL), supramarginal gyrus (SMG), as well as the postcentral gyrus (Figure 3D; Table 3). Exploratory analyses of extracted mean peak activity from significant clusters for the interaction effect, showed that heavy cannabis users have lower WM-related brain activity in these areas when presented with cannabis flankers compared to neutral flankers (Figure 4). The control group showed a similar pattern in the insula (Figure 4B), although less pronounced. However, WM-related brain activity in the left

thalamus (Figure 4C), SMG (Figure 4D) and SPL (Figure 4E) was higher in controls when presented with cannabis flankers compared to neutral flankers.

Further exploratory analyses revealed that cannabis use (grams per week) and symptoms of dependence (DSM-5 symptom count) were not predictive of the observed differences in brain activity (smallest p-value = .51). With regards to performance (accuracy and reaction time), WM-load related activity (2-1) in the STG could not be predicted by WM-load related performance (2-1) in the cannabis group (Accuracy: β = .38, t(31) = .60, p = .55; Reaction time: β = -.02, t(31) = .50 , p = .62) nor control group (Accuracy: β = .38 , t(23) = .26 , p = .80; Reaction time: β = .03, t(23) = .29 , p = .78).

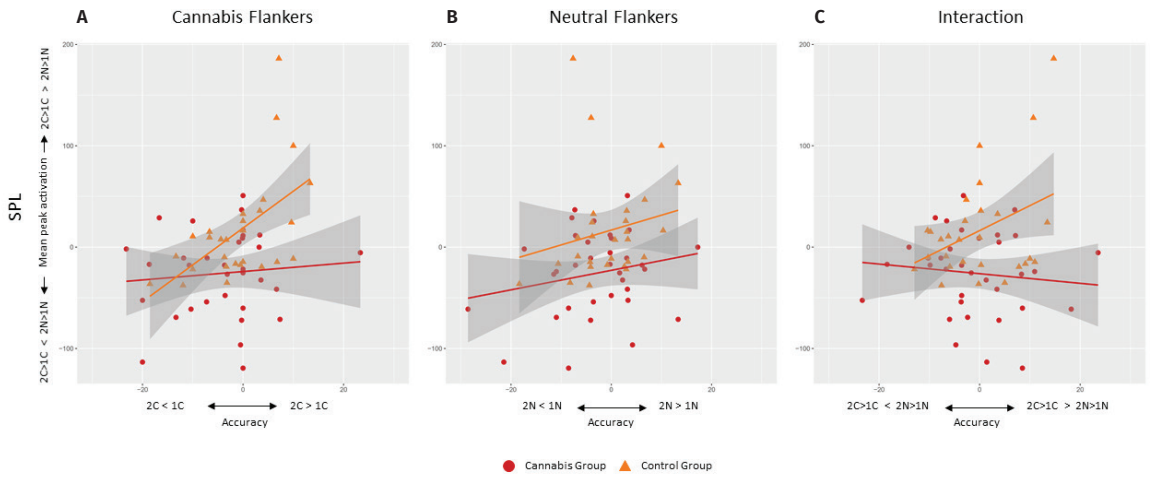


Figure 5. Association between mean peak activation of the SPL and accuracy.

A) Mean peak activation (unitless beta-estimates) in the SPL for the interaction contrast plotted against the performance on cannabis flanker trials;

B) Mean peak activation (unitless estimates) in the SPL for the interaction contrast plotted against the performance on neutral flanker trials;

C) Mean peak activation (unitless estimates) in the SPL for the interaction contrast plotted against the performance on cannabis flanker trials minus the performance on neutral flanker trials (interaction); Grey area reflects standard error (SE) of the mean.

For the interaction effect (2C – 1C) - (2N – 1N), performance was not predictive of activity in the insula, thalamus, SMG, and SPL in the cannabis group (smallest uncorrected p-value accuracy = .39 (SMG); smallest uncorrected p-value reaction time = .50 (insula)). Similarly, no significant results were found for the reaction time data in controls (smallest uncorrected p-value reaction time = .07 (SPL)). This was different for the accuracy data in the control group, where interaction related accuracy ((2C –

1C) - (2N – 1N)) was predictive of interaction related brain activity ((2C – 1C) - (2N – 1N)) in the SPL (β = 2.46, t(26) = 2.08 , uncorrected p-value = .048; Figure 5C). Further visual inspection of the data (Figure 5) revealed that this effect was guided by a positive association between relative increased activity for the WM-effect in cannabis flankers (compared to neutral flankers; y-axis Figure 5A) and a relatively higher performance for 2-back trials with cannabis flankers (compared to 1-back trials with cannabis flankers; x-axis Figure 5A). This effect was not observed in the cannabis group or for the neutral flanker trials (Figure 5B). While multiple comparison correction was not performed due to the explorative nature of these analyses, it must be noted that the significant association between interaction related accuracy and related brain activity in the SPL (uncorrected p-value = .048) is not significant when Bonferroni correction is applied (corrected p-value = .192).

Discussion

We aimed to elucidate the role of a distracting cannabis context in WM load-dependent performance as well as the related brain activity in heavy cannabis users. In contrast to our expectations, the presence of cannabis flankers did not reduce WM load-dependent performance in cannabis users. However, fMRI results showed that in heavy cannabis users compared to controls, the presence of cannabis flankers related to less WM load-related activity than neutral flankers did in multiple regions including the insula, thalamus, SPL, and SMG. These results suggest that the presence of cannabis words affects brain activity underlying attention reliant cognitive processes like WM in cannabis users and the brain areas involved highlight the potential role of saliency (Peters et al., 2016), attention (Vandenberghe et al., 2012), somatosensory processing (Saadon-Grosman et al., 2020), and sensorimotor integration (Wolpert et al., 1998) herein.

While a different activation pattern emerged for cannabis flankers compared to neutral flankers, no group differences were found. Nevertheless, flanker type seems to affect brain activity at a higher WM load only, with reduced activity for cannabis versus neutral flankers in the left insula, left thalamus, right SMG and right SPL in cannabis users, but not controls. Previous studies in non-cannabis users showed that increased cognitive effort for emotional stimuli during a WM task can result in reduced activity in emotion related areas, while having no effect on WM performance (Erk et al., 2007; Grimm et al., 2012). This is in line with the observed reduced activity in the insula and thalamus, areas implicated in SUDs through craving and salience attribution (Garavan, 2010; Huang et al., 2018), in response to stimuli with a higher emotional load. The cannabis group also showed reduced WM load-related activity for cannabis flankers compared to neutral flankers in the right SPL and right SMG. This could point towards

a cannabis-flanker distraction effect shifting away resources from the SMG and the SPL. The SMG has been implicated in remembering serial order during memory tasks (Guidali et al., 2019) and word processing (Stoeckel et al., 2009), while the SPL is often involved in attentional processes (Shapiro & Hillstrom, 2002) and thereby also in WM performance (Koenigs et al., 2009). Exploratory post-hoc analyses indicated that the group differences in brain activity could not be explained by behavioral performance on the n-back flanker task.

The cannabis flanker words included in our N-back flanker task have been shown to induce an attentional bias in heavy cannabis users that was stronger in more severe cannabis users (Cousijn, Watson, et al., 2013). In contrast to these results, cannabis use and CUD symptom severity did not relate to any of the observed flanker effects on WM load-related brain activity. It is possible that the apparent cannabis flanker distraction effect under high WM load does not directly relate to use or problem severity or that the limited variability in use patterns prevented us from finding an association. Alternatively, the cannabis stimuli may have been of limited salience to the present users, reducing engagement with the stimuli, or processing of the words was limited due to task speed. Future paradigms should explore how flanker modality and relative salience (e.g., picture stimuli or multimodal stimuli) affect performance and related activity in groups with more variable cannabis use, including more severe clinical populations.

The adapted N-back flanker task showed similar behavioral results to previous fMRI studies using the letter N-back (Cousijn, Vingerhoets, et al., 2014; Cousijn, Wiers, et al., 2014; Hatchard et al., 2020). Performance was found to be WM load dependent, with accuracy going down and reaction times going up with increasing difficulty, accompanied by increasing WM-load-related activity in frontoparietal regions. In contrast to our previous study in heavy cannabis users (Cousijn, Vingerhoets, et al., 2014), we found higher WM load-related activation in the left STG, MTG and angular gyrus in controls compared to cannabis users. Compared to our previous study, a clear strength of the current study is the close matching of cannabis users and controls on depression, anxiety, alcohol use and cigarette use. These confounding factors may have masked group differences in our previous study. The STG, MTG and angular gyrus are primarily found to be involved in word processing (Diaz & McCarthy, 2009; Kuchinke et al., 2005), but the STG has also been implicated in attentional processes (Shapiro & Hillstrom, 2002). Exploratory analysis of mean peak activation shows that activity in these regions increased with increased WM load in controls only, a difference that could not be explained by high activity for low WM-load in cannabis users. Increased involvement of language processing specific areas might not be surprising as the primary alteration made to the N-back task is adding words as emotional distractors,

but the underlying cause for group differences remain entirely speculative. Moreover, our observation of increased WM-related activity in the left STG in cannabis users contradicts several earlier studies that found the exact opposite in the left (Hatchard et al., 2020) and right STG (Kanayama et al., 2004; Smith et al., 2010). The recent study by Hatchard et al. (2020) suggests left STG activity is related to semantic processing during the letter N-back but found increased activity in the cannabis group rather than the control group. Using different types of WM tasks and relatively small samples, Kanayama et al. (Kanayama et al., 2004) and Smith et al. (Smith et al., 2010) interpreted the observed increases in right STG activity as compensatory activity in cannabis users. Future research should assess how different types of flankers (e.g., words or pictures), and relevance of word stimuli for task performance (e.g., task-irrelevant, or task-relevant words) affect task-related brain activity to clarify these apparent contradictions.

Besides the closely matched cannabis users and controls, a clear strength of this study is the addition of distracting cannabis and neutral words to an established task to create a novel N-back flanker task. This allowed us to gain important new insights into the effect of a distracting cannabis context on the neurocognitive mechanisms underlying cognitive control related processes in heavy cannabis users. Nevertheless, some limitations should be considered. First, the relatively high levels of accuracy indicate a ceiling effect and future studies are encouraged to incorporate higher WM-load (e.g., 3-back trials). Second, groups were not matched on other illicit drug use, potentially confounding the current results. However, total lifetime use in the cannabis group was minimal (Median = 12) and exclusion of subjects testing positive on other illicit drugs make it unlikely that (sub-) acute effects of these drugs affected the results. Third, history of cannabis use was determined through self-reports and the inclusion of more objective measures of cannabis use may gain better insights into associations between brain functionality and cannabis exposure. Similarly, we did not include an objective measure to verify participant adherence to the 24-hour cannabis abstinence before the session. While future studies should aim to include more objective verification methods, the lack of a group difference in reaction time and performance on the N-back task indicate that it is unlikely our results are the result of intoxication effects in the cannabis group (Hartman & Huestis, 2013). Furthermore, the cross-sectional nature and sample size of our study prevents us from drawing conclusions about causality and prevent the detection of small effects. Our sample size is relatively large compared to existing WM studies in cannabis users (Hatchard et al., 2020; Kanayama et al., 2004), highlighting the general need for larger longitudinal neuroimaging studies and replication studies (Poldrack et al., 2017). Finally, future studies are warranted to assess the replicability of our results using this novel paradigm.

In conclusion, the presence of distracting cannabis-related words reduced WM load-related brain activity in cannabis users compared to controls in various brain areas implicated in saliency, attention, somatosensory processing, and sensorimotor integration. This implies that heavy cannabis users process cannabis related cues differently and that cannabis cue exposure might interfere with other cognitive processes under cognitively demanding circumstances. Future studies should focus on the role of context in cognitive control and attention related processes like WM to further elucidate the potential cognitive impairments in heavy cannabis users and how these relate to loss of control over drug seeking itself.

Chapter 8

The who and how of attentional bias in cannabis users: associations with use severity, craving, and interference control

This chapter is based on:
Kroon, E., Kuhns, L., Dunkerbeck, A., & Cousijn, J. (2023). The who and how of attentional bias in cannabis users: associations with use severity, craving and interference control. *Addiction, 118*(2), 307-316. https://doi.org/10.1111/add.16059

Abstract

Background and Aim. Cognitive and motivational processes are thought to underlie cannabis use disorder (CUD), but research assessing how cognitive processes (e.g., interference control (IC)) interact with implicit (e.g., attentional bias (AB)) and explicit motivation (i.e. craving) is lacking. We assessed the presence of AB in cannabis users with varying use severity and tested models of moderation, mediation, and moderated mediation to assess how AB, craving, and IC interact in their association with measures of cannabis use.

Design. Cross-sectional.

Setting and Participants. Eight studies performed by our lab in the Netherlands including never-sporadic, occasional (≤1/month), and regular cannabis users (≥2/week), and individuals in treatment for CUD were combined (N = 560; 71% male).

Measurements. Studies included a Classic Stroop task (IC), a Cannabis Stroop task (AB), and measures of session induced and average session craving. Both heaviness of cannabis use (grams/week) and severity of use related problems were included.

Findings. Only those in treatment for CUD showed an AB to cannabis ($p = .019$) and group differences were only observed when comparing CUD with never-sporadic users ($p = .007$). In occasional and regular users, IC was negatively associated with heaviness ($\beta = .015$, $p < .001$), but not severity of use. Average session craving (exploratory), but not session induced craving (confirmatory), mediated this association between AB and heaviness ($\beta = .050$, $p = .011$) as well as severity of use ($\beta = .083$, $p = .009$); higher AB was associated with heavier use and more severe problems through increased craving.

Conclusions. AB only appears to be present in cannabis users with the most severe problems and craving appears to mediate the association between AB and both heaviness and severity of use in occasional and regular users. The association of IC with heaviness but not severity of use may point to sub-acute intoxication effects of cannabis use on IC.

Introduction

Excessive cannabis use and cannabis use disorder (CUD) are considered major health problems. Trends in cannabis legalization, increasing potency, and decreasing harm perceptions (UNODC, 2021) highlight the urgency of research into the mechanisms underlying CUD. Traditional theories of addiction propose central roles for both cognitive and motivational processes (Bickel et al., 2018), but research assessing both cognitive and motivational processes and their interactions in cannabis users is lacking.

The increased salience of substance-related cues in substance users is thought to bias behavior towards substance use, which can present itself as a cue-induced attentional bias (AB) and craving (Field & Cox, 2008). These drug-oriented motivational processes may more easily result in actual substance use in individuals with relatively limited cognitive control (Hester & Luijten, 2014; Robinson & Berridge, 2008). The classical Stroop task has been used to measure interference control (IC; Stroop, 1935), in which slower responses on incongruent trials, controlled for congruent trials, are an indication of lower IC. Modified drug Stroop tasks have been developed (e.g., Ataya et al., 2012) and the extent to which substance-related (e.g., weed or blunt) relative to matched neutral words (e.g. floor or table) slow down color naming is taken as an index of AB, which is expected to relate to substance use (Smith & Ersche, 2014).

Several studies investigated the role of IC, AB and craving in cannabis use and CUD. One study using the classical Stroop to measure IC found poorer IC and altered brain activity in weekly to daily users relative to non-sporadic using controls when responding to incongruent trials (Battisti et al., 2010). However, others found no performance differences when comparing near-daily users and controls (e.g., Takagi et al., 2011) or only found differences in task-related brain activity in at-risk and treatment samples (e.g., Banich et al., 2007; Kober et al., 2014; Thayer et al., 2015). Similarly, AB has been identified in cannabis users ranging from lifetime users to those in treatment for CUD (Cane et al., 2009; Cousijn et al., 2015; Cousijn, Watson, et al., 2013), while others do not observe AB using a Cannabis Stroop even in near daily users and those in treatment for CUD (Asmaro et al., 2014; Carpenter et al., 2006; van Kampen et al., 2020). Craving, however, has consistently been associated with heavier use (Kroon et al., 2020) and has been shown to be predictive of cannabis use and related problems six months later (Cousijn et al., 2015). Also, craving has been association with both AB (e.g., Field, 2009) and IC (e.g., Cousijn, Watson, et al., 2013) in studies using the Cannabis and Classical Stroop.

These mixed findings could in part be explained by the differential role that AB, craving, and IC play across trajectories of cannabis use towards CUD. IC may be lower, and AB and craving may be higher in heavier and dependent users (Cousijn, Watson, et

al., 2013; Hallgren & McCrady, 2013; Kroon et al., 2020; Marhe et al., 2013; van Kampen et al., 2020; Waters et al., 2015). Unfortunately, most studies look at these constructs separately and have a limited range of cannabis use severity included in the sample. Hence, it remains unclear which cannabis users have an AB and how this relates to craving and IC (e.g., Cousijn et al., 2015). Furthermore, a meta-analysis (Field, 2009) found a small but significant association between AB and craving in substance users, indicating that previous studies might lack power to detect such small effects. To overcome these problems and systematically assess the potential interactions between cognitive and motivational processes in a large sample of cannabis users with variable use frequency, this study combines eight studies conducted in our lab that included a pencil and paper version of the Classical Stroop and the Cannabis Stroop, and similar assessments of craving.

First, focusing on AB, we will assess whether groups of never-sporadic users, occasional users, regular users, and those in treatment for CUD show an AB towards cannabis and whether AB differs between these groups. We expect an AB in regular users and those in treatment for CUD only, that differs from the never-sporadic users (Kroon et al., 2020). In occasional and regular users, excluding the CUD group to avoid effects of recent cessation on the outcomes, we will assess whether AB, craving, IC, heaviness of current use, and severity of cannabis use-related problems are indeed associated with each other in this broad range of users.

Second, we will assess how the cannabis AB, craving, and IC interact in their association with heaviness and severity of cannabis use. We will test different theory informed models; we will assess whether AB, craving, and/or IC are predictive of heaviness of cannabis use and/or severity of cannabis use-related problems (Figure 1A; e.g., Kroon et al., 2021). Then we will assess the proposed moderating role of cognitive processes – in this case IC - in overcoming motivational urges (Figure 1B & Figure 1C; Hester & Luijten, 2014; Robinson & Berridge, 2008). AB could increase craving or vice versa, subsequently leading to increased cannabis use or use-related problems (e.g., Field et al., 2014; Field & Cox, 2008). Therefore, we will also separately assess whether AB or craving act as a mediator in the association between the other variable with heaviness of use and severity of cannabis-use-related problems (Figure 1D & Figure 1E). Then, to combine these moderation and mediation models, we will assess whether IC moderates the association of craving and/or AB with heaviness/severity cannabis use in the proposed mediation models (Figure 1F & figure 1G).

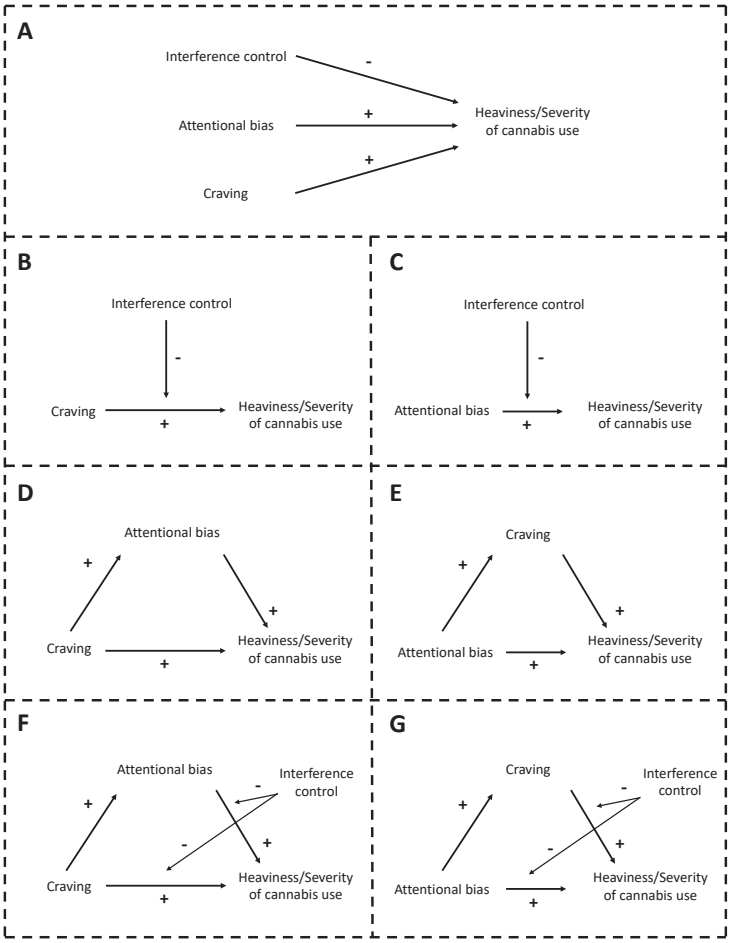


Figure 1.
Visual representation of hypotheses.

Methods

We combined data from eight studies (See Appendix E - Figure S1 for study descriptions; Cousijn et al., 2015; Cousijn, Snoek, et al., 2013; Cousijn, Watson, et al., 2013; Cousijn & van Duijvenvoorde, 2018; van Kampen et al., 2020) conducted by our lab that included the same measure of AB, IC, and similar measures of craving, resulting in a total of 569 participants. The analysis plan was pre-registered (https://aspredicted.org/7JT_TN7; November 10, 2021). Deviations from the pre-registration are reported as exploratory throughout the manuscript and an overview of the deviations can be found in Appendix E - Figure S2. In all studies, procedures were approved by the ethics committee of the corresponding department and all participants were fully informed and provided informed consent before the start of the experiment.

Materials

Assessments

Participants reported age, gender, weekly cannabis use in grams (heaviness of use) and completed the cannabis use disorder identification test-revised (CUDIT-R; Adamson et al., 2010) to assess severity of cannabis use-related problems. Smoking (yes/no), the Fagerström test for Nicotine dependence (FTND; Heatherton et al., 1991), and the alcohol use disorder identification test (AUDIT; Saunders et al., 1993) were included to assess the severity of drug use other than cannabis.

Craving

Craving was assessed using a visual analogue scale (Craving VAS) or the marijuana craving questionnaire (MCQ; Heishman et al., 2001; Appendix E - Figure S1) at the start and the end of the session. To account for differences in measures across studies, session induced (SI) craving (start - end score) and an exploratory measure of average session (AS) craving were calculated before the scores were standardized within each scale and combined into single measures of AS craving and SI craving. Comparability of the MCQ and VAS craving scores was assessed in a sub-sample (N = 40) in which both were collected during the same session, showing a moderate to high within person correlation between the AS craving scores ($r = .806$, $p < .001$) as well as SI craving scores ($r = .500$, $p = .001$) as calculated from the VAS and MCQ. Furthermore, VAS and MCQ were similarly associated with the measures of cannabis use included in this study (Appendix E - Table S2).

Classical Stroop: interference control

The Classical Stroop task included three different cards that were presented in a fixed order (Hammes, 1971; Stroop, 1935). All cards included ten rows of ten words/blocks which participants were instructed to read over row-by-row, as fast as possible, according to the card instructions. First, participants were instructed to read the words red, green, blue, and yellow as printed in black (word card). Second, participants were instructed to name the color of the color blocks (color card). Last, participants were instructed to name the incongruent color in which the words red, green, blue, and yellow were printed (color-word card). Reaction times were recorded using a stopwatch and IC scores were calculated using this formula: *reaction time color-word card*/((*reaction time word card* + *reaction time color card*)/2) (Scarpina & Tagini, 2017). Higher scores indicated lower IC.

Cannabis Stroop: attentional bias

The Cannabis Stroop task included two different cards presented in counterbalanced

order (Cousijn et al., 2015). Each card included eight rows of seven words that were all printed in red, green, blue or yellow. The words on both cards were matched on word length and number of syllables, but on one card the words were neutral (e.g., poster), while the words on the other card were cannabis-related (e.g., stoned). Participants were instructed to name the color in which each word was printed, row by row, from left to right, as fast as they could. A stopwatch was used to record the time needed to complete each card. AB scores were calculated using the following formula: *reaction time cannabis card – reaction time neutral card*, with higher scores being indicative of a relatively higher bias for cannabis words.

Procedures

While there were variations in the full study protocol and session length between studies (Appendix E - Figure S1), the overlapping measures were identical across studies. Also, the Cannabis Stroop was always completed before the Classical Stroop. Craving measures were conducted at both the start and the end of the session in all studies. Furthermore, cannabis-related questionnaires, aside from the pre-session craving, were always completed after the Stroop tasks.

Data analysis

Grouping & exclusion

Participants were classified as never-sporadic user (no lifetime or no use in the last year), occasional users (maximum of once per month during the last year), regular users (minimum of twice per week during the last year) or CUD (in treatment at the moment of testing; Table 1) using the first question of the CUDIT-R (Adamson et al., 2010; note: in study 8, grouping was based on self-reported last year use) and treatment status. Individuals that did not fit any of these groups (N = 8) were excluded (Appendix E - Table S1). IC, AB, craving, grams/week of use and CUDIT-R scores that were more than 3 standard deviations from the mean were excluded to reduce effects of measurement error (e.g., implausibly high levels of cannabis use or IC scores indicative of potential methodological problems).

Attentional bias

One-sample t-tests were run to assess whether there was an AB to cannabis words (whether the AB was different from zero) per group. An ANOVA was performed to assess group differences in AB, with post-hoc independent sample t-tests to explore the differences. Then, in all occasional and regular users, correlation analyses were conducted to assess how heaviness of cannabis use (grams/week), severity of cannabis use-related problems (CUDIT-R score), AB, IC, and session induced (SI) craving were

associated with each other. The attentional bias analyses as described above were conducted in JASP (version 0.14.1.0; JASP Team, 2020).

Attentional bias, interference control and craving: their association with cannabis use

Only current occasional and regular users were included in the following analyses (Table 1; excluding CUD group due to potential effects of recent cessation). Simple regression analyses were conducted to assess whether AB, IC, and/or SI craving were predictive of heaviness of cannabis use and severity of cannabis use-related problems (Figure 1A). Moderation analyses were conducted to assess whether IC moderates the association between SI craving (Figure 1B) or AB (Figure 1C) and heaviness of cannabis use and severity of cannabis use-related problems. Then, to assess the proposed relation between AB and SI craving in their association with cannabis use outcomes, we ran a mediation analysis to see whether AB mediates the association between SI craving and heaviness of cannabis use or severity of cannabis use related problems (Figure 1D) or the reverse (Figure 1E, Appendix E - Figure S4A). Combining this, moderated-mediation analyses were run to assess whether IC moderates the association between SI craving and AB with heaviness of cannabis use or cannabis use related problems in the proposed mediation models (Figure 1F & Figure 1G, Appendix E - Figure S4B). All included variables were mean centered. Additional exploratory analyses were conducted replacing SI craving with AS craving. The models as described above were run in R (version 4.1.2) creating the models (Figure B-G) using the processR (version 0.2.6) package and running them in lavaan (version 0.6-9) using maximum likelihood estimation. Bonferroni corrected p-values (p_{bonf}) were provided for analysis requiring multiple comparison correction.

Results

Sample characteristics

Individuals with known color-blindness (N = 2) and those that tested positive on drugs other than cannabis during the test session (N = 7) were excluded from the analyses, resulting in a total sample of 560 participants (71% male). Outlier exclusion resulted in the omission of 6 participants' data regarding grams/week of use, 4 participants' craving scores, 7 participants' AB scores, and 7 participants' IC scores.

Groups significantly differed on all variables (see Table 1). Exploratory independent sample t-tests showed varying patterns of differences for all variables with a general tendency of more severe alcohol, cigarette use, and more limited IC in more severe cannabis users and no differences between never-sporadic users and occasional users. Notably, session induced craving was only positive in regular users.

Table 1. Sample characteristics

Variables	Groups						Occasional & Regular (N=358)
	Never-Sporadic (N = 97)	Occasional (N = 35)	Regular (N = 323)	CUD (N = 97)	Group Difference	Pairwise Difference[#]	
Gender, *% male*	57.7	45.7	75.9	77.7	$\chi^2(3, N = 549) = 24.9, p < .001$	2, 3, 4, 5	72.9
Age, *Median (MAD)*	22.0 (2.5)	22.0 (2.0)	21.0 (2.0)	20.0 (2.0)	$F(3,539) = 7.2, p < .001, \eta^2 = .04$	3, 6	23.2(5.8)
CUDIT-R, *Median (MAD)*	-	1.0 (0.0)	15.0 (4.0)	23.0 (4.0)	$F(2,441) = 169.0, p < .001, \eta^2 = .43$	4, 5, 6	14.1(6.4)
Gram/Week, *Median (MAD)*	-				$F(2,415) = 46.0, p < .001, \eta^2 = .18$	4, 5, 6	4.2(4.0)
Age of onset, *Median (MAD)*	-	17.0 (2.0)	16.0 (1.0)	16.0 (1.5)	$F(2,429) = 3.7, p < .001, \eta^2 = .02$	4, 5	15.8(2.4)
Smoking, % smokers	19.6	40.0	64.1	85.3	$\chi^2(3, N = 550) = 97.5, p < .001$	2, 3, 4, 5, 6	61.7
FTND, *Median (MAD)*	0.0 (0.0)	2.0 (1.0)	3.0 (2.0)	4.0 (2.0)	$F(3,344) = 13.6, p < .001, \eta^2 = .11$	2, 3, 5, 6	2.7(2.3)
AUDIT, *Median (MAD)*	5.0 (2.0)	6.0 (2.0)	8.0 (4.0)	8.0 (4.0)	$F(3,481) = 6.5, p < .001, \eta^2 = .06$	2, 3	8.6(5.5)
Session induced craving, *Median (MAD)*	-.22 (.1)	-.22 (.1)	.02 (.6)	-.23 (.4)	$F(3,528) = 8.7, p < .001, \eta^2 = .05$	2, 6	.58(2.3)
Average session craving, *Median (MAD)*	-.85 (.0)	-.85 (.1)	.41 (.7)	-.39 (.6)	$F(3,528) = 45.1, p < .001, \eta^2 = .20$	2, 3, 4, 5, 6	.21(1.0)
Interference control, *Median (MAD)*	25.5 (7.5)	23.0 (4.6)	31.3 (8.9)	33.2 (8.4)	$F(3,540) = 7.3, p < .001, \eta^2 = .04$	2, 3, 5	31.6(12.5)
Attentional bias, *Median (MAD)*	-.5 (1.9)	.0 (2.0)	.3 (2.1)	1.0 (2.3)	$F(3,541) = 3.1, p = .026, \eta^2 = .02$		.28(3.4)
	Never-sporadic vs. occasional				$t(130) = .42, p = .673, d = .08$		
	Never-sporadic vs. regular				$t(415) = 1.96, p = .050, d = .23$		
	Never-sporadic vs. CUD				$t(188) = 2.71, p = .007, d = .39$		
	Occasional vs. regular				$t(353) = .85, p = .398, d = .15$		
	Occasional vs. CUD				$t(126) = 1.59, p = .114, d = .32$		
	Regular vs. CUD				$t(411) = 1.74, p = .084, d = .20$		

Note: AUDIT: alcohol use disorder identification test; CUD: cannabis use disorder; CUDIT-R: cannabis use disorder identification test; FTND: Fagerström test for nicotine dependence; MAD = median absolute deviation; [#] Pairwise differences ($p < .05$) after Bonferroni correction; Pairwise comparisons: 1 = never-sporadic vs. occasional, 2 = never-sporadic vs. regular, 3 = never-sporadic vs. CUD, 4 = occasional vs. regular, 5 = occasional vs. CUD, 6 = regular vs. CUD;

Group differences in attentional bias & correlations between variables

Only the CUD group showed an AB to cannabis ($t(92) = 2.39$, $p = .019$, $d = .25$). However, no significant AB to cannabis was observed in the never-sporadic ($t(96) = 1.31$, $p = .192$, $d = .13$), occasional ($t(34) = 0.38$, $p = .704$, $d = .07$), and regular users ($t(319) = 1.72$, $p = .087$, $d = .10$). AB differed between groups ($F(3,541) = 3.1$, $p = .026$, $\eta 2 = .017$; Table 1), with post-hoc analyses revealing a higher bias in CUD (and regular users at $p = .050$) versus never-sporadic users (Figure 2). Exploratory sensitivity analyses, adding the variables that differed between groups (Table 1) as covariates in an ANCOVA, showed that the effect was independent of age and IC but no longer significant after correction for AUDIT and FTND.

Focusing on occasional and regular users, correlational analysis revealed a positive association between heaviness of cannabis use (Gram/week) and severity of cannabis use (CUDIT-R scores; $r_s(347) = .49$, $p_{bonf} < .001$). CUDIT-R score was not associated

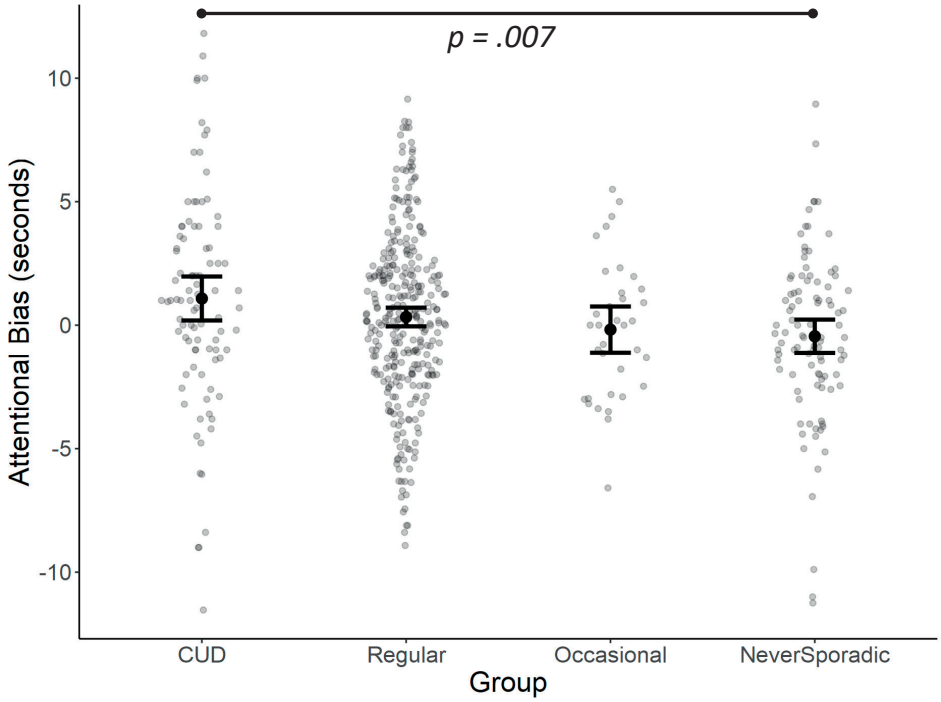


Figure 2. Group differences in attentional bias (AB). Error bars presenting standard error (SE) of the mean.

with any of the other variables (highest r_s = .10, with uncorrected p = .06), but gram/week was positively associated with Classical Stroop scores ($r_s(343)$ = .20, p_{bonf} < .001), indicating worse IC in more severe users. No other correlations between IC, craving and AB were observed (highest r_s = .08, with uncorrected p = .16).

Attentional bias, interference control and craving: their association with cannabis use

In line with the correlational results, simple regression analyses (Figure 1A) showed an association between poorer IC and gram/week (R^2 = .037, F(1, 343) = 14.23, β = .015, β_{SE} = .004, t = 3.772, p_{bonf} < .001), but not CUDIT-R score (R^2 = -.003, F(1, 350) = .023, β= .004, β_{SE} = .027, t = .150, p_{bonf} = 1.0). AB and craving did not directly predict gram/week or CUDIT-R score (Appendix E - Table S3; Appendix E - Figure S3).

Moderation (Figure 1B & Figure 1C; Appendix E - Table S4), mediation (Figure 1D & Figure 1E; Table S5) and moderated-mediation (Figure 1F & Figure 1G; Appendix E - Table S6) models revealed no other associations than the consistently present direct association between IC and gram/week (Appendix E - Figure S3).

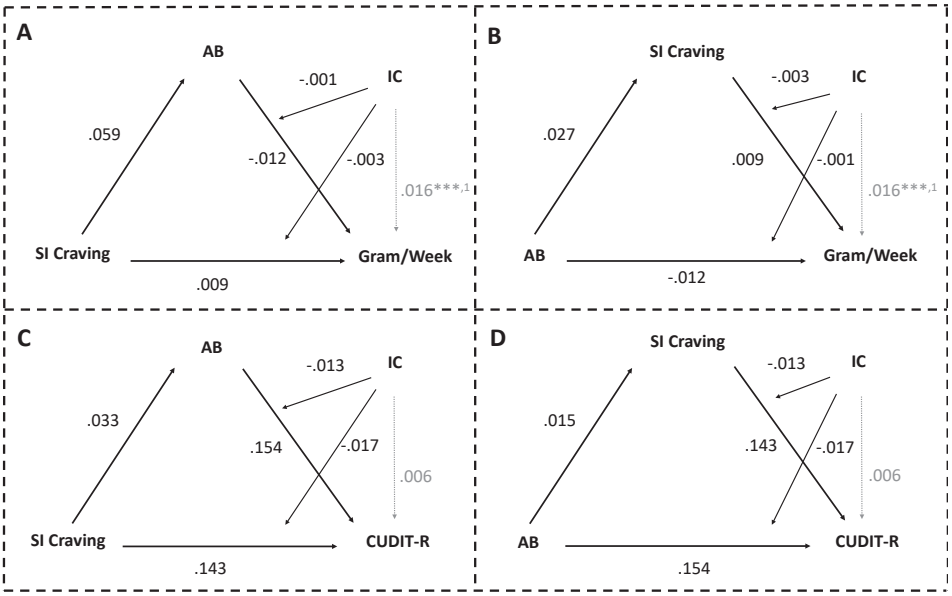


Figure 3. Moderated-mediation analysis results. Analyses assessing the conditional indirect effects of session induced (SI) craving/ attentional bias (AB) on heaviness or severity of use through AB/SI craving, at different levels of interference control (IC). Estimates for all paths reported with indicators of significance: *** p < .001, ¹p < .001.

Exploratory analyses: the role of average session craving

As session induced changes in craving do not necessarily reflect absolute feelings of craving, but rather to what extent the session affected craving in the individual, we re-ran the correlations, simple regressions, moderation, mediation, and moderated-mediation models with AS craving instead of SI craving (Figure 3).

Correlational and simple regression analyses showed that AS craving was positively associated with gram/week ($r_s(330) = .30$, $p_{bonf} < .001$; $R^2 = .057$, $F(1, 330) = 20.93$, $\beta = .977$, $\beta_{SE} = .214$, $t = 4.575$, $p_{bonf} < .001$) and CUDIT-R ($r_s(338) = .26$, $p_{bonf} < .001$; $R^2 = .074$, $F(1, 338) = 28.19$, $\beta = 1.75$, $\beta_{SE} = .331$, $t = 5.309$, $p_{bonf} < .001$; Appendix E - Table S7). Furthermore, higher AS craving was associated with higher AB ($r_s(336) = .15$, $p_{bonf} = .024$) and lower IC (i.e., higher Stroop score; $r_s(333) = .18$, $p_{bonf} = .004$). Moderation analyses revealed similar associations, also including the association between IC and heaviness of use (Appendix E - Table S8). However, mediation analyses revealed that AS craving mediated the association between AB and both gram/week (indirect effect: $\beta = .050$, $\beta_{SE} = .020$, $z = 2.556$, $p_{bonf} = .021$) and CUDIT-R score (indirect effect: $\beta = .083$, $\beta_{SE} = .032$, $z = 2.602$, $p_{bonf} = .019$; Appendix E - Table S8). These mediations were stable across the moderated-mediation models (CUDIT-R – indirect effect: $\beta = .089$, $\beta_{SE} = .033$,

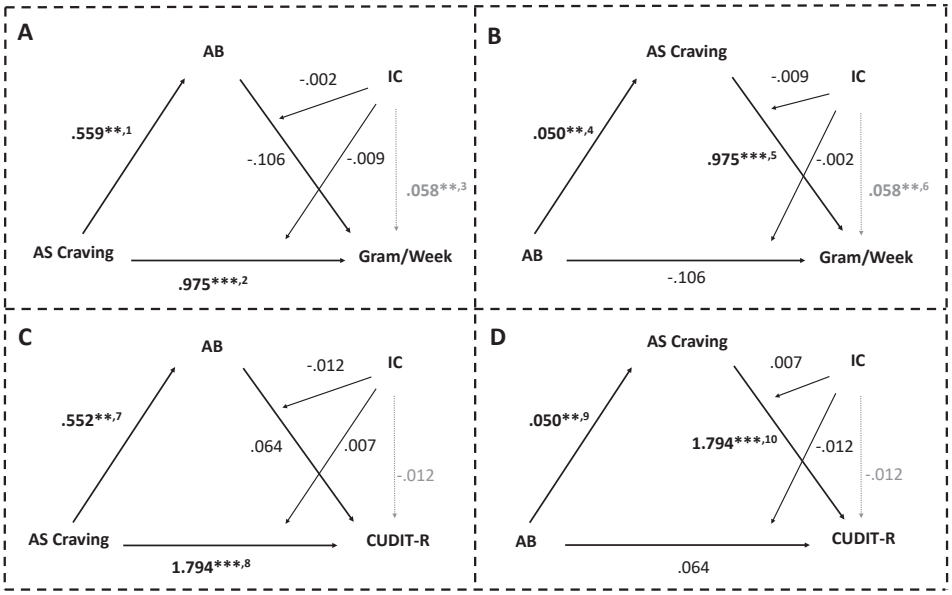


Figure 4. Exploratory moderated-mediation analysis results including average session (AS) craving instead of session induced (SI) craving. Analyses assessing conditional indirect effects of AS craving/attentional bias (AB) on heaviness or severity of use through AB/AS craving, at different levels of interference control (IC). Estimates for all paths reported with indicators of significance: ** p < .01*** p < .001, [1]p = .002, [2]p < .001, [3]p = .001, [4]p = .002, [5]p < .001, [6]p = .001, [7]p = .002, [8]p < .001, [9]p = .002, [10]p < .001.

z = 2.655, p_{bonf} = .016; gram/week – indirect effect: β = .049, β_{SE} = .019, z = 2.552, p_{bonf} = .021), but IC did not act as a moderator but rather was directly associated with gram/week only (Appendix E - Table S9; Figure 4).

Discussion

We assessed the presence of AB in cannabis users with different levels of use and evaluated how AB interacted with craving and IC in its relationship with heaviness and severity of cannabis use. A clear strength of this study is the inclusion of a large sample with a large range of cannabis use severity (N = 560). Only those users in treatment for CUD showed an AB to cannabis (significantly > 0), which was significantly higher compared to never-sporadic users, but not compared to occasional and regular users. Poorer IC was consistently associated with heavier cannabis use, but not the severity of use related problems. However, in contrast to our hypotheses, IC did not moderate the association between AB and craving in their association with measures of cannabis use. Moreover, session induced craving did not mediate the association between AB (nor vice versa) and measures of cannabis use, yet results changed when using average

craving instead; craving mediated the association between AB and heaviness as well as severity of use.

Our results suggest that AB may be a clinical marker of CUD severity, while IC may generally be poorer in heavier users regardless of CUD problem severity. However, the associations between AB, craving IC, and cannabis use are complex. Looking at Figure 2, AB appears higher in more frequent users, but AB did not directly relate to our measures of cannabis use (also not when exploratively including the CUD group in the regression analysis). It only did through its positive association with craving; those with higher AB might have higher, potentially more 'trait-like' levels of craving, triggering a higher general likelihood to use. Most studies indicate that the relationship between craving and AB is likely reciprocal (Field & Cox, 2008), however, our results in which AB affects use through craving are in line with earlier research in alcohol users in which training to increase AB resulted in increased craving and subsequent use (Field & Eastwood, 2005). The indirect effects of AB via craving could also explain why some studies did not find direct associations between AB and measures of use (e.g., Hallgren & McCrady, 2013, alcohol Stroop; Hester et al., 2006, cocaine Stroop). However, our findings are cross-sectional and were only significant for average craving, not session induced craving. Studies investigating the temporal dynamics between AB and craving are needed to further investigate this.

The specific presence of AB in the treatment (most severe) group could explain some of the null findings of previous studies (e.g., Field et al., 2007) and could indicate its potential value as a clinical marker. However, research evaluating the relevance of assessing AB for other substance use disorders in clinical settings is inconsistent (e.g., Christiansen et al., 2015; Field et al., 2014) - while some studies show AB to be associated with worse treatment outcomes or increased relapse rate (Marissen et al., 2006, heroin; Carpenter et al., 2011, cocaine; Cox et al., 2002, alcohol) this is not the case in all studies (Marissen et al., 2006, cocaine; Spiegelhalder et al., 20011, tobacco) - and studies on the value of AB as a marker of CUD severity and treatment outcomes are largely lacking. Hence, further research is required to systematically assess the clinical relevance of AB to cannabis cues in clinical and non-clinical samples of cannabis users.

It must be noted that the group differences disappeared when controlling for AUDIT and FTND. Poly substance use is very common (UNODC, 2016) and the higher use of alcohol and tobacco might arise from the same underlying factors as their heavy cannabis use (e.g., Field, 2009; Pennington et al., 2020). Including AUDIT and FTND as covariates is suboptimal for it likely deletes cannabis use-relevant variance. Furthermore, it seems theoretically unlikely that alcohol and tobacco use directly affect AB for cannabis words, but further research with samples (more closely) matched on these variables are needed to confirm this.

Partially in line with our expectations, we consistently found lower IC to be associated with heavier cannabis use (small-medium effect; r_s = .20). While it is often argued that this could indicate of a lack of control over use (Hester & Luijten, 2014; Robinson & Berridge, 2008), the lack of association with severity of cannabis use related problems and the lack of interactions with AB and craving may indicate that this association is a result of current heaviness of use and the associated sub-acute effects. Some earlier studies also failed to find a moderating role if IC (e.g., Cousijn, Watson, et al., 2013; van Kampen et al., 2020). Cannabis intoxication has been found to negatively affect Stroop performance (e.g., Hooker & Jones, 1987) and there is evidence that several cognitive functions recover with increased abstinence (e.g., Crean et al., 2011). In line with this, an exploratory check in the CUD group, of which the majority have been abstinent for multiple days (53% at least 7 days of abstinence), showed that there was no association between IC and heaviness of use in the CUD group (Appendix E - Table S10). Further research is needed to assess (sub)acute effects and the potential for recovery.

A few limitations of this study should be noted. While combining different studies increases the sample size and allows for more complex models to be tested, it potentially introduces differences in experimenter effects and methodology between studies. However, the classical and cannabis Stroop methodology was the same across studies and it is likely that experimenter variability was as large within some studies as between them (in line with low (≤ .126) ICC). Differences between sessions might particularly have affected the results of session induced craving as they differed in length and content aside from the measures included in our analysis. It must be noted that all standardized craving scores were based on two different measures of craving. While sub-sample analyses showed that within person associations between the measures were moderate to high and they displayed similar associations with cannabis use outcomes, it is unclear how this approach could have affected the results. Also, the difference in the results between session induced and average craving highlight the potential influence of the chosen outcome, even when calculated from the same measures, and the potential incomparability of the results of studies using different outcome measures. Replication of our results using a single measure of craving but using both average session craving and session induced craving as outcomes, is warranted. Furthermore, it must be investigated whether our results generalize to other measures of cognitive functioning and AB and whether these effects generalize to more ecologically valid situations in which AB could affect craving and cannabis use.

Our results indicate that AB as measured by the Cannabis Stroop might only be present in those cannabis users with the most severe problems but that even in less severe cannabis users greater AB could be associated with higher craving and in

turn higher cannabis use and related problems. While systematic research into the clinical relevance of these associations is crucial, these results highlight the potential importance of AB in both heaviness and severity of cannabis use as well as the mechanisms by which AB through increased craving could affect efforts to reduce or stop using cannabis.

Chapter 9

Resting state functional connectivity in dependent cannabis users: the moderating role of cannabis attitudes

This chapter is based on the following preprint:
Kroon, E., Toenders, Y.J., Kuhns, L.N., Cousijn, J., Filbey, F., (n.d.). Resting state functional connectivity in dependent cannabis users: the moderating role of cannabis attitudes. https://doi.org/10.31234/osf.io/t2c6w

Abstract

Background. The global increase in lenient cannabis policy has been paralleled by reduced harm perception, which has been associated with cannabis use initiation and persistent use. However, it is unclear how cultural attitudes towards cannabis use might affect the brain processes underlying cannabis use.

Methods. Resting state functional connectivity (RSFC) within and between the executive control network, salience network, and default mode network was assessed in 110 near-daily dependent cannabis users and 79 controls from The Netherlands and Texas, USA. Participants completed a questionnaire assessing the perceived benefits and harms of cannabis use from their personal, friends-family's and country-state's perspective and reported on their cannabis use (gram/week), DSM-5 cannabis use disorder (CUD) symptoms, and cannabis related problems.

Results. RSFC within the dorsal salience network was lower in cannabis users than controls and was negatively associated with cannabis use in the cannabis group. Cultural attitudes – from personal, friends-family's and country-state's perspectives – moderated the associations of cannabis use, CUD symptoms, and cannabis use related problems with RSFC within the salience, executive control, and default mode networks. No group differences in between-network RSFC were observed, but personal perceived benefits and country-state perceived harms moderated the association between CUD symptoms and RSFC between the dorsal and ventral default mode network.

Conclusions. This study highlights the importance of considering individual differences in the perceived harms and benefits of cannabis use as a factor in the associations between brain functioning and cannabis use, CUD symptoms, and cannabis use related problems.

Introduction

The global increase in lenient cannabis policies parallels a reduction in perceived harm (UNODC, 2021). This reduction is associated with higher chances of initiation and persistent cannabis use (Buckner, 2013; Piontek et al., 2013; UNODC, 2021). Also, research into positive (perceived benefits) and negative (perceived harms) attitudes towards cannabis showed that both lower harm perception and higher perceived benefits are associated with higher cannabis use at 12-month follow-up (Holm et al., 2016), with some studies suggesting a larger effect of perceived benefits on use outcomes (e.g., Holm et al., 2014). Given evidence from the growing field of cultural neuroscience demonstrating interactions between sociocultural factors and brain mechanisms it is likely that similar sociocultural neuroscience mechanisms influence cannabis use behaviors (e.g., Ames & Fiske, 2010). However, to date, how cultural attitudes towards cannabis may moderate brain processes related to cannabis use behaviors has not yet been examined.

While interest in the role of cultural factors in brain functioning is growing, the cultural neuroscience perspective has not taken off in the field of substance use disorders. Currently, there is substantial evidence that culture affects cannabis use through its effect on perceived benefits and harms of use (e.g., Holm et al., 2014 and 2016) and that permissive cannabis policies could increase the risk for CUD through earlier initiation of use and higher product potency (Taylor et al., 2019). Cultural factors might also affect the willingness to endorse CUD symptoms and the likelihood to experience the social and interpersonal symptoms associated with CUD (Prashad et al., 2017). Furthermore, cultural differences have been observed in a broad range of brain processes – such as emotion processing (Chiao, 2015), social support processing (Sherman et al., 2009), and cognitive functioning (Kim & Sasaki, 2014) – that have been proposed to be relevant to substance use behavior including CUD. Nevertheless, there is currently no research assessing the more complex interactions between attitudes towards cannabis use, cannabis use, and the brain networks underlying substance use behaviors.

In terms of brain mechanisms, excessive substance use is associated with altered resting-state functional connectivity (RSFC) in a variety of neural networks including the executive control network (ECN; e.g., Hester et al., 2010), salience network (SN; e.g., Zhang & Volkow, 2019), and default mode network (DMN; e.g., Hester et al., 2010; Zhang & Volkow, 2019; Zilverstand et al., 2018). In substance use disorders, it is proposed that increased SN activity in combination with increased DMN involvement at the expense of the ECN results in increased salience of substance related cues and internal mental processes related to use, with a lack of ability to control the resulting urges to use (Zhang & Volkow, 2019).

Studies focusing on RSFC in cannabis users are sparse. Samples are generally small, methods and networks of interest vary over studies, and the direction of the results is inconsistent. Focusing on a central node of the DMN, the posterior cingulate cortex (PCC), Ritchay et al. (2021) showed that regular cannabis users had weaker resting-state functional connectivity between the left PCC and other nodes of the DMN, but had relatively stronger connectivity between the left PCC, cerebellum and left supramarginal gyrus compared to controls. Using EEG, Imperatori et al. (2020) showed that cannabis users had increased connectivity (delta-band) between the SN and ECN, which was also associated with cannabis use related problems. Moreover, Prashad et al. (2018) showed decreased delta power and increased beta, theta, and gamma power in cannabis users compared to controls, indicating increased activity, and reduced inhibitory functioning at rest. These preliminary RSFC finding in cannabis users are in line with findings in other substance use disorder and indicate increased brain activation during rest, which could interfere with a variety of cognitive processes (Prashad et al., 2018). Furthermore, cannabis use has been associated with altered associations between ECN RSFC and behavioral inhibition (Taylor et al., 2021) compared to controls, which might affect control over cannabis use, as well as greater RSFC connectivity in frontolimbic regions associated with symptoms of depression (Shollenbarger et al., 2019), potentially negatively affecting CUD treatment outcomes (Kroon et al., 2020).

The goal of the current study is twofold. First, we aimed to assess differences in within and between network RSFC of three networks proposed to be important in substance use disorders - the ECN, SN, and DMN – between near-daily cannabis users with CUD and controls and evaluate how these differences are associated with measures of cannabis use. Based on limited earlier research and theories explaining the potential role of these networks in substance use disorders, we expect cannabis users to show increased within- and between-network RSFC in the SN and DMN compared to controls. For the ECN we expect the opposite effect, with cannabis users showing a relative decrease in within-network RSFC compared to controls and decreased between-network RSFC with the DMN and SN. In cannabis users, we expect these differences in RSFC to be associated with increased heaviness of use, severity of dependence, and severity of use related problems, but the potential directionality of these effects is unclear from previous studies. Second, this study aimed to explore the potential moderating role of positive (perceived benefits) and negative (perceived harms) attitudes towards cannabis use in the association between RSFC and measures of cannabis use, dependence and cannabis use related problems.

Methods

Participants

Data used in this study were collected in Dallas (Texas, United States of America) and Amsterdam (The Netherlands). A total of 136 near-daily cannabis users with CUD (NL: N = 80; TX: N = 56) and 103 closely matched controls (NL: N = 61; TX: N = 42) were recruited online (i.e., social media) and offline (i.e., flyers) and completed an online and phone screening to examine illegibility (Total: N = 239). Cannabis users were eligible if they used cannabis near-daily (6-7 days/week), scored >1 on the CUD section of the Mini International Neuropsychological Interview (MINI, inclusion based on screening score; Sheehan et al., 1997), and were not seeking treatment for cannabis use disorder (CUD). Individuals in the control group were eligible if they used cannabis less than 25 times in their lifetime and no more than 5 times during the last year but not in the last three months. Additional exclusion criteria for both groups included being a lifetime regular (monthly or more) user of other drugs, being left-handed, current or previous psychological disorders (except ADHS/ADD, anxiety, and depression), current or previous use of medication affecting the brain (e.g., methylphenidate; exception for antidepressants), persistent or severe physical disorders requiring treatment (e.g., diabetes, cancer), excessive alcohol consumption (Alcohol use disorder identification test (AUDIT) score > 12; Saunders et al., 1993), and last month drug use (except cannabis in the CUD group). Participants were asked to not use alcohol or cannabis in the 24 hours before the session. A urine test was used to assess the presence of other substances, and all individuals that tested positive for any drugs (except cannabis in the CUD group) were excluded. Study procedures were approved by the ethical committees of the Department of Psychology of the University of Amsterdam (2018-DP-9616) and the University of Texas Dallas (19-107). All participants provided informed consent before participation.

Measures

fMRI acquisition

fMRI data were collected in Amsterdam (the Netherlands) and Dallas (Texas, USA). In the Netherlands, data was collected using a 3T Philips Achieva MRI scanner with 32-channel SENSE head coil located at the behavioral science lab (University of Amsterdam). In the USA, data was collected using a 3T Siemens Prisma MRI scanner with 64-channel head coil located at the University of Texas at Dallas' Brain Performance Institute. Matched sequences were used to record T1 anatomical scans (T1 fast field echo, TR = 8.3s, TE = 3.9ms, slices = 220, slice thickness = 1mm, FOV = 240 x 188 x 220mm, voxel size = 1mm x 1mm, flip angle = 8°) and T2* functional scans (T2* single-shot multiband accelerated (MB4) EPI sequence; TR = 0.55 s, TE = 30ms,

slices = 36, slice thickness = 3mm, inter slice gap = 0.3mm, FOV = 240 x 240 x 118.5mm, voxel size = 3mm x 3mm, flip angle = 55°) assessing BOLD responses during rest (eyes closed).

Questionnaires

General. All participants reported on their age, gender (man/woman/other), and years of completed education. IQ was estimated based on the vocabulary and matrix reasoning subtests of the Wechsler Adult Intelligence Scale (Wechsler, 2012). Symptoms of depression and anxiety were assessed using Beck's depression inventory (BDI-II; Beck et al., 1961) and the state-trait anxiety inventory (STAI; Spielberger & Sydeman, 1994) respectively.

Cannabis use. DSM-5 CUD symptom severity was assessed using the MINI CUD semi-structured interview (version 7.0.2.; Sheehan et al., 1997). Heaviness of cannabis use was assessed as self-reported grams per week. Cannabis use related problems were assessed using the marijuana problem scale (MPS; Stephens et al., 2000). The cannabis use disorder identification test (CUDIT-R; Adamson et al., 2010) and age of onset were used as additional descriptive measures as these are commonly used in the literature to describe cannabis use behavior.

Other substance use. The AUDIT was used to assess alcohol consumption and associated problems. The Fagerström test for nicotine dependence (FTND; Heatherton et al., 1991) and a self-report measure of daily cigarette use were used to assess nicotine dependence and nicotine use, respectively. A substance use history questionnaire was used to assess lifetime use of other drugs.

Cannabis attitudes. To assess cannabis attitudes, we used an adapted 2-scale version of the cannabis culture questionnaire (CCQ; Holm et al., 2016). The two scales reflected positive (perceived benefits of cannabis) and negative (perceived harms of cannabis) attitudes towards cannabis use and participants were asked to complete all items three times to assess these attitudes from three different perspectives: personal perspective, perceived perspective of friends/family, and perceived perspective of country (NL) or state (TX-US). Separate scores were calculated for each perspective, per subscale, resulting in six cultural attitude scores.

Data analysis

Sample characteristics

Chi-square tests were conducted to assess group (CUD – Control) differences on categorical variables. Independent sample t-tests were used to assess group differences on continuous variables. A linear mixed model approach with maximum likelihood estimation and random intercepts was used to assess the effects of group, perspective

(Personal/FamilyFriends/CountryState), and their interaction on cultural attitude scores. Subject and perspective were added as random variables to account for the repeated measures structure (i.e., all perspectives presented to all participants) of the data. Analyses were conducted in RStudio version 2022.12.0 (RStudio Team, 2022) using R version 4.2.2 (R Core Team, 2022), and JASP version 0.17.1.0 (JASP Team, 2023).

fMRI data – pre-processing

fMRI data pre-processing and analysis were conducted in Harmonized AnaLysis of Functional MRI pipeline (HALFpipe version 1.2.2 (Waller et al., 2022)), running fmriprep (Esteban et al., 2017) and FSL (version 6.0; Jenkinson et al., 2012). Denoising (ICA-AROMA), spatial smoothing (FWHM = 6mm), grand mean scaling (M = 10.000), and temporal filtering (125s) were applied to the data before registration to the MNI152 template. Output was manually checked for quality, registration problems, and excessive movement (maximum framewise displacement >4 mm, average framewise displacement >.5 mm).

fMRI data – within-network

Using Dual Regression in FSL (version 6.0; Jenkinson et al., 2012), we estimated within-network resting state functional connectivity (RSFC) for each network of interest: the left executive control network (LECN), right executive control network (RECN), ventral default mode network (vDMN), dorsal default mode network (dDMN), anterior salience network (aSN) and the dorsal salience network (dSN). Mean time series were extracted from the ROI templates representing these networks (Shirer et al., 2012) before the activity time series from each of these networks were regressed out of the individual timeseries, resulting in an individual within-network RSFC map for each network of interest. Focusing on our networks of interest, randomise permutation tests (5000 permutations, threshold-free cluster enhancement and family-wise error (FWE) correction applied) as implemented in FSL (version 6.0; Jenkinson et al., 2012) were used to assess 1) group differences in within-network RSFC, 2) associations between measures of cannabis use (CUD, MPS, Gram/Week) and within-network RSFC in the CUD group, and 3) whether cultural attitudes towards cannabis use moderated those associations. Site was added as a regressor to the models to control for potential effects of scanner differences and sensitivity analyses were conducted to assess whether any of the observed interactions with cannabis attitudes could also be explained by site differences. As all moderation analyses were exploratory, no strict multiple comparison corrections were applied across the different cannabis attitude measures. However, moderation effects that survived Bonferroni multiple comparison correction are highlighted in the results table.

fMRI data – between-network

To assess between-network RSFC of our networks of interest, individual between-network partial correlation networks were created from the within-network RSFC maps using FSLnets toolbox in Matlab (as implemented in FSL version 6.0; Jenkinson et al., 2012). Using randomise permutation tests (5000 permutations, FWE-correction applied) as implemented in FSLnets, between-network RSFC was compared between groups, before assessing the associations of measures of cannabis use (CUD, MPS, Gram/Week) with between-network RSFC in the CUD group, and whether cultural attitudes towards cannabis use moderated those associations. Site was added as a regressor to the models to control for potential effects of scanner differences and sensitivity analyses were conducted to assess whether any of the observed interactions with cannabis attitudes could also be explained by site differences. The analyses were pre-registered (August 24, 2022, https://osf.io/sx84t/?view_only=e762208b257543e78b21131a75f22d59).

Table 1. Sample characteristics

Measure	Unit	CUD (N=110)	Control (N=79)	Total (N=189)	T-test
Gender[1]	%m/f/o	56.364/42.727/.909	43.038/56.962/.000	50.794/48.677/.529	$X^2(2,N=189) = 4.240$, $p = .120$
Age	M(SD)	22.964(3.359)	22.759(3.211)	22.878(3.291)	t(187) = .420, $p = .678$
Education years	M(SD)	15.568(2.928)	16.563(2.504)	15.984(2.795)	t(187) = 2.446, $p = .015$
Estimated IQ	M(SD)	9.191(2.660)	10.687(2.464)	9.875(2.671)	t(162) = 3.709, $p < .001$
BDI	M(SD)	12.018(9.000)	5.810(5.411)	9.423(8.279)	t(187) = 5.460, $p < .001$
STAI-trait	M(SD)	40.673(10.398)	34.658(8.517)	38.159(10.082)	t(187) = 4.223, $p < .001$
DSM-cross level 1	M(SD)	15.882(9.126)	9.544(5.463)	13.233(8.396)	t(187) = 5.503, $p < .001$
AUDIT	M(SD)	6.181(3.308)	6.491(3.910)	6.298(3.538)	t(149) = .521, $p = .603$
Daily smoker	%yes/no	13.924/86.076	30.909/69.091	23.810/76.190	$X^2(1,N=189) = 7.312$, $p = .007$
Cigarettes per day	M(SD)	8.029(4.380)	7.000(2.966)	7.778(4.073)	t(43) = .725, $p = .473$
Other drug use	M(SD)	2.618(2.116)	.785(1.499)	1.852(2.086)	t(187) = 6.601, $p < .001$
Cannabis use and related problems					
CUD score	M(SD)	5.627(2.102)	-	-	-
MPS	M(SD)	6.464(5.455)	-	-	-
Gram/Week	M(SD)	9.081(7.456)	-	-	-
CUDIT-R	M(SD)	16.064(5.407)	-	-	-
Last month use days	M(SD)	26.796(7.801)	-	-	-
Age of onset	M(SD)	16.083(1.910)	-	-	-
Cultural attitudes					
Pos: Personal	M(SD)	24.645(4.340)	17.759(3.956)	21.767(5.386)	t(187) = 11.160, $p < .001$
Pos: Friends/Family	M(SD)	20.518(4.900)	16.620(4.462)	18.889(5.089)	t(187) = 5.597, $p < .001$
Pos: Country/State	M(SD)	17.409(4.327)	16.025(3.389)	16.831(4.011)	t(187) = 2.368, $p = .019$
Neg: Personal	M(SD)	14.745(4.534)	19.278(4.452)	16.640(5.017)	t(187) = 6.831, $p < .001$
Neg: Friends/Family	M(SD)	18.527(4.883)	20.532(4.870)	19.365(4.965)	t(187) = 2.786, $p = .006$
Neg: Country/State	M(SD)	22.555(4.363)	22.304(4.558)	22.450(4.436)	t(187) = .382, $p = .703$

Note. M = mean, SD = standard deviation, m = male, f = female, o = other gender, BDI = Beck's depression inventory, STAI = state trait anxiety inventory, DSM-cross level 1 = DSM-5 cross level 1 mental health symptom checklist, AUDIT = alcohol use disorder identification test, CUD = cannabis use disorder, MPS = marijuana problem scale, CUDIT-R = cannabis use disorder identification test – revised, Pos = positive, Neg = negative.

Results

Sample characteristics

A total of 22 participants were excluded based on data quality (including excessive motion and registration problems; N = 15), brain anomalies (N = 1), and positive drug tests (N = 6), resulting in a total sample of 189 (CUD: N = 110, Control: N = 79; See Appendix F - Table S1 for full exclusion overview). The CUD and control group were closely matched on gender, age, alcohol use and related problems, and cigarettes per day within the group of daily smokers (Table 1). However, the CUD group included more daily cigarette smokers, reported less years of education, had lower estimated IQ, more mental health problems, and reported higher other drug use (excluding alcohol, tobacco, and cannabis). In the CUD group, the mean CUD symptoms indicated moderate CUD severity (M = 5.6, SD = 2.1) and near-daily cannabis use in the month prior to the study (M = 26.8, SD = 7.8). Appendix F - Table S2 provides an overview of the sample characteristics separated by site and group.

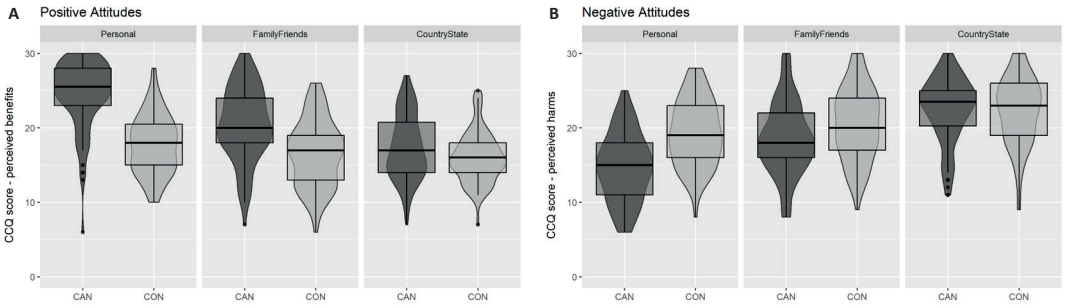


Figure 1. Group differences in cultural attitude scores depending on perspective

A) positive attitude scores on the personal, family/friends, and Country-State level split over groups.

B) negative attitude scores on the personal, family/friends, and Country-State level split over groups; Violin plots showing the data distribution with boxplots showing median and quartiles. CAN = cannabis users with cannabis use disorder group, CON = control group, CCQ = cannabis culture questionnaire.

Cultural attitudes

Linear mixed model analyses showed a group-by-perspective interaction in their effects on cultural attitude scores (Appendix F - Table S3) for both positive (Group*CS-FF: B = -2.502, SE(B) = .750, t = 3.352, p < .001; Group*CS-P: B = -5.502, SE(B) = .750, t = 7.335, p < .001) and negative (Group*CS-FF: B = 2.255, SE(B) = .762, t = 2.960, p = .003; Group*CS-P: B = 4.784, SE(B) = .762, t = 6.280, p < .001) attitudes. Follow-up simple comparisons showed that the CUD group was more positive and less negative than controls (personal attitudes), perceived their friends to be more positive and

less negative than controls, and perceived their country/state to be more positive than controls (Table 1; Figure 1). However, no group differences between perceived country/state negative attitudes were observed.

Within-network functional resting state connectivity

Looking at group differences, controls showed higher within-network RSFC in the dSN - particularly in a cluster including the lateral occipital lobe (LOL), superior parietal lobe (SPL), and precuneus - compared to CUD (Appendix F - Table S4). Regression analyses showed a small but significant negative association between grams of cannabis used per week and dSN (small cluster in supramarginal gyrus) RSFC in the CUD group (Appendix F - Table S4), while no associations of MPS and CUD scores with RSFC in any of the networks were observed.

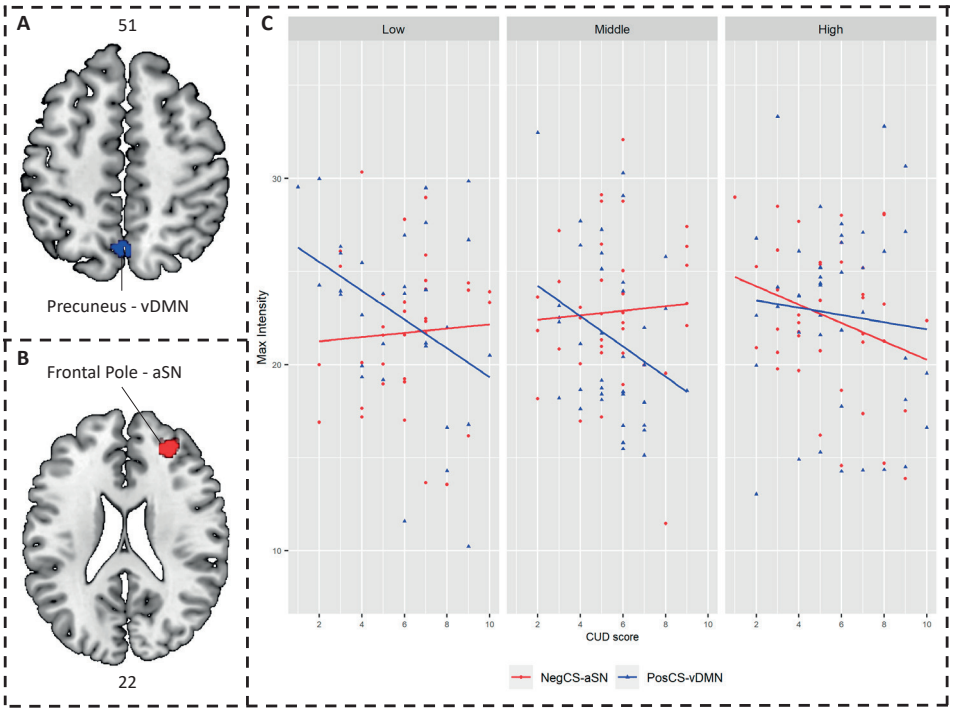


Figure 2. Associations between within-network resting state functional connectivity and CUD scores: the moderating role of cannabis attitudes.

A) transversal view of the precuneus cluster as part of the ventral default mode network (vDMN), image MNI Z-coordinate = 51,
B) transversal view of the frontal pole cluster as part of the anterior salience network (aSN), image MNI Z-coordinate = 22,
C) moderating effects of negative country/state (NegCS) and positive country/state (PosCS) attitudes on the associations between maximum extracted cluster intensity (y-axis) and CUD scores (x-axis). A tertiary split was used to visualize the effect of the continuous culture variables.

Moderation analyses showed that positive country/state attitudes moderated the association between vDMN RSFC and CUD scores (Figure 2A & C; precuneus), while negative country-state attitudes moderated the association between aSN RSFC and CUD scores (Figure 2B & C; frontal pole). The association between CUD scores and vDMN (precuneus) RSFC appears less negative in those perceiving more positive country-state attitudes. Additionally, the association between CUD score and aSN (frontal pole) RSFC is positive in those perceiving less negative country-state attitudes, while this association is negative in those perceiving more negative country-state attitudes.

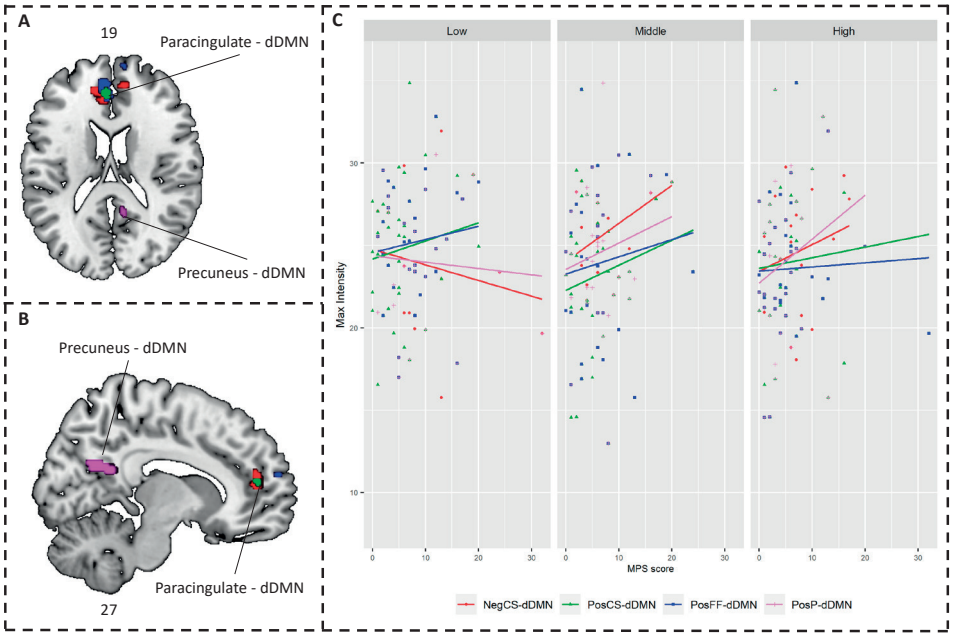


Figure 3. Associations between within-network resting state functional connectivity and MPS scores: the moderating role of cannabis attitudes.

A) transversal view of the three paracingulate and the precuneus clusters as part of the dorsal default mode network (dDMN), image MNI Z-coordinate = 19,

B) sagittal view of the three paracingulate and the precuneus clusters as part of dDMN, image MNI Z-coordinate = 27,

C) moderating effects of negative country/state (NegCS), positive country/state (PosCS), positive friends/family (PosFF) and personal positive (PosP) attitudes on the associations between maximum extracted cluster intensity (y-axis) and marijuana problem scale (MPS) scores (x-axis). A tertiary split was used to visualize the effect of the continuous culture variables.

The association between MPS scores and dDMN RSFC was moderated by personal positive (Figure 3A-C; precuneus, PCC), friend/family positive (Figure 3A-C; paracingulate, ACC), country/state positive (Figure 3A-C; paracingulate, ACC), and country/state negative attitudes (Figure 3A-C; paracingulate, ACC). Looking at perceived family/friend and country/state positive attitudes, the association between MPS scores and dDMN (paracingulate) RSFC appears to become less positive with higher perceived positive attitudes. Conversely, looking at perceived country/state negative attitudes, this association becomes more positive with higher perceived negative attitudes. A different pattern is observed for the association between MPS scores and dDMN (precuneus) RSFC: the association appears to be more positive in those with more positive personal attitudes.

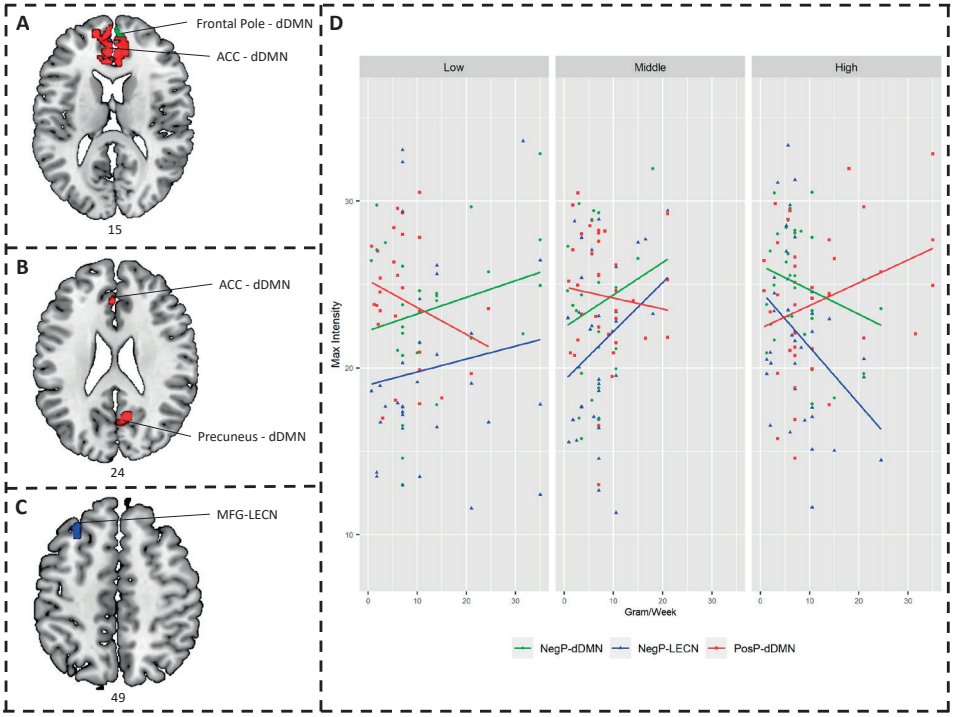


Figure 4. Associations between within-network resting state functional connectivity and gram/week: the moderating role of cannabis attitudes.

A) transversal view of the anterior cingulate cortex (ACC) and the frontal pole clusters as part of the dorsal default mode network (dDMN), image MNI Z-coordinate = 15,
B) transversal view of the ACC and the precuneus clusters as part of dDMN, image MNI Z-coordinate = 24,
C) transversal view of the medial frontal gyrus (MFG) cluster as part of the lateral executive control network (LECN), image MNI Z-coordinate = 49,
D) moderating effects of personal negative (NegP) and personal positive (PosP) attitudes on the associations between maximum extracted cluster intensity (y-axis) and grams of cannabis used per week (gram/week; x-axis). A tertiary split was used to visualize the effect of the continuous culture variables.

Furthermore, personal positive (ACC, paracingulate, precuneus; Figure 4A, B & D) and negative attitudes (frontal pole; Figure 4A & D) moderated the association between dDMN RSFC and grams of use per week. Personal negative attitudes (middle frontal gyrus; Figure 4 C & D) moderated the association between LECN RSFC and grams of use per week (Figure 4A & B). Looking at personal negative attitudes, the association between grams/week and both dDMN (frontal pole) and LECN (middle frontal gyrus (MFG)) RSFC appears to be more negative in those with more negative attitudes towards cannabis. Looking at personal positive attitudes, the pattern is reversed: the association between grams/week and dDMN (ACC & precuneus) RSFC is more positive in those with more positive attitudes towards cannabis.

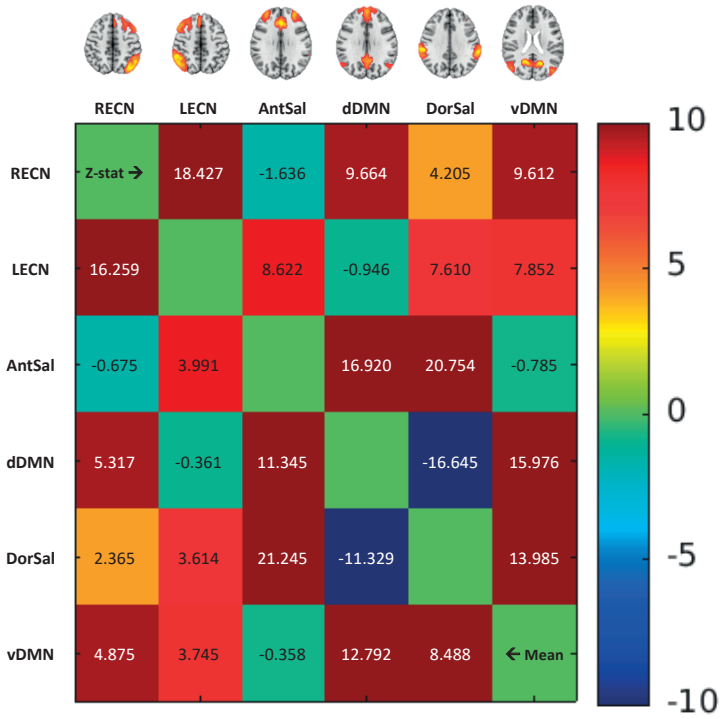


Figure 5. Between network connectivity across groups.
Overview of mean (arbitrary unit; below diagonal) between-network resting state functional connectivity (RSFC) strength across group and standardized scores (z-stat; above diagnonal) around the mean (color grading indicating Z-stat). Positive mean scores indicate positive RSFC between networks (positive partial correlation) and negative scores indicate negative RSFC between the networks (partial anti-correlation). RECN = right executive control network, LECN = left executive control network, AntSal = anterior salience network, dDMN = dorsal default mode network, DorSal = dorsal salience network, vDMN = ventral default mode network.

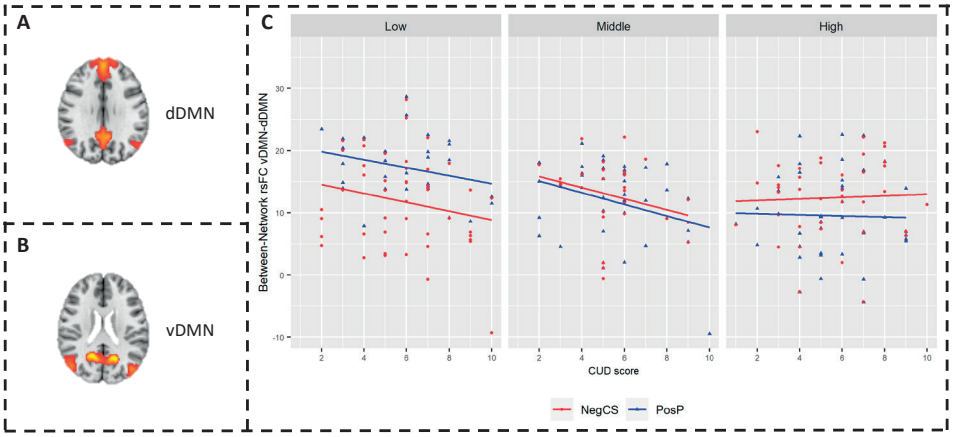


Figure 6. Moderating role of cannabis attitudes in association between CUD scores and between-network RSFC of the dorsal default mode network (dDMN; A) and ventral default mode network (vDMN; B). C) moderating effects of personal positive (PosP) and negative country/state attitudes on the associations between mean between-network RSFC of the vDMN and dDMN (y-axis) and CUD (x-axis) scores. A tertiary split was used to visualize the effect of the continuous culture variables.

Between-network functional resting state connectivity

Between-network connectivity across groups is presented in Figure 5. No group differences in between-network RSFC were observed (lowest p = .501). Similarly, between-network RSFC was not associated with CUD scores (lowest p = .816), MPS scores (lowest p = .699), or grams/week (lowest p = .360). However, personal positive (p = .021) and perceived negative country/state (p = .015) attitudes moderated the association between CUD scores and between-network RSFC of the dDMN and vDMN (Figure 6). Between-network RSFC of the dDMN and vDMN was negatively associated with CUD scores in those that had less positive personal attitudes or perceived their country to be less negative. However, this negative association of between network RSFC between the dDMN and vDMN and CUD scores is diminished with increasing personal positive attitudes and increasing perceived country state negative attitudes. No other moderation effects were observed (CUD: lowest p = .163, MPS: lowest p = .111, grams/week: lowest p = .101).

Discussion

In this study we assessed differences in within- and between-network RSFC between near-daily cannabis users and controls - recruited from two sites with varying cannabis jurisdiction – and assessed whether RSFC was associated with measures of cannabis use and related problems. Furthermore, we explored how individual differences in attitudes towards cannabis use moderated these associations.

The CUD group showed more positive and less negative attitudes towards cannabis use and reported their proximal environment to be more positive and less negative. However, looking at country/state attitudes, the CUD group reported higher perceived positive attitudes than controls while no differences in perceived negative attitudes were observed. Group differences and associations with cannabis use measures were only observed in the salience network – which contrasted with our hypotheses. However, cultural attitudes from varying perspectives moderated the association between measures of cannabis use related problems and RSFC, revealing a complex pattern of interactions in the salience, executive control, and default mode networks.

In contrast to what we expected, RSFC within the dSN (SPL, LOL, and precuneus RSFC with other dSN areas) was lower in the CUD than the control group. In line with this, within the CUD group, cannabis use (gram/week) was negatively associated with RSFC in this network, suggesting the group difference might be partially guided by heaviness of use. These results add to a mixed evidence base in which studies with different methods have found evidence for increases as well as decreases in RSFC in the CUD compared to the control group between parietal regions and other brain regions (e.g., Thomson et al., 2021). However, within dSN network RSFC is rarely studied and using a data-driven approach to identify RS networks (i.e., rather than seed-based connectivity) Filbey et al. (2018) also found relatively higher within-network RSFC in controls in parietal regions that are part of the dSN (Filbey et al., 2018). No group differences in between-network RSFC were observed and between-network RSFC was not directly associated with measures of cannabis use in the CUD group. These results are inconsistent with previous studies commonly showing seed based RSFC differences between regions of different networks (Thomson et al., 2021). This could be attributed to the difference in methods as our study focussed on partial correlations – controlling for all other associations between networks – which might result in lower connectivity indices in general.

Moderation analyses revealed complex interactions between measures of cannabis use and cultural attitudes in their association with within-network RSFC, suggesting that cultural attitudes play a role in within-network RSFC beyond group membership. Across networks, RSFC of the frontal pole – as part of the aSN and dDMN – was more negatively associated with cannabis use measures (CUD and gram/week) in those with relatively more negative attitudes (personal and country/state) towards cannabis use, with the same pattern being observed in the RSFC of another frontal region (MFG – as part of the LECN). Precuneus RSFC - as part of the dDMN and vDMN – was more positively (or less negatively) associated with cannabis use measures (CUD, MPS, gram/week) in those with relatively higher positive attitudes (personal and country/state) towards cannabis use. So, within the CUD group, those that were personally

more negative or perceived more negative country state attitudes showed lower RSFC of frontal regions with increasing use and CUD symptoms. Similarly, those that were personally less positive or perceived their country/state to be less positive showed lower RSFC of the precuneus with increasing use and CUD symptoms. Although speculative, those who are more negative/less positive and score high on CUD might be more aware of the severity of their problems, with self-awareness about severity being associated with altered functioning of brain regions involved in introspection (default mode network) and cognitive control (frontal regions).

In the paracingulate/ACC – as part of the dDMN – the exact opposite patterns were observed for both country/state negative and country/state and friends/family positive attitudes towards cannabis in their associations with cannabis use related problems (MPS). Individuals with CUD that were personally less negative or more positive showed lower RSFC in the paracingulate with higher experienced cannabis use related problems (MPS). Although speculative and in contrast with RSFC of the frontal and precuneus regions, it could be the case that those who have a more positive/less negative attitude but score high on cannabis related problems, have a larger mismatch between expectations (attitudes) and experiences, which might be associated with altered functioning of the paracingulate and anterior cingulate cortex, a known hub between networks associated with functions important in addiction such as emotion, cognition, reward, and salience (Zhao et al., 2021).

These results indicate that while positive and negative attitudes (within the same brain region) appear to have opposite moderating effects, the direction is highly dependent on the network/area. Furthermore, moderating effects with CUD were only observed with country/state attitudes and moderating effects with gram/week were only observed with personal attitudes. MPS scores interacted with all perspectives in their association with within-network RSFC. Although speculative, this could indicate that personal attitudes are more associated with quantity of use, while more proximal perceived attitudes are more associated with self-reported psycho-social problems experienced by their use.

The between-network RSFC moderation analyses revealed interactions between CUD scores and both positive personal and negative country/state attitudes in their association with vDMN-dDMN connectivity. Those that were personally more positive and those experiencing more negative country/state attitudes both showed a less negative association between CUD scores and vDMN-dDMN connectivity. Although methods differed, these results differ from the within-network RSFC analyses in the sense that positive and negative attitudes did not follow opposite patterns within the same region, or in this case connection between regions. Although speculative, it appears that those with less prominent cannabis attitudes (in both directions) that

experience less CUD symptoms show relatively stronger RSFC between networks that have been associated with valence (dDMN) and vividness of imagined events (vDMN) – which could be associated with more accurate evaluation of personal problems and expectations of use in those with less severe problems when they do not hold very strong opinions about the benefits and harms associated with cannabis use (Lee et al., 2021).

In general, results suggest that cannabis attitudes might primarily interact with RSFC in parietal and frontal regions that are part of the default mode, salience, and executive network, indicating widespread influence on resting state connectivity of networks crucial for a variety of substance use related functions including salience processing, cognition, introspection, and emotion regulation (Hester et al., 2010; Zhang & Volkow, 2019; Zilverstand et al., 2018). Sensitivity analyses, replacing cannabis attitudes by site in the moderation, revealed that only the interaction between personal negative attitudes and gram/week in their association with frontal pole (aSN and dDMN) within-network RSFC could be explained by site effects as well. All other moderation effects were selective to cannabis attitudes, and not the difference in country and potentially legislation, highlighting the importance to look beyond site effects when assessing the role of cannabis culture. However, replication is crucial to confirm these preliminary findings. Additionally, this study only tested associations in a limited number of networks, therefore future studies are needed to test for similar interactions in other relevant networks, including limbic regions.

While this study is an important first step towards unravelling the complex role of cultural attitudes towards cannabis use in the brain processes underlying CUD, a couple of limitations should be noted. First, the CUD and control groups were not matched on all variables. The CUD group included more cigarette users, reported higher lifetime other drug use, had lower education, and estimated IQ, and reported more mental health problems. While part of the effects could be associated with those differences, these differences also reflect the real-world differences between the general population and the population of near-daily cannabis users with CUD who are likely to be lower educated (e.g., Lorenzetti et al., 2020), use more drugs (e.g., Degenhardt et al., 2001) and experience more mental health problems (e.g., Van Ours & Williams, 2011) and these differences are common in similar studies (Thomson et al., 2021). Second, causality of the effects of cultural attitudes on the associations between RSFC and cannabis use outcomes cannot be determined with the current design. Longitudinal studies are needed to assess changes of cultural attitudes over time during the development of CUD and during times of changes in legislation to investigate how these moderation effects arise. Third, replication is crucial to conform our preliminary findings, also because not all associations do survive strict multiple

comparison correction. Furthermore, research is needed to investigate the differences between perceived positivity/negativity towards cannabis use and objective legal measures across multiple locations over time.

In a time of constant changes in legislation and attitudes towards cannabis use, this study highlights the importance of considering individual differences in attitudes towards the harms and benefits of cannabis use as a factor in the associations between brain functioning and cannabis use, CUD and cannabis use related problems. This study provides a starting point for future research, encouraging others to look beyond group and location differences in brain-behavior associations, and to invest in longitudinal studies assessing how changes in cannabis attitudes might affect those associations.

Chapter 10

Working memory related brain activity in cannabis use disorder: the role of cross-cultural differences in cannabis attitudes

This chapter is based on:
Kroon, E., Kuhns, L., Colyer-Patel, K., Filbey, F. & Cousijn, J. (2023) Working memory related brain activity in cannabis use disorder: the role of cross-cultural differences in cannabis attitudes. *Addiction Biology, 28*(6), e13283. https://doi.org/10.1111/adb.13283

Abstract

Cannabis legislation and attitudes towards use are changing. Given that evidence from cultural neuroscience research suggests that culture influences the neurobiological mechanisms underlying behavior, it is of great importance to understand how cannabis legislation and attitudes might affect the brain processes underlying cannabis use disorder. Brain activity of 100 dependent cannabis users and 84 controls was recorded during an N-back working memory (WM) task in participants from the Netherlands (NL; users = 60, controls = 52) and Texas, US (TX; users = 40, controls = 32). Participants completed a cannabis culture questionnaire as a measure of perceived benefits (positive) and perceived harms (negative) of cannabis from their personal, friends-family's, and country-state's perspectives. Amount of cannabis use (grams/week), DSM-5 CUD symptoms, and cannabis-use-related problems were assessed. Cannabis users self-reported more positive and less negative (personal and friends-family) cannabis attitudes than controls, with this effect being significantly larger in the TX cannabis users. No site difference in country-state attitudes were observed. TX cannabis users, compared to NL cannabis users, and those cannabis users perceiving more positive country-state attitudes showed a more positive association between grams/week and WM-related activity in the superior parietal lobe. NL cannabis users, compared to TX cannabis users, and those cannabis users with less positive personal attitudes showed a more positive association between grams/week and WM-load-related activity in the temporal pole. Both site and cultural attitudes moderated the association of quantity of cannabis use with WM- and WM-load related activity. Importantly, differences in legislation did not align with perceived cannabis attitudes and appear to be differentially associated with cannabis-use-related brain activity.

Introduction

Daily life is influenced by cultural norms and values, and regional differences herein can give rise to differences in behaviors. The emerging field of cultural neuroscience (Chiao et al., 2013; Kim & Sasaki, 2014) focuses on the interactions between neurobiological mechanisms and culture in their effects on behavior. These interactions may be particularly evident for the strongly polarized cultural norms and values associated with cannabis use. Cannabis is the most commonly used illicit substance worldwide (UNODC, 2021), but there are substantial regional differences in use prevalence (e.g. ±2% in Asia vs. ±15% in Noth America, UNODC, 2021), legislation, and local cannabis culture and norms (Reinarman & Cohen, 2007). In this study comparing individuals from The Netherlands (NL) and Texas, United States (TX), the legislative differences are evident: while recreational cannabis use has been decriminalized since 1976 in The Netherlands, recreational cannabis use is still illegal in Texas. Past-decade changes in cannabis legislation have been paralleled by reductions in harm perception (Buckner, 2013; Piontek et al., 2013; UNODC, 2021). On an individual level, the tendency to neutralize cannabis-related harms (Holm et al., 2016) and glorify its benefits is associated with higher cannabis consumption (Holm et al., 2014). While the effects of cultural attitudes on cannabis use are relatively well-established, it is unclear how this affects underlying neurobiological processes. Differences in the neurobiology of Cannabis Use Disorder (CUD) between individuals and regions with different attitudes towards cannabis could affect CUD trajectories and treatment.

Cultural neuroscience research revealed cross-cultural differences in the neural processes underlying the representation of the self (Kitayama & Park, 2010), emotion processing (Chiao, 2015), processing social support (Sherman et al., 2009), as well as cognitive functions (Kim & Sasaki, 2014). Moreover, where East-Asians showed higher brain activity in fronto-parietal regions during an attentional task that required ignoring context, the reverse was true for European Americans when required to attend to the context (Hedden et al., 2008). However, cultural differences in the neurobiological underpinnings of maladaptive behavior has been largely unexplored.

Most addiction theories highlight the importance of cognitive control related brain processes in escalation and eventual loss of control over use (Bickel et al., 2018; Robinson & Berridge, 1993). Focusing on working memory (WM; a central executive function underlying cognitive control) results are inconsistent (Kroon et al., 2021). Multiple studies reported altered WM-related activation in cannabis users compared to controls, including higher fronto-parietal activation (putative compensation mechanism, Owens et al., 2019; Padula et al., 2007; Sagar & Gruber, 2019; Schweinsburg et al., 2010) and relatively higher default mode-related activation when task difficulty

increased (altered resource allocation, Kroon et al., 2022), sometimes even in the absence of performance differences (Cousijn, Wiers et al., 2014; Hatchard et al., 2020).

Given the observed links between 1) cannabis use and cultural attitudes towards use, 2) cannabis use and altered cognitive control-related brain processes, and 3) culture and brain function, the goal of this study was to assess how cultural attitudes towards cannabis relate to the cognitive brain processes implicated in CUD. First, we assessed positive (perceived benefits) and negative (perceived harms) personal attitudes, perceived attitudes of friends and family, and perceived attitudes of those living in the same state/country towards cannabis use in individuals with a CUD and closely matched controls living in TX and NL. Based on their polarized cannabis legislation (i.e. decriminalized in the Netherlands and illegal in TX), we expected the NL participants to experience a more permissive cannabis culture (more positive/less negative) than the TX participants (less positive/more negative). Second, we assessed WM performance and WM-related brain activity, expecting worse performance in cannabis users versus controls and higher WM-related brain activity in fronto-parietal (Schweinsburg et al., 2010) and default mode regions (Kroon et al., 2022). Third, we assessed whether WM-related brain activity was associated with measures of cannabis use, differentiating between heaviness of use (quantity) and severity of the problems associated with use (self-reported problem measure and DSM-5 CUD symptoms), before assessing the role of site (NL vs. TX) and cultural attitudes in these associations.

Loss of control and compromised functioning of the fronto-parietal network is thought to be central to substance use disorders (Bickel et al., 2018; Robinson & Berridge, 1993). Development and maintenance of substance use disorders are also affected by ones' social environment (Ewald et al., 2019). Social (and non-social) conflict is considered an important instigator of control behavior (Inzlicht et al., 2015). Social conflict, in part shaped by cultural norms, is expected to influence the need to control cannabis use and the internal conflict one experiences with regards to their cannabis use. However, it is unclear to what extent CUD in opposing cultural environments is shaped more strongly by 1) psychosocial symptoms (e.g. symptoms indicative of a failure to fulfil responsibilities, a reduction of social interactions, and experiencing social/interpersonal problems), 2) loss of control (i.e. altered control-related brain functioning, or behavioral indicators of loss of control such as substantial time spend on use, craving, and inability to quit), or both.

We proposed two conflicting hypotheses that might explain how cultural attitudes in Dutch and Texan individuals with CUD affect associations of their heaviness of use and severity of cannabis use related problems with WM-related brain activity; the 'need to control' and 'social symptoms' hypotheses. Individuals who experience a more permissive cannabis culture may not need to conceal their use and receive

less negative social feedback regarding their use. Hence, they might experience less internal conflict and a reduced perceived 'need to control' their use. Consequently, their reported heaviness of use might be less indicative of control problems than in similarly heavy users from a more restrictive cultural environment. In this case, one would expect to find smaller associations between heaviness of cannabis use and brain measures of control (i.e. altered activation in fronto-parietal regions or default mode regions during the N-back task) in permissive environments: individuals might be able to control their use, but do not experience the 'need to control'. In contrast, users in permissive compared to restrictive environments may experience less 'social symptoms' due to the positive social and legal environment. Hence, similarly high severity levels of cannabis use might be less reflective of 'social symptoms' – their symptom count largely reflective of loss of control (e.g. craving, substantial time spend on use, inability to quit) rather than social problems - in individuals from permissive compared to restrictive environments. In this case, one would expect stronger associations between the severity of cannabis use (i.e. CUD scores and self-reported problems) and brain measures of control (e.g. altered activation in fronto-parietal regions or default mode regions during the N-back task) in the more permissive environment.

Methods and materials

Participants

Data was collected in the Netherlands (NL, Amsterdam) and the United States (US, Dallas, Texas) simultaneously. Participants were recruited both offline (flyers) and online through social media advertisements (i.e. facebook and Instagram) and the university research pool (i.e. students and external research contributors). The cannabis group included 131 non-treatment seeking near-daily (6-7 days/week) cannabis users (NL: 76; TX: 55) with at least a mild CUD (score >1 on MINI International Neurospsychiatric Interview (MINI) 7.0.2; Sheehan et al., 1997). The control group (N = 97; NL: 60; TX: 37) used cannabis a maximum of 25 times, no more than 5 times in the last year, and not within the last 3 months. Exclusion criteria were lifetime regular (monthly or more) other drug use (except cannabis, alcohol and nicotine use), illicit drug use (except cannabis in the cannabis group) in the last month, left-handedness, previous or current psychological diagnoses (except anxiety, depression and ADHD/ADD), severe physical conditions (e.g. cancer), previous or current use of psychotropic medication, or excessive alcohol use (AUDIT score > 12, Saunders et al., 1993). All participants were requested to refrain from alcohol and cannabis 24 hours before testing. A urine drug screen was conducted during the session. All individuals that tested positive on any drugs (except THC in the cannabis group) were excluded from the analysis. All procedures were approved by the ethical committees of the

Department of Psychology of University of Amsterdam (2018-DP-9616 – subset of the collected data published before in Kroon et al., 2022) and the University of Texas Dallas (19-107) and participants signed informed consent before participation.

Measures

N-back task

A letter N-back WM task that included 0-back (recognition), 1-back (low WM-load), and 2-back (high WM-load) blocks, was performed inside an MRI scanner while blood-oxygen-level-dependent (BOLD) signals were recorded. The task included 12 blocks in which all three WM-levels were presented four times in a fixed order (2-back – 0-back – 1-back). Each block (30s) included 15 trials (2s) followed by a break (5s) with written instructions for the next block on screen. Participants were instructed to press the target or non-target button on every trial. For 0-back blocks, the letter 'X' was the target. For 1-back blocks, participants pressed the target button if the letter presented was identical to the previous letter. For 2-back blocks, participants pressed the target button if the letter presented was identical to the letter presented in the trial before last. No feedback was provided during the task.

Questionnaires

General. Participants reported their age, gender, and years of education. IQ scores were estimated with the matrix reasoning and the vocabulary sub-tasks of the Wechsler Adult Intelligence Scale (WAIS-IV, Coalson et al., 2010). Participants completed the Beck's Depression Inventory (BDI-II, Beck et al., 1961) and State-Trait Anxiety Inventory (STAI, Spielberger & Sydeman, 1994) to assess depression and anxiety symptoms.

Cannabis use and related problems. Quantity of cannabis use was assessed as self-reported grams per week (visual tools and experimenter guidance available to enable accurate estimations). DSM-5 CUD severity and related problems were assessed as symptom count on the CUD section of the MINI (Sheehan et al., 1997) and Marijuana Problem Scale (MPS, Stephens et al., 2000) scores respectively. For descriptive purposes, participants reported age of onset and completed the cannabis use disorder identification test (CUDIT-R, Adamson et al., 2010) to assess cannabis use and related problems during the last year.

Other drug use. The AUDIT (Saunders et al., 1993) and the Fagerström test for nicotine dependence (FTND, Heatherton et al., 1991) were used to assess alcohol use and related problems and nicotine dependence during the last year, respectively. Participants reported their daily cigarette use and lifetime use of substances other than cannabis, cigarettes, and alcohol.

Cannabis culture. Cannabis cultural attitudes were assessed using an adapted version – completed from difference perspectives - of the Cannabis Culture Questionnaire (CCQ, Holm et al., 2016). The questionnaire includes twelve items of which six assess positive (perceived benefits/glorification of use; e.g. enhancement effects of cannabis) and six negative (perceived harmful effects/neutralization; e.g. dependence risk) attitudes towards cannabis (See Appendix G - Figure S1). Participants completed all questions three times; from their personal perspective, and from the perceived perspective of their friends/family and their state(TX)/country(NL). Sum scores were calculated per perspective for both positive and negative attitudes.

fMRI acquisition & pre-processing

Data acquisition

Scanning in NL was performed using the 3T Philips Achieva MRI scanner with 32-channel SENSE head coil at the Spinoza Center at the University of Amsterdam. Scanning in TX was performed using the 3T Siemens Prisma MRI scanner with 64-channel head coil at the BrainHealth Performance Institute at the University of Texas at Dallas. Scan sequences were closely matched to record structural reference scans (T1 fast field echo, TR = 8.3s, TE = 3.9ms, slices = 220, slice thickness = 1mm, FOV = 240mm x 188mm x 220mm, voxel size = 1mm x 1mm, flip angle = 8°) and BOLD responses during the N-back task (T2*single-shot multiband accelerated (MB4) EPI sequence; TR = 0.55 s, TE = 30ms, slices = 36, slice thickness = 3mm, inter slice gap = 0.3mm, FOV = 240mm x 240mm x 118.5mm, voxel size = 3mm x 3mm, flip angle = 55°).

Data analysis

Sample characteristics & culture

Group and site differences in descriptive measures were assessed using ANOVAs with Bonferroni corrected post-hoc comparisons, Bonferroni corrected simple comparison chi-square tests, or Bonferroni-corrected Mann-Whitney-U tests. A linear mixed model approach (maximum likelihood estimation, random intercepts) was used to assess the effect of group, site, level, and their interaction on cultural attitudes, considering the grouping structure of the data by adding subject, group, and site as random effects. Analysis were conducted in JASP version 0.14.1 (JASP Team, 2020) and R version 4.1.2 (R Core Team, 2021).

N-back task performance

Accuracy (% correct) was used as the outcome measure and calculated per trial type. All blocks in which an individual scored below 50% correct (chance performance) were deleted. A linear mixed model approach (maximum likelihood estimation,

random intercepts) was used to assess the effect of group, site, and their interaction on accuracy while considering the grouping structure by adding subject, group, and site as random effects. All possible models that included at least group and site were ran and model selection was based on Akaike Information Criterion (AIC). Analyses were conducted in R version 4.1.2 (R Core Team, 2021).

Pre-processing & fMRI analysis

fMRI pre-processing was conducted using fmriprep (Esteban et al., 2017) as implemented in Harmonized AnaLysis of Functional MRI pipeline (HALFpipe version 1.2.2., Waller et al., 2022). fMRI analyses were conducted in FSL (Jenkinson et al., 2012). Pre-processing and initial analysis steps included denoising (ICA-AROMA), spatial smoothing (6mm FWHM), grand mean scaling (mean = 10000), temporal filtering (90s), and registration to the MNI 152 template. A general linear model (GLM) analysis was performed (FSL FEAT, Woolrich et al., 2001) with the different trial types added as regressors, convolved with a double gamma hemodynamic response function. Two contrasts of interest were included to assess the effect of WM (2-back (high load) – 0-back (recognition)) and WM-load (2-back (high load) – 1-back (low load)). After manual quality control, participants with excessive motion (maximum framewise displacement >3mm) and poor registration were excluded.

Whole brain mixed effects analyses (FSL FLAME1, Woolrich et al., 2004) were performed to assess the effects of group and group by site interaction on WM and WM-load related activity. Within the cannabis group, whole brain mixed effects regression analyses were conducted to assess the association of heaviness of cannabis use (grams/week), CUD severity (MINI CUD score), and cannabis related problems (MPS score) with WM and WM-load related activity. Then, whole brain mixed effects regression analyses were conducted to assess the effect of site on these associations. Individual peak activation was extracted (FSL featquery, Jenkinson et al., 2012) from the significant clusters to conduct follow-up regression analyses assessing whether group differences were associated with task performance, and whether cultural attitudes moderated the association between WM- and WM-load related activity and measures of cannabis use. Sensitivity analyses were conducted to assess whether regression results held after controlling for differences in age, gender, and daily cigarette use. All reported results reflect analyses not including these covariates that were still significant when adding the covariates. Cluster-based multiple comparison correction ($Z>2.3$, $p<.05$) was applied in all analyses and site was added as a regressor to the models to correct for average within site activity associated with scanner differences. Follow-up sensitivity analyses were conducted at a stricter cluster-based multiple comparison correction threshold ($Z>3.1$, $p<.05$) to assess whether the results would survive stricter correction.

Analyses were preregistered (May 18, 2022; https://doi.org/10.17605/OSF.IO/UX74B) and additional analyses are considered exploratory.

Table 1. Sample characteristics

	NL (N = 112)				TX (N = 72)				ANOVA	Post Hoc[1] Simple comparison[1]
	Cannabis (N = 60)		Control (N = 52)		Cannabis (N = 40)		Control (N = 32)			
Measures	**Med (MAD)**	**M(SD)**	**Med (MAD)**	**M(SD)**	**Med (MAD)**	**M(SD)**	**Med (MAD)**	**M(SD)**		
General										
Gender (f/m/o)[2] - %	26.7/73.3/0.0		48.1/51.9/0.0		55.0/40.0/5.0		65.6/34.4/0.0		-	*: 4; ***: 6
Age	21.0(2.0)	21.4(3.2)	21.5(1.5)	22.4(3.2)	24.0(2.0)	24.3(2.6)	23.0(2.5)	23.8(3.2)	Site	*: 5; **: 6; ***: 4
Estimated IQ	10.5(1.5)	10.4(2.4)	12.3(1.3)	11.5(2.1)	11.0(1.5)	11.5(2.1)	12.5(1.0)	12.6(1.8)	Group, Site	*: 1; ***: 6
Education years	15.0(2.0)	15.3(2.1)	16.5(0.5)	16.5(1.9)	14.0(2.0)	14.3(2.7)	16.0(2.0)	15.4(2.5)	Group, Site	*: 1; ***: 5
Cannabis use										
Gram/Week	5.6(2.7)	8.3(19.3)	-	-	7.0(3.5)	11.6(8.8)	-	-	-	***: 4
MINI CUD	5.5(1.5)	5.4(1.9)	-	-	6.0(1.5)	6.0(2.0)	-	-	-	NS
MPS	6.0(3.0)	5.9(3.6)	-	-	4.0(2.0)	4.1(2.2)	-	-	-	*: 4
CUDIT-R	15.5(4.5)	15.4(4.9)	-	-	16.0(3.0)	16.8(5.3)	-	-	-	NS
Age of onset	15.0(1.0)	15.3(1.5)	-	-	17.0(2.0)	16.7(4.5)	-	-	-	NS
Other substance use										
AUDIT	6.0(2.0)	5.9(3.0)	7.0(3.0)	7.5(4.0	5.5(2.0)	6.5(3.9)	4.0(1.0)	3.8(1.4)	Group*Site	**: 3
Daily Cigarette Use - %	46.7		25.0		7.5		0.0		-	*: 3; ***: 4 ,6
FTND	5.0(1.0)	4.9(1.7)	5.0(2.0)	5.5(1.5)	3.0(0.0)	3.7(1.2)	-	-	-	NS
Lifetime drug use	13.5(12.5)	33.3(60.1)	0.5(0.5)	7.9(12.5)	14.5(12.5)	37.8(63.4)	0.0(0.0)	0.2(0.7)	Group	**:2, 6; ***: 1,5
Mental health										
BDI-II	8.0(5.0)	9.9(8.2)	5.5.(3.0)	6.3(4.9)	10.5(7.0)	13.1(9.5)	3.0(3.0)	4.5(6.0)	Group*Site	**: 6; ***: 2, 5
STAI-trait	37.5(6.5)	38.1(9.3)	32.0(5.0)	34.4(8.4)	42.0(9.0)	41.8(11.0)	33.0(5.5)	33.9(8.1)	Group	**: 2, 5
STAI-state	33.5(5.5)	34.4(8.7)	33.0(5.0)	33.3(7.3)	35.0(7.5)	35.5(9.4)	29.0(6.0)	29.4(7.1)	Group	*: 2, 6
Culture assessments										
Positive attitudes										
Personal	24.0(2.0)	23.1(4.3)	17.5(2.5)	17.4(3.7)	27.0(1.0)	26.9(2.1)	18.0(4.0)	18.3(4.5)	Group*Site	***: 1, 2, 4, 5, 6
Friends & Family	20.0(2.5)	19.6(3.9)	17.0(2.0)	16.7(3.3)	23.0(4.0)	22.1(4.9)	17.0(4.0)	16.6(5.0)	Group*Site	*: 4; **: 1,6; ***: 2,5
State or Country	17.0(2.0)	17.0(3.2)	16.0(2.0)	16.8(3.2)	17.0(3.5)	17.5(5.1)	15.0(3.0)	15.8(3.8)	NS	-
Negative attitudes										
Personal	16.0(2.0)	16.8(3.8)	20.0(3.0)	19.5(4.5)	12.5(2.5)	12.3(3.9)	18.0(3.0)	18.0(4.2)	Group*Site	**: 1; ***: 2,4,5
Friends & Family	19.0(3.0)	19.9(4.1)	21.0(3.0)	20.5(4.1)	16.5(2.5)	16.5(4.5)	19.5(4.5)	20.3(5.5)	Group*Site	**: 3, 4; ***: 5
State or Country	24.0(2.0)	23.3(4.3)	22.0(3.0)	21.6(4.1)	22.0(3.0)	21.7(4.9)	23.5(3.5)	22.8(4.6)	Group*Site	NS

Note. All comparisons of continuous data represent significance levels of Mann Whitney U tests; All comparison of categorical data represent significance level of Chi-Square tests; [1] Bonferroni corrections were applied; [2] individuals identifying with a non-binary gender were omitted from the comparison tests; AUDIT: Alcohol Use Disorder Identification Test; BDI-II: Beck's Depression Inventory II; CUDIT-R: Cannabis Use Disorder Identification Test – Revised; FTND: Fagerström Test for Nicotine Dependence; M: Mean; MAD: Median Absolute Deviation; Med: median; MINI CUD: Mini International Neuropsychiatric Interview – Cannabis Use Disorder; MPS: Marijuana Problem Scale; SD: Standard deviation; STAI: State Trait Anxiety Inventory; 1 = NL-CON vs. NL-CAN; 2 = TX-CON vs. TX-CAN; 3 = NL-CON vs. TX-CON; 4 = NL-CAN vs. TX-CAN; 5 = NL-CON vs. TX-CAN; 6 = NL-CAN vs. TX-CON; * $p < .05$, ** $p < .01$, *** $p < .001$

Results

Sample characteristics

From the 228 participants, 44 were excluded resulting in a total of 184 participants (cannabis users: N = 100; controls: N = 84; See overview in Appendix G - Table S1). All cannabis users used 6 or 7 days per week and were well matched across sites on CUD severity, estimated IQ, education duration, alcohol use and related problems, nicotine dependence in daily cigarette smokers, as well as measures of mental health (Table 1). However, the TX cannabis group was older, included more women and less daily cigarette users, and reported higher grams/week cannabis use and more cannabis-use-related problems on the MPS.

The control groups were well matched aside from more daily cigarette users and more alcohol use and related problems in NL than TX. Lifetime other drug use and anxiety levels were higher in the cannabis groups than the control groups.

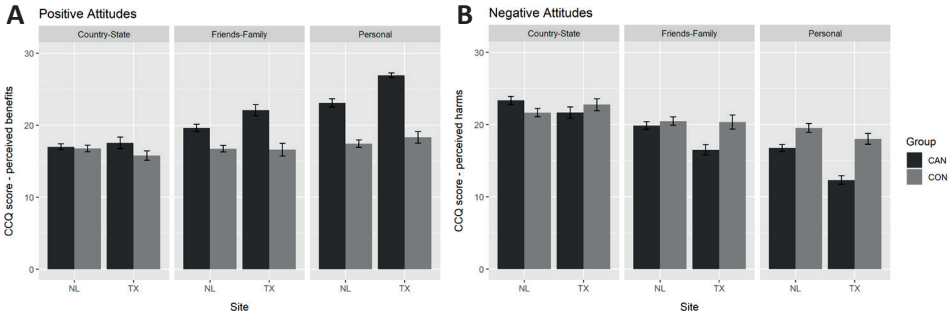


Figure 1. Cultural attitudes towards cannabis.

A) positive attitude scores on the Country-State, Friends-Family and Personal level split over site and group.

B) negative attitude scores on the Country-State, Friends-Family and Personal level split over site and group; Error bars reflect SE of the mean.

Table 2. The effect of group, site, and cannabis culture questionnaire level on positive and negative attitudes towards cannabis

Model	**Model coefficients**					
	Fixed effects					**Random effects**
Positive attitudes	***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***
Intercept	16.858	15.905:17.790	.484	34.830	<.001	2.065
Group: CAN-CON	.097	-1.213:1.407	.670	.145	.885	-
Site: NL-TX	.905	-.480:2.291	.708	1.278	.203	-
Level: CS-FF	2.812	1.743:3.882	.549	5.126	**<.001**	3.067
Level: CS-P	6.361	5.292:7.430	.549	11.592	**<.001**	
Group: CAN-CON * Level: CS-FF	-3.077	-4.431:-1.722	.695	4.426	**<.001**	-
Group: CAN-CON * Level: CS-P	-5.989	-7.343:-4.634	.695	8.615	**<.001**	-
Group: CAN-CON * Site: NL-TX	-2.354	-4.035:-.674	.860	2.739	**.007**	-
Site: NL-TX * Level: CS-FF	1.443	.061:2.826	.710	2.035	**.043**	-
Site: NL-TX * Level: CS-P	2.648	1.265:4.031	.710	3.732	**<.001**	-
Negative attitudes	***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***
Intercept	23.370	22.322:24.417	.538	43.476	<.001	2.602
Group: CAN-CON	-1.777	-3.244:-.309	.750	2.368	**.019**	-
Site: NL-TX	-1.749	-3.304:-.193	.796	2.198	**.029**	-
Level: CS-FF	-3.549	-4.659:-2.440	.569	6.233	**<.001**	3.262
Level: CS-P	-6.609	-7.719:-5.500	.569	11.607	**<.001**	
Group: CAN-CON * Level: CS-FF	2.490	1.085:3.896	.721	3.452	**<.001**	-
Group: CAN-CON * Level: CS-P	4.543	3.137:5.949	.721	6.298	**<.001**	-
Group: CAN-CON * Site: NL-TX	2.973	1.019:4.929	1.000	2.974	**.003**	-
Site: NL-TX * Level: CS-FF	-1.502	-2.937:-.067	.736	2.040	**.042**	-
Site: NL-TX * Level: CS-P	-2.702	-4.136:-1.267	.736	3.669	**<.001**	-

Linear mixed model results using random intercept and maximum likelihood estimation; AIC: Akaike information criterion, BM: baseline model, CAN: cannabis group, CI: Confidence Interval, CON: control group, CS: country-state, FF: friends-family, P: personal, NL: Netherlands, SE: Standard Error, SD: Standard deviation, TX: Texas; CAN, NL & CS were used as the reference categories. Final models as discussed in the manuscript are presented in italic and significant results are presented in bold.

Cannabis culture

For both positive (Figure 1A) and negative attitudes (Figure 1B) towards cannabis use, significant interactions were observed between group and site, group and level, and site and level (Table 2, Appendix G – Table S2 & S3). Regardless of site, cannabis users showed more positive ($t(180) = 12.398$, $p_{bonf} < .001$, $d = 1.848$) and less negative ($t(180) = -6.814$, $p_{bonf} < .001$, $d = 1.016$) personal attitudes and more positive friend-family attitudes ($t(180) = 6.571$, $p_{bonf} < .001$, $d = .980$) than the control group. TX

cannabis users reported lower friend's/family's negative attitudes than the TX control group ($t(71) = 3.630$, $p_{bonf} = .002$, $d = .862$), but no difference was observed between the NL groups ($p_{bonf} = 1.00$). The cannabis and control group did not differ in perceived country/state positive or negative attitudes (lowest $p_{bonf} = .086$). Within the control groups, there were no site differences in positive or negative attitudes (lowest $p_{bonf} = .625$). Within the cannabis groups, TX cannabis users were more positive (Personal: $t(99) = -4.942$, $p_{bonf} < .001$, $d = .993$; Friends-Family: $t(99) = -2.871$, $p_{bonf} = .027$, $d = .577$) and less negative (Personal: $t(99) = 5.278$, $p_{bonf} < .001$, $d = 1.061$; Friends-Family: $t(99) = 3.695$, $p_{bonf} = .002$, $d = .743$) than NL cannabis users on the personal and friends-family's positive attitudes level.

N-back task performance

Performance on the N-back task depended on WM-load in all groups: lower accuracy with increasing difficulty (Appendix G - Table S4; $\beta = 3.571$, $p < .001$). No site or group differences in accuracy were observed. However, a significant WM-load by group interaction was observed: when the task was most difficult (2-back), the cannabis group performed worse than the control group ($\beta = -2.259$, $p = .004$).

Table 3. fMRI results: group differences and interaction between group and site in WM- and WM-load-related activity

					MNI coordinates			
	Test	Cluster size (voxels)	Brain regions	Hemisphere	X	Y	Z	Zmax
WM effect								
2 > 0	Can > Con	ns	ns	ns	ns	ns	ns	ns
2 > 0	Con > Can	ns	ns	ns	ns	ns	ns	ns
2 > 0	Group*Site	611	Occipital fusiform gyrus	Right	22	-70	-18	3.62
WM-load effect								
2 > 1	Can > Con	ns	ns	ns	ns	ns	ns	ns
2 > 1	Con > Can	992	Superior lateral occipital cortex*	Left	-22	-64	46	4.69
		836	Precuneus*	Right	8	-62	52	4.87
		385	Medial frontal gyrus	Left	-28	16	54	3.56
		312	Medial frontal gyrus	Right	40	22	28	3.42
2 > 1	Group*Site	ns	ns	ns	ns	ns	ns	ns

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 2.3$); * survives whole-brain cluster correction at $p < 0.05$, $Z > 3.1$; Can = cannabis group, Con = control group; 0 = 0-back, 1 = 1-back, 2 = 2-back

fMRI results

Group differences & the role of site in WM- and WM-load-related brain activity

The main WM and WM-load effects, across groups, were similar to previous studies using the N-back task in cannabis users and general populations (Appendix G - Figure S2; Kroon et al., 2022; Owens et al., 2019). Controls showed higher WM-load-related activity in a cluster including the left superior lateral occipital cortex (also significant at $Z > 3.1$, $p < .05$), right precuneus (also significant at $Z > 3.1$, $p < .05$), and the left and right medial frontal gyrus (MFG) than cannabis users (Table 3; Figure 2A-B), but

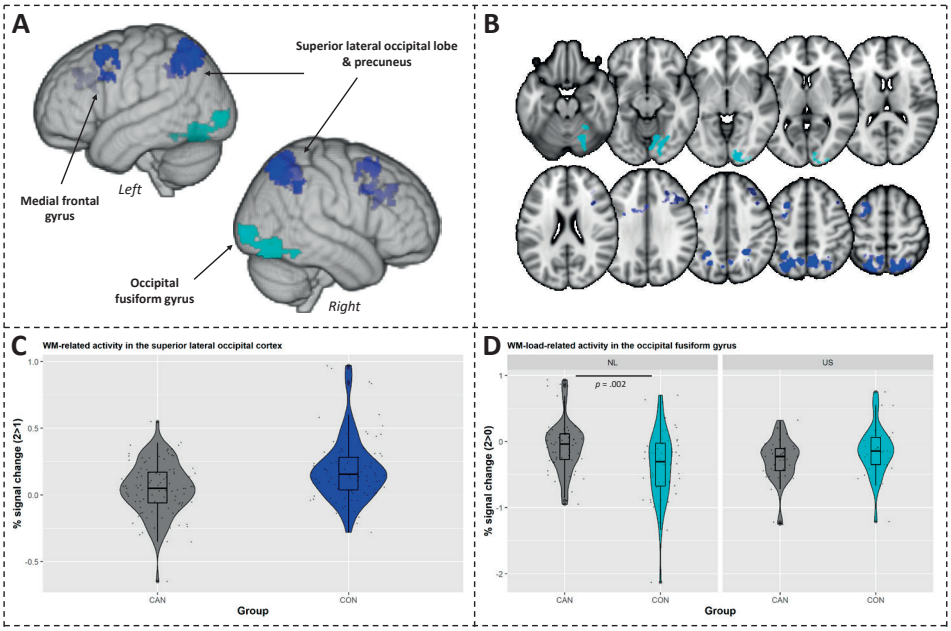


Figure 2. Group differences and the interaction between group and site on WM and WM-load-related activity.

A) Overview of clusters showing significant group differences (WM-related activity, dark colored) and interactions between group and site (WM-load-related activity, light colored);
B) overview of clusters showing significant group differences (WM-related activity, dark colored – bottom row) and interactions between group and site (WM-load-related activity, light colored – top row);
C) Violin boxplots displaying group differences in WM-related activity in the superior lateral occipital cortex;
D) Violin boxplots displaying interaction between group and site on WM-load-related activity in the occipital fusiform gyrus.

no WM-related differences were observed. All groups showed an increase in activity with increasing task difficulty, but this increase was larger in the control group ($t(182) = -4.410$, $p < .001$; Figure 2C). A small but significant association between increased activity and reduced performance was observed ($R^2 = .034$, $F(1, 171) = 6.015$, $\beta = -.007$, $\beta_{SE} = .003$, $t = -2.453$, $p = .015$).

Significant group by site interactions were only observed for WM-related activity in the occipital fusiform gyrus (Table 3; Figure 2D). Activity decreased with increasing difficulty in all groups, but this decrease was larger in the NL control group than the NL cannabis group ($t(111) = 3.625$, $p_{bonf} = .002$; Figure 2D), while no other group differences were observed.

Table 4. fMRI results: associations between measures of cannabis use and WM- and WM-load-related activity

	Association	Cluster size (voxels)	Brain regions	Hemisphere	MNI coordinates X	Y	Z	Zmax
CUD								
WM effect								
2 > 0	CUD	1019	Precentral gyrus*	Left	-20	-18	76	3.99
2 > 0	CUD*NL>US	ns	ns	ns	ns	ns	ns	ns
2 > 0	CUD*US>NL	ns	ns	ns	ns	ns	ns	ns
WM-load effect								
2 > 1	CUD	384	Precentral gyrus	Left	-38	-20	62	3.70
2 > 1	CUD*NL>US	ns	ns	ns	ns	ns	ns	ns
2 > 1	CUD*US>NL	ns	ns	ns	ns	ns	ns	ns
MPS								
WM effect								
2 > 0	MPS	292	Postcentral gyrus	Left	-16	-38	60	3.63
2 > 0	MPS*NL>US	ns	ns	ns	ns	ns	ns	ns
2 > 0	MPS*US>NL	ns	ns	ns	ns	ns	ns	ns
WM-load effect								
2 > 1	MPS	ns	ns	ns	ns	ns	ns	ns
2 > 1	MPS*NL>US	ns	ns	ns	ns	ns	ns	ns
2 > 1	MPS*US>NL	ns	ns	ns	ns	ns	ns	ns
Gram/Week								
WM effect								
2 > 0	Gram/Week	ns	ns	ns	ns	ns	ns	ns
2 > 0	Gram/Week*NL>US	ns	ns	ns	ns	ns	ns	ns
2 > 0	Gram/Week* US>NL	284	Superior parietal lobe	Left	-32	-42	-42	3.81
WM-load effect								
2 > 1	Gram/Week	ns	ns	ns	ns	ns	ns	ns
2 > 1	Gram/Week*NL>US	519	Temporal pole*	Right	48	8	-6	4.00
		355	Parahippocampal gyrus	Left	-18	-26	-22	3.89
2 > 1	Gram/Week* US>NL	ns	ns	ns	ns	ns	ns	ns

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 2.3$); * survives whole-brain cluster correction at $p < 0.05$, $Z > 3.1$; Can = cannabis group, Con = control group; 0 = 0-back, 1 = 1-back, 2 = 2-back

Association of cannabis use with WM- and WM-load-related brain activity and the role of site

CUD scores were positively associated with WM-related (also significant at $Z > 3.1$, $p < .05$) and WM-load-related activity in the precentral gyrus (Table 4). A similar positive association was observed between MPS score and WM-related activity in the postcentral gyrus. No direct associations between grams/week and WM- or WM-load-related activity were observed, but there was a significant effect of site on these associations. NL cannabis users showed a significantly stronger positive association between grams/week and WM-load-related right temporal pole (also significant at $Z > 3.1$, $p < .05$) and left parahippocampal gyrus activity than the TX cannabis users ($R^2 = .160$, $F(3, 92) = 5.862$, $\beta = -.044$, $\beta_{SE} = .011$, $t = -3.948$, $p < .001$; Figure 3A). However, TX cannabis users showed a significantly stronger positive association between grams/week and WM-related activity in the left superior parietal lobe (SPL) than the NL cannabis users ($R^2 = .119$, $F(3, 92) = 4.159$, $\beta = -.031$, $\beta_{SE} = .009$, $t = 3.473$, $p < .001$; Figure 3B).

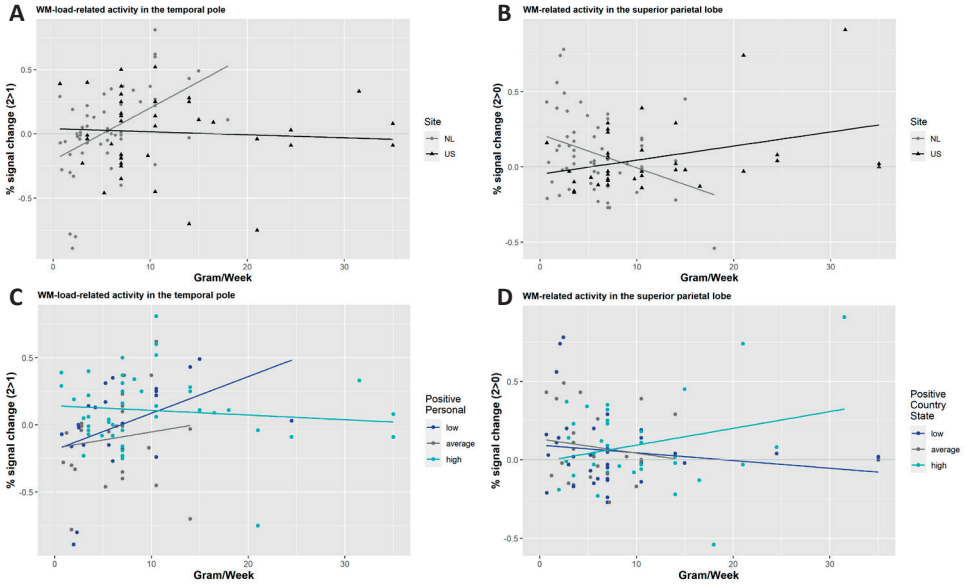


Figure 3. Site differences and the effect of cultural attitudes on the associations between WM and WM-load-related activity and heaviness of cannabis use.

A) Site differences in the association between heaviness of use (grams/week) and WM-load-related activity in the temporal pole;
B) Site differences in the association between heaviness of use (grams/week) and WM-related activity in the superior parietal lobe;
C) Moderating role of Personal positive attitudes towards cannabis use in the association between heaviness of use (grams/week) and WM-load-related activity in the temporal pole;
D) Moderating role of Country-State positive attitudes towards cannabis use in the association between heaviness of use (grams/week) and WM-load-related activity in the superior parietal lobe.

Association of cannabis use with WM- and WM-load-related brain activity and the role of cultural attitudes

Personal positive attitudes moderated the association between grams/week and WM-load-related activity in the temporal pole. Those with less positive personal attitudes showed a more positive association between grams/week and activity (R^2 = .059, $F(3, 92) = 1.906$, $\beta = -.003$, $\beta_{SE} = .001$, $t = -2.038$, $p = .044$; Figure 3C).

Positive attitudes in the country/state moderated the association between grams/week and WM-related activity in the SPL: the more positive the perceived Country/State attitudes, the more positive the association between grams/week and WM-related SPL activity ($R^2 = .051$, $F(3, 92) = 1.645$, $\beta = .002$, $\beta_{SE} < .001$, $t = 2.171$, $p = .032$; Figure 3D).

Discussion

Despite cannabis legislation being prohibitive in TX compared to NL, TX and NL participants reported similar perceived country/state cannabis attitudes and TX compared to NL cannabis users perceived more positive and less negative attitudes of friends and family. We observed site-independent differences in WM performance and WM-load related activity between cannabis users and controls, and site-independent associations of cannabis use related problems and CUD severity with WM- and WM-load related activity. However, site differences emerged in the association between weekly amount of cannabis use and both WM- and WM-load related activity in parietal and temporal regions known to be involved in perception, attention, and (WM) memory processes (Herlin et al., 2021; Koenigs et al., 2009; Lin et al., 2021), and those differences were associated with positive cultural attitudes.

NL versus TX cannabis users showed a stronger positive association between grams/week and WM-load-related activity in the right temporal pole. Further examining temporal pole activity, only those with lower positive personal attitudes showed an association between cannabis use and WM-load-related activity in the temporal pole, in line with the NL cannabis users reporting less positive personal attitudes than the US cannabis users. The direction of these effects aligns with the 'need to control' hypothesis in which the experience of less positive cannabis environments increases the experienced need to control. Hence, their use might be a better indicator of loss of control and they might show a larger association between control related brain activity and use. However, conflicting with this hypothesis, TX versus NL cannabis users showed a stronger positive association between grams/week and WM-load-related activity in the left SPL. Only those who perceived high positive country/state attitudes showed an association between cannabis use and WM-related SPL activity. Site and cannabis attitudes did not affect associations between severity of cannabis use related problems and WM- or WM-load-related activity, providing no support for the 'social symptoms' hypothesis.

Performance on the N-back task confirmed our hypothesis that control participants only outperform cannabis users when the task gets most difficult. Controls showed more normative WM-load-dependent increases in activity in a cluster including the superior lateral occipital lobe, precuneus, and MFG than the cannabis users. Activity increases when the task became more complex, which is also reflected in the small negative association between activity in these regions - involved in task-relevant perception, attention, memory, and executive functioning (de La Vega et al., 2016; Ganis et al., 2004; Vatansever et al., 2017) - and reduced performance. However, contrary to expectations, cannabis users did not show increased WM- and WM-load-related activity in fronto-parietal regions or default mode network (DMN) regions. It must

be noted that while the precuneus is a central node of the DMN (Utevsky et al., 2014), we saw relatively more activity in control participants than cannabis users in dorsal posterior regions of the precuneus (extending to the SPL) thought to be involved in cognition and shifting towards cognitive processes (Cavanna & Trimble, 2006) rather than interoceptive default mode processes (Vatansever et al., 2017).

Site only related to group differences in WM-related activity in the occipital fusiform gyrus, lingual gyrus, and occipital pole, primarily involved in visual perception (Ganis et al., 2004). With increasing difficulty, activity in this region appeared to reduce, but group differences were only observed in the NL group: the reduction in activity was larger in the control group than the cannabis group. While this activity might be associated with processing task-relevant information and reducing attention to task irrelevant features, there were no associations with performance.

Severity of CUD and cannabis-use-related problems were positively associated with left sided motor activity when difficulty increased. While in line with right-handed task responses, it is unclear how severity of use affects this increase in activity. As no association was observed with heaviness of cannabis use it is unlikely to be caused by sub-acute effects of THC on motor responses (Ramaekers, Moeller et al., 2006).

Several limitations must be noted. We proposed two speculative hypotheses on the potential role of culture in the association between control-related brain activity and measures of cannabis use. In line with this speculative nature, whole brain cluster-based multiple comparison correction was performed at $Z > 2.3$ for $p < .05$, with not all results surviving more conservative correction. Similarly, moderation effects of culture on the associations between quantity of cannabis use and control-related brain activity are small and would not survive stricter multiple comparison correction. Groups were not fully matched, but controlling for the most prominent group differences (age, gender, and cigarette use) did not affect the presented results. Importantly, matching groups in cross-cultural research is inherently challenging due to existing cultural differences such as differences in the prevalence of co-use of tobacco and cannabis (Hindocha et al., 2016). While data on tobacco use is often collected when studying cannabis use, it remains important to focus on improving quantification of the (co-) use of tobacco in these studies to further investigate the potential interactions between nicotine and cannabis. Furthermore, cultural attitudes are likely to be affected by additional external factors that could have affected our results. For example, living in the US where cannabis advertisement is common, individuals in Texas might have had higher exposure to cannabis advertisement than individuals in The Netherlands due to differences in cannabis advertisement policy (Rup et al., 2020). As individuals increasingly travel beyond their local and national borders – either online or offline - there should be an increased focus on the development of measures assessing how

media, adverstisement, and travel could affect cultural perceptions towards cannabis and other drugs. Finally, further exploration of the 'social symptoms' hypothesis depends on measurements that can distinguish specific types of CUD symptoms and self-reported problems (i.e. indicative of social or loss of control symptoms). However, the available measures are not developed to examine these sub-types. Similarly, further exploration of the 'need to control' hypothesis will require assessment of experienced need to control use. Hence, future studies should consider developing and including measures that can assess these symptom sub-types and self-reported need to control use to further examine the potential evidence for these hypotheses.

Our results provide initial support for a moderating role of cannabis legislation and cultural attitudes on the association between quantity of cannabis use and control-related brain processes, highlighting the importance of considering cultural attitudes and legislation differences as a potential source of variation in fMRI studies. Objective differences in legislation and subjective cultural attitudes did not always align on a behavioral level and might differentially affect the association between use and control related brain activity. Both site and positive cultural attitudes matter, but the interactions are complex and replication of these effects in different samples is crucial to understand how different legistlative policies and attitudes towards cannabis use might affect the processes underlying CUD.

Chapter 11

For better or for worse? A pre-post exploration of the impact of the covid-19 lockdown on cannabis users

This chapter is based on:
Cousijn, J., Kuhns, L., Larsen, H., & Kroon, E. (2021). For better or for worse? A pre–post exploration of the impact of the COVID-19 lockdown on cannabis users. *Addiction, 116*(8), 2104-2115. https://doi.org/10.1111/add.15387

Abstract

Aims. Lockdown measures aimed at limiting the number of infections and deaths from the coronavirus disease 2019 (COVID-19) have introduced substantial psychosocial stressors in everyday life. We aimed to investigate the influence of the Dutch lockdown on cannabis use and Cannabis Use Disorder (CUD) and investigate relations with change in mental wellbeing and experienced psychosocial stressors during the lockdown.

Design. Explorative longitudinal baseline-, pre- and during lockdown survey study.

Setting. The Netherlands, online between January 2019 and May 2020.

Participants. Community sample of 120 monthly to daily cannabis users and reference group of 63 non-using controls.

Measurements. Change in cannabis use and CUD symptom severity from baseline to pre-lockdown to post-lockdown. Change in cannabis use motives, mental health, quality of social relationships and job status from pre-lockdown to post-lockdown.

Findings. In cannabis users, lockdown related to increased cannabis use (B = 1.92, 95%CI = 0.23–3.61, p = 0.027), but not CUD symptom severity. Cannabis users experienced 30% job loss and increased loneliness ($p < 0.001$, $BF_{10} > 100$), while contact with partners ($p = 0.005$, $BF_{10} = 8.21$) and families improved ($p < 0.001$, $BF_{10} = 19.73$), with no differences between cannabis users and control. Generally, mental health problems (all p's > 0.277, all $BF_{10} < 0.139$) did not change but individual differences were significant, and severity of cannabis use pre-lockdown, COVID-19 related worries, change in anxiety, expansion motives, social motives, and family contact all uniquely related to variance in change in cannabis use or CUD.

Conclusions. While cannabis use increased at the group level, the effect of the first months of lockdown on CUD severity and mental wellbeing varied significantly between individuals.

Introduction

The social distancing measures aimed at limiting the number of infections and deaths from the novel SARS-CoV-2 virus and associated coronavirus disease 2019 (COVID-19) have introduced substantial psychosocial stressors in everyday life, raising concerns regarding the wellbeing of vulnerable populations, including substance users (Dubey et al., 2020; Marsden et al., 2020). The current explorative study assessed the influence of the Dutch lockdown initiated in March 2020 on cannabis use and Cannabis Use Disorder (CUD) severity in a community sample of monthly to daily cannabis users. Furthermore, we investigated if individual change in use and CUD symptoms was related to change in mental well-being and experienced psychosocial stressors during the lockdown.

The Dutch lockdown measures involved social isolation and prolonged confinement at home, including work and school from home. Pandemic-specific anxieties have emerged in the population, with increased levels of worry around personal health and economic consequences (Lee, 2020). Sudden job loss and unemployment have also been an unfortunate reality for many, particularly individuals who work in the retail and food services, culture, accommodation, and cleaning sectors (Statistics Netherlands (CBS), 2020). Moreover, emerging evidence suggests a 16-28% increase in anxiety and depression symptoms, and an 8% increase in self-reported stress in the general population (Rajkumar, 2020). The increase in experienced stressors and mental health problems, combined with the reduction in alternative positive activities, led to substantial concern from the scientific community about the potential impact on vulnerable populations like substance users (Dubey et al., 2020; Marsden et al., 2020). From previous research on the effects of economic crises on substance use (e.g., the 2008 global recession), we know that high rates of job loss are associated with increased substance use and addiction, especially in young men (Dom et al., 2016). Job loss is a demonstrated risk factor for cannabis use and unemployed young adults in particular have higher rates of developing a CUD (Henkel, 2011; Poulton et al., 1997). CUD is also highly comorbid with anxiety and depression (Agosti et al., 2002; Van der Pol, Liebregts, De Graaf, Ten Have et al., 2013), and stress is an important factor in the escalation of use, development of addiction, and relapse (Briand & Blendy, 2010; Sinha, 2007). In regular cannabis users particularly, stress and tension reduction are commonly reported motives for use (Hyman & Sinha, 2009), correlating with CUD severity (Benschop et al., 2015).

To our knowledge, previous studies have only cross-sectionally investigated the effect of the virus and lockdown on cannabis use. Increases in cannabis use have been reported in medical cannabis users from the US (Vidot et al., 2020), adult recreational cannabis users in France (Rolland et al., 2020), and adolescent recreational users

from Canada (Dumas et al., 2020). In contrast, a survey conducted among the general population in Belgium reported no increase in use (Vanderbruggen et al., 2020). These studies suggest that cannabis use may have increased during the lockdown period. To build upon this, the main aim of this exploratory study was to i) investigate if lockdown was associated with change in cannabis use and CUD symptom severity in cannabis users. We invited a unique sample of cannabis users and non-cannabis using controls who completed a survey about their cannabis use *prior* to the pandemic (baseline) to fill out an online survey about cannabis use just before (pre-lockdown) and since the lockdown (post-lockdown), and other sociopsychological consequences of the lockdown. The second aim was to ii) investigate if pre-to-post-lockdown change in cannabis use and CUD symptom severity related to change in cannabis use motives, mental wellbeing, quality of social relationships, and job status. For reference, we checked iii) if changes observed in cannabis users differed from changes observed in a smaller group of non-cannabis using controls. Given the unique nature of the lockdown, all analyses were explorative. However, we expected a general increase in cannabis use and CUD symptom severity pre-to-post lockdown (Rolland et al., 2020), that related to decreases in general mental wellbeing. We also expected that increases in cannabis use and CUD symptoms would relate to increases in cannabis coping motives (Benschop et al., 2015), decreases in social relationship quality (Boman & Heck, 2017; Mason et al., 2017), and job loss (Henkel, 2011; Poulton et al., 1997).

Materials and methods

Participants

Study protocols were approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences, University of Amsterdam (2020-DP-12211). Individuals who completed an eligibility screener for a different CUD study and agreed to be contacted for future studies were invited to participate. Individuals were originally recruited using social media advertising and in-person flyers targeted at daily or near-daily cannabis users and non-using controls (<25 lifetime uses) who do not regularly use other illicit substances. Of the 1030 invited individuals, 186 agreed to participate in this new study for which they completed the follow-up survey and consented to merging of the screening data with the follow-up survey. Among those, 8 x 25 Euro online shop vouchers were raffled. Three participants were excluded due to daily other substance use (1 control for daily GHB use, 1 control for regular use of multiple illicit drugs other than cannabis, and 1 cannabis user for daily methamphetamine use). The final sample consisted of 120 cannabis users aged 18-46 who reported monthly to daily cannabis use before lockdown (baseline and/or pre-lockdown) and, for reference, a group of 63 sporadic to non-cannabis using controls aged 18-31.

Table 1 Overview alcohol and substance use measures assessed for baseline, pre-lockdown and post-lockdown periods

	Cannabis Users (N = 120)						Controls (N = 63)					
	Baseline	Follow-up					Baseline	Follow-up				
		pre-lockdown		post-lockdown				pre-lockdown		post-lockdown		
	N	mean (SD, range)	N	mean (SD, range)	N	mean (SD, range)	N	mean (SD, range)	N	mean (SD, range)	N	mean (SD, range)
Substance use												
DSM-5 CUD symptoms	96	4.4 (2.9, 0-11)	104	4.6 (3.0, 0-10)	104	4.3 (3.0, 0-11)	--		--		3	0.0 (0.0, 0-0)
Cannabis use, days month	96	22.2 (9.4, 0-30)	109	20.8 (10.7,0-31)	109	22.0 (10.5, 0-31)$^{\#}$	--		--		9	6.4 (4.6, 2-15)
Cannabis use, grams month	--		109	17.2 (18.4, 0-94.5)	109	**21.53 (20.8, 0-105.4)*****	--		--		9	3.4 (1.8, 1.5-7.5)
Illicit substance use, n month	120	3.0 (2.8, 0-11)	120	0.8 (1.5, 0-8.3)	120	1.0 (3.8, 0-31.9)	63	**1.3 (1.9, 0-9)*****	63	0.3 (0.6, 0-3.6)**	63	0.5 (1.8, 0-13.5)
Cigarette use per day	53	7.4 (5.1, 0-22)	63	8.7 (6.5, 0-25)	64	8.4 (7.3, 0-30)	6	7.8 (4.7, 2-15)	10	8.5 (4.2, 4-18)	8	9.9 (8.2, 0-24)
Alcohol use, drinks month	--		111	28.1 (36.4, 0-202)	111	28.9 (46.4, 0-264)	--		58	26.2 (25.8, 0-118)	58	28.7 (46.6, 0-264)
AUDIT, past year	96	6.8 (3.9, 0-18)	--	--	115	7.9 (5.7, 0-31)	57	7.1 (4.9, 0-24)	--		61	7.0 (5.0, 0-22)

*DSM-5: Diagnostic and Statistical Manual of Mental Disorders; CUD: Cannabis Use Disorder; AUDIT: Alcohol Use Disorder Identification Test; SD: standard deviation; Group differences; ** p < 0.01, *** p < 0.001; Within-group effects of time $^{\#}$p < 0.05; $^{\#\#\#}$p < 0.001. Bold mean refers to significant results with at least moderate Bayesian evidence support.*

Table 2 Overview all measures assessed at follow-up for pre-lockdown and post-lockdown periods and for pre-to-post lockdown change.

	Cannabis Users (N = 120)						Controls (N = 63)					
	pre-lockdown			post-lockdown			pre-lockdown			post-lockdown		
	mean	sd	range	mean	sd	range	mean	sd	range	mean	sd	range
Motives for cannabis use												
Enhancement	16.4	4.1	0-23	16.6	4.4	5-25	--	--	--	--	--	--
Coping	10.6	4.7	0-23	11.6$^{\#}$	5.4	5-25	--	--	--	--	--	--
Expansion	11.1	6.3	0-25	10.9	6.4	5-25	--	--	--	--	--	--
Social	12.7	5.6	0-25	**10.5**$^{\#\#\#}$	5.4	5-25	--	--	--	--	--	--
Mental health (DSM-5-CCSM)												
total	18.1	11.9	0-55	17.9	13.4	0-68	**11.1*****	7.8	0-49	**11.8****	8.8	0-56
depression	2.7	1.8	0-8	2.9	2.1	0-8	**1.9*****	1.3	0-8	2.1**	1.5	0-6
anxiety	3.0	2.6	0-12	2.9	3.0	0-12	4.2	1.9	0-9	2.5	2.2	0-12
sleep problems	1.3	1.2	0-4	1.4	1.3	0-4	0.7**	0.8	0-3	0.9*	1.0	0-4
COVID-19 related worries												
Personal health	--	--	--	2.2	1.0	1.0-5.0	--	--	--	1.9	0.9	1.0-5.0
Personal economics	--	--	--	2.2	1.3	1.0-5.0	--	--	--	2.0	1.1	1.0-5.0
Contamination	--	--	--	2.6	0.8	1.0-4.7	--	--	--	2.5	0.8	1.0-4.3
Societal functioning	--	--	--	2.6	0.8	1.0-4.8	--	--	--	2.6	0.8	1.0-4.3
Employment												
Weekly working hours	16.6	15.0	0-50	9.5	14.0	0-50	16.4	13.6	0-46	8.7	12.7	0-52
Job loss	--	--	--		30%		--	--	--		34%	
	pre-to-post lockdown change						pre-to-post lockdown change					
	mean		sd		range		mean		sd		range	
Social contact												
Loneliness	**3.6**$^{\#\#\#}$		0.9		1-5		**3.5**$^{\#\#\#}$		0.8		2-5	
In-person, partner	3.1		0.9		1-5		3.2		0.9		1-5	
In-person, family	**2.6**$^{\#\#\#}$		1.1		1-5		2.6$^{\#}$		1.2		1-5	
In-person, friends	**1.8**$^{\#\#\#}$		0.9		1-5		**1.5**$^{\#\#\#**}$		0.7		1-5	
Online, partner	3.0		0.9		1-5		3.1		0.9		1-5	
Online, family	**3.3**$^{\#\#\#}$		0.8		1-5		3.2$^{\#}$		0.7		1-5	
Online, friends	**3.7**$^{\#\#\#}$		1.0		1-5		**4.0**$^{\#\#\#}$		0.9		1-5	
Quality, partner	**3.2**$^{\#\#}$		0.7		1-5		3.2$^{\#}$		0.7		1-5	
Quality, family	**3.2**$^{\#\#\#}$		0.5		2-5		3.1$^{\#}$		0.5		1-4.5	
Quality, friends	2.8$^{\#}$		0.9		1-5		2.9		0.8		1-5	

*Group differences; *p < 0.05, ** p < 0.01, *** p < 0.001; Within-group effects of time $^{\#}$p < 0.05; $^{\#\#}$p < 0.01, $^{\#\#\#}$p < 0.001. Bold means refer to significant results with at least moderate Bayesian evidence support.*

Questionnaires

March 12, 2020 marked the onset of the Dutch lockdown. Each participant completed a baseline and follow-up questionnaire. The *baseline* questionnaire was completed on average 265 days (SD = 144.4, range: 26-467 days) prior to the lockdown and assessed the use of cannabis and other substances. The *follow-up* questionnaire contained retrospective questions about the period before the lockdown (*pre-lockdown*) and during the lockdown (*post-lockdown*) and was conducted on average 59 days (SD = 8.6, range: 47-79) after the lockdown began, before any regulations were loosened. Table 1 shows an overview of the substance use measures collected for the baseline, pre-lockdown, and post-lockdown periods. Table 2 shows an overview of all other measures collected at follow-up. The assessment time frames for each participant are shown in Appendix H - Figure S1.

Cannabis use and CUD symptom severity

Our main outcome variables were DSM-5 CUD symptom severity and cannabis use. DSM-5 CUD symptoms were assessed with the MINI 7.0.0 DSM-5 CUD section (American Psychiatric Association, 2013a; Sheehan et al., 1998) for the previous year in weekly users at baseline (Cronbach's $\alpha = 0.86$), and for the previous year pre-lockdown (Cronbach's $\alpha = 0.83$) and the period since lockdown (Cronbach's $\alpha = 0.83$) in monthly users, with scores ranging from 0 to 11. At baseline, cannabis use was assessed in days per week for screening purposes. Days per week were multiplied by 4.3 to compute days per month. At follow-up, cannabis use was assessed in days per month over the pre-lockdown and post-lockdown period. Cannabis use in grams per month was assessed over the pre-lockdown and post-lockdown period for descriptive purposes.

Other substance use

Alcohol use and related problems were assessed with the 10-item Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993) at baseline (Cronbach's $\alpha = 0.73$) and at follow-up (Cronbach's $\alpha = 0.80$), both assessments referring to the past year. AUDIT item scores ranged from 0-4 and AUDIT total scores were computed by summing item scores. Alcohol use in drinks per month was assessed at follow-up over the pre-lockdown and post-lockdown period. Cigarette use (yes/no), number of cigarettes per day, and frequency of past month illicit substance use were assessed over the baseline, pre-lockdown, and post-lockdown period.

Motives for cannabis use

Motives for use in the year preceding lockdown and period since lockdown were assessed with the 5-item coping (i.e., to reduce negative affect, Cronbach's α pre-

lockdown = 0.81, post-lockdown = 0.88), 5-item social (i.e., to enhance social events, Cronbach's α pre-lockdown = 0.89, post-lockdown = 0.90), 5-item enhancement (i.e., to enhance positive affect, Cronbach's α pre-lockdown = 0.74, post-lockdown = 0.81) and 5-item expansion (i.e., expand thoughts and experiences, Cronbach's α pre-lockdown = 0.96, post-lockdown = 0.96) subscales from the Marijuana Motives Measure (MMM; Simons et al., 1998). Each scale contained 5 questions scored on a 5-point Likert scale from 'almost never' (1) to 'almost always' (5). Scale scores were computed by summing item scores.

Mental health

The DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure-Adult (DSM-5 CCSM; American Psychiatric Association, 2013b) was administered at follow-up to assess general mental health over the pre-lockdown and post-lockdown period. Substance use items were excluded and assessment time was changed to reflect the year preceding lockdown and period since lockdown. Each item was scored on a 5-point Likert scale from 'never' (0) to 'always' (4). Given the high comorbidity with CUD (Van der Pol, Liebregts, De Graaf, Ten Have et al., 2013), we included the total (20-items; Cronbach's α pre-lockdown = 0.91, post-lockdown = 0.92), depression (2-items; Cronbach's α pre-lockdown = 0.80, post-lockdown = 0.80), anxiety (4-items; Cronbach's α pre-lockdown = 0.78, post-lockdown = 0.82) and sleep problems (1-item) scores in further analysis.

COVID-19 related worries

Worries about personal health consequences (2 items; Cronbach's α = 0.59), personal economic consequences (2 items; Cronbach's α = 0.80), contamination (2 items; Cronbach's α = 0.72), and societal consequences (4 items; Cronbach's α = 0.71) were assessed with a self-developed questionnaire (see Appendix H - Table S1). Each item was scored on a 5-point Likert scale from 'no worries' (1) to 'many worries' (5). Each worry score reflects the average of the item scores (Cronbach's α = 0.59-0.80).

Social contact

Pre to post-lockdown change in frequency of online and in-person contact with partners, family and friends was assessed with 5-point Likert scales from 'a lot less' (1) to 'a lot more' (5). Pre-post-lockdown change in the quality of contact with partners, family and friend were assessed with 5-point Likert scales from 'much worse' (1) to 'much better' (5). Change in loneliness pre- to post-lockdown was assessed with a single item, scored on a 5-point Likert scale from 'a lot less' (1) to 'a lot more' (5).

Statistical analysis

Main analyses in cannabis users

To investigate if lockdown was associated with change in cannabis use (days per month) and CUD symptom severity, two separate linear mixed model analyses were conducted. Participants with at least 2 assessments for cannabis use [3 timepoints: N = 96, 2 timepoints: N = 24] or CUD [3 timepoints: N = 81, 2 timepoints: N = 26] were included (missing data resulted from no to minimal cannabis use at either baseline or pre-lockdown). The effects of time [continuous variable with 3 data-points; baseline (minus days before lockdown), pre-lockdown (March 12, 2020 = 0), and post-lockdown (plus days since lockdown)] on both outcomes were assessed using maximum likelihood estimation and a random intercept, with subject and time as random variables to account for repeated measures. Lockdown status (0 at baseline, 0 at pre-lockdown, 1 at post-lockdown) was subsequently added to the model to assess the additional effect of lockdown, followed by the interaction between time and lockdown status. To assess a) individual differences in effects of time and lockdown status, b) potential effects of differences in time between measures, and c) potential non-linear time effects, we assessed model fit after allowing for variable slopes (random slope model), adding a continuous autocorrelation structure of order 1 (with participant as the grouping factor), and assessing quadratic and cubic effects of time respectively. Model fit was assessed using AIC and BIC values of model comparison.

Next, we exploratively investigated if pre-to-post-lockdown change in cannabis use and CUD symptom severity related to change in cannabis use motives, mental wellbeing, social contact, and job status. This was done in multiple steps, first assessing pre-to-post change in cannabis use motives, mental wellbeing, and quality of social relationships. Given the non-normal data distributions, non-parametric repeated-measures Friedman tests and Wilcoxon signed-rank tests were used. Next, pre-to-post-lockdown change scores were computed (pre-lockdown minus post-lockdown, reflecting change between lockdown period and the period just before lockdown onset) for these variables and non-parametric Kendall tau correlations were computed to assess if change correlated with pre-to-post-lockdown change in cannabis use and CUD symptom severity. Moreover, non-parametric Kruskal-Wallis tests, as part of ANCOVAs, were run to investigate if pre-to-post lockdown change in CUD symptoms and use (corrected for baseline CUD symptoms and use respectively) differed between cannabis users that did or did not lose their job. Finally, two explorative regression models with feedforward model selection (Bootstrap = 5000, to account for assumption violations) were run to assess which variable(s) uniquely explained change in CUD symptoms and cannabis use, entering both pre-lockdown and change scores in mental wellbeing, marijuana motives, quality of social relationships, and job status.

Comparison between cannabis users and controls

For reference and descriptive purposes, group differences in sample characteristics (including alcohol, cigarette, and illicit substance use) and changes in mental wellbeing, quality of social relationships, and job status were assessed. Group differences in pre-to-post-lockdown change scores - i.e., loneliness, alcohol use (AUDIT and drinks per months), illicit substance use, and DSM-5-CCSM total and sub-scores - were assessed with ANCOVAs (Clifton & Clifton, 2019), correcting for pre-lockdown scores and gender. Given the non-normal data distributions, non-parametric repeated-measures Friedman tests and Mann Whitney U tests were used. Group differences in repeated measures assessed at follow-up - i.e., COVID-19-related worries and change in social contact - were assessed using linear mixed models with maximum likelihood estimation, random intercept, and the within subject variable as a random effect to account for repeated measures.

Bayesian analyses

Given the novelty of the topic, the explorative nature of this study, and to allow for novel hypothesis formation, we decided not to correct for multiple comparisons. Instead, complementary Bayesian analyses were conducted and interpretation of the evidence strength followed Jeffreys benchmarks (Jeffreys, 1961): anecdotal (i.e., not enough evidence to support or refute H0) = BF 1-3, moderate = BF 3-10, strong = BF 10-30, very strong = BF 30-100, and extremely strong = BF > 100. Analyses were run in JASP (JASP team, 2019) and R (version 4.0.2). We considered an effect significant if both $p < 0.05$ and BF > 3. Analyses were not preregistered.

Table 3 Overview of final models to assess change in cannabis use (days per month) and CUD symptom severity as a function of time and lockdown status.

	Model coefficients						
Model	**Fixed effects**					**Random effects**	
Cannabis use in days per month	**B**	**95% CI (B)**	**SE (B)**	***t***	***p***	**SD**	**95% CI**
(Intercept)	19.26	17.30 – 21.22	1.00	19.25	<.001	9.16	7.91 – 10.65
Time	-0.01	-0.01 – -0.00	0.00	2.30	0.022	-	-
Lockdown Status	1.96	0.26 – 3.66	0.87	2.26	0.024	-	-
	Fixed effects					**Random effects**	
DSM-5 CUD symptom severity	**B**	**95% CI (B)**	**SE (B)**	***t***	***P***	**SD**	**95% CI**
(Intercept)	4.61	4.06 – 5.17	0.28	16.30	< .001	2.67	2.31 – 3.09
Time	0.00	-0.00 – 0.00	0.00	0.20	0.839	0.01	0.00 – 0.01
Lockdown Status	2.30	0.04 – 4.55	1.15	2.00	0.047	-	-
Time x Lockdown Status	-0.04	-0.08 – -0.01	0.02	2.26	0.025	-	-

DSM-5: Diagnostic and Statistical Manual of Mental Disorders; CUD: Cannabis Use Disorder; Note: models assessing the effect of a continuous autocorrelation structure of order 1, quadratic effects of time and cubic effects of time did not improve model fit. An overview of the model selection can be found in Table S2.

Results
Pre-lockdown to post-lockdown change in cannabis users

Cannabis use and CUD symptom severity

While time had a small but significant negative effect on cannabis use (Table 3; B = -0.01, 95%CI = -0.01–-0.00, p = 0.022), lockdown was associated with an increase in cannabis use (B = 1.96, 95%CI = 0.26–3.66, p = 0.024). Similarly, comparing pre-lockdown to post-lockdown cannabis use in grams per week, there was very strong evidence for an increase in use (W = 1488.5, p < 0.001, BF_{10} = 62.5, see Table 1). For CUD symptom severity, there was a small but significant interaction between time and lockdown status (B = -0.04, 95%C = -0.08–-0.01, p = 0.025), indicative of a difference in the effect of time on CUD symptom severity during and before lockdown. Post-hoc regression analyses showed no associations between total assessment time (days between baseline and follow-up) and baseline to post-lockdown change in CUD (B = -0.00, t(79) = -0.75 .34, p = 0.457) or between time (days between baseline and lockdown onset) and change in CUD before lockdown (B = -0.00, t(79) = 0.34, p = 0.729). There was a small negative association between time and change in CUD score during lockdown (B = -0.05, t(105) = 2.40, p = 0.018). There was no evidence for a pre-lockdown to post-lockdown change in CUD symptoms (W = 1509.5, p = 0.66, BF_{10} = 0.57).

Marijuana use motives

Enhancement motives were most prevalent (Table 2). A Friedman test assessing differences in change in coping, enhancement, social, and expansion motives was significant ($\chi^2(3) = 37.36$, p < 0.001). Post-hoc tests indicated moderate evidence for no change in enhancement (W = 1289.00, p = 0.732, BF_{10} = 0.110) and expansion motives (W = 1016.50, p = 0.452, BF_{10} = 0.193), but extremely strong evidence for a decrease in social motives (W = 3077.00, p < 0.001, BF_{10} > 100) and anecdotal evidence for an increase in coping motives (W = 645.50, p = 0.003, BF_{10} = 2.84).

Mental wellbeing

DSM-5-CCSM total, depression, anxiety, and sleep problem scores did not change (all p's > 0.277, all BF_{10} < 0.139). COVID-19-related worries about personal health, personal economic consequences, contamination, and societal functioning significantly differed from each other ($\chi^2(3) = 35.59$, p < 0.001). Post-hoc tests indicated equal worries about contamination and societal consequences (W = 3380.00, p = 0.649, BF_{10} = 0.102) that were higher than worries about personal health (contamination-personal health: W = 4741.00, p < 0.001, BF_{10} > 100; societal consequences-personal health: W = 1050.00, p < 0.001, BF_{10} > 100) and economic consequences (contamination-economic

consequences: W = 4707.00, p < 0.001, BF_{10} = 25.62; societal-economic consequences: W = 1791.50, p < 0.001, BF_{10} > 100). Participants were equally worried about personal health and economic consequences (W = 2293.00, p = 0.899, BF_{10} = 0.101).

Social contact

Evidence was extremely strong for an increase in loneliness (W = 2690.00, p < 0.001, BF_{10} > 100, see Table 2). Regarding pre-to-post lockdown change in social contact (Figure 1, Table 2), change in online ($\chi^2(2) = 37.09$, p < 0.001), in-person ($\chi^2(2) = 73.48$, p < 0.001), and quality of ($\chi^2(2) = 22.51$, p < 0.001) contact differed between partner, family, and friends. Post-hoc tests indicated that partner contact in-person (W = 588.00, p = 0.265, BF_{10} = 0.219) and online (W = 344.00, p = 0.675, BF_{10} = 0.106) did not change (test-value = 3), but relative to partners, family contact was reduced in-person (W = 2843.00, p < 0.001, BF_{10} > 100) and increased online (W = 918.50, p = 0.002, BF_{10} = 15.12). Relative to family, friend contact was reduced in-person (W = 3445.00, p < 0.001, BF_{10} > 100) and increased online (W = 1086.50, p = 0.002, BF_{10} = 20.99). Regarding contact quality, there was moderate evidence for improved contact with partners (W = 578.00, p = 0.005, BF_{10} = 8.21) and strong evidence for improved contact with family (W = 1006.00, p < 0.001, BF_{10} = 19.73). Evidence was only anecdotal for decreased contact quality with friends (W = 919.00, p = 0.023, BF_{10} = 1.38).

Pre-to-post lockdown change in cannabis use and CUD symptom severity; associations with change in use motives, mental-wellbeing, social contact, and job status

The current data provide strong evidence for a small positive correlation between change in CUD symptoms and change in enhancement motives and worries about COVID-19 contamination (Table 4). Change in CUD symptoms also correlated weakly positively with DSM-5-CCSM total, anxiety and sleep problems, but with moderate evidence strength. Regarding cannabis use, there was moderate evidence for a weak positive correlation with change in enhancement motives only. Pre-to-post-lockdown change in CUD symptoms ($\chi^2(1) = 0.88$, p = 0.348) and use ($\chi^2(1) = 3.22$, p = 0.073) did not differ between cannabis users that did and did not lose their job.

The regression analysis to explore which variables uniquely explained change in CUD symptoms revealed extremely strong evidence that lower pre-lockdown CUD symptoms, lower worries about personal economic consequences and higher worries about personal health related to increases in CUD symptoms, each significantly explaining unique variance in change (see Table 5). Moreover, larger increases in both anxiety and the quality of family relationships related to increases in CUD symptoms, but with moderate evidence strength. Change in coping motives was a non-significant predictor in the final model.

Table 4 Relations between change cannabis use and change in use motives, mental wellbeing and quality of social relationships

		Self-reported change pre- to post COVID-19 lockdown			
		DSM-5 CUD symptoms		Cannabis use, days month	
		Kendall's tau	BF_{10}	Kendall's tau	BF_{10}
Self-reported change pre to post COVID-19 lockdown	Cannabis use, days month	0.13	0.94		
	Social motives	-0.05	0.17	0.14	1.13
	Enhancement motives	**0.23****	**45.85**	**0.19***	**7.32**
	Coping motives	0.08	0.28	0.15*	1.71
	Expansion motives	0.04	0.15	0.16*	2.44
	DSM-5-CCSM total	**0.19****	**6.90**	-0.03	0.14
	DSM-5-CCSM depression	0.16*	2.47	0.07	0.20
	DSM-5-CCSM anxiety	**0.18***	**4.90**	-0.09	0.33
	DSM-5-CCSM Sleep problems	**0.18***	**5.91**	0.12	0.73
	Pre-post change Loneliness	0.12	0.69	0.15	1.71
	Contact quality partner	-0.06	0.18	-0.03	0.14
	Contact quality family	0.12	0.68	-0.04	0.15
	Contact quality friends	-0.06	0.20	0.06	0.20
	COVID-19 related worries				
	- Personal health	-0.00	0.13	0.04	0.15
	- Personal economics	-0.11	0.56	0.03	0.14
	- Contamination	**0.21****	**20.86**	0.109	0.51
	- Societal functioning	-0.00	0.13	-0.03	0.14

*DSM-5: Diagnostic and Statistical Manual of Mental Disorders; CUD: Cannabis Use Disorder; Motives were measured with the Marijuana Motives Measure; CCSM: Cross-Cutting Symptom Measure; *p < 0.05, **p < 0.01, ***p < 0.001; BF_{10}: Bayes factor likelihood H1 relative to H01 with default priors. Bold correlations and Bayes factors refer to significant results with at least moderate Bayesian evidence support.*

The regression analysis to explore which variables uniquely explained change in cannabis use revealed very strong evidence that lower pre-lockdown cannabis use and higher expansion motives related to larger increases in cannabis use, each significantly explaining unique variance in change. Moreover, change in CUD symptoms, and social motives also related to increases cannabis use, but with moderate evidence strength. Change in loneliness was a significant predictor in the final model, but with anecdotal evidence strength.

Control analyses adding alcohol, illicit substance use, and cigarette use revealed similar results (of note: Power was low due to missing data of non-users).

Table 5 Predictors of change in cannabis use: feed forward model selection

	B	95% CI bca (B)	SE (B)	*b*	*t*	*p*	BF_{10}
Pre- to post COVID 19 lockdown change DSM-5 CUD symptoms: *Final model F (6,96) = 11.33, adjuster R^2 = 0.48, p < 0.001*							
DSM-5 CUD, pre-lockdown	**- 0.20**	**- 0.30 – - 0.09**	**0.05**	**- 0.32**	**4.00**	**<0.001**	**>100**
Coping motives, change	0.09	- 0.03 – 0.22	0.06	0.17	1.81	0.074	1.18
DSM-5-CCSM anxiety, change	**0.21**	**0.04 – 0.38**	**0.08**	**0.25**	**2.65**	**0.009**	**6.16**
Change contact quality family	**0.72**	**0.19 – 1.27**	**0.28**	**0.20**	**2.46**	**0.016**	**4.07**
COVID-19 related worries, personal economic	**- 0.49**	**- 0.80 – - 0.23**	**0.14**	**- 0.35**	**3.79**	**<0.001**	**>100**
COVID-19 related worries, personal health	**0.77**	**0.38 – 1.19**	**0.21**	**0.39**	**4.08**	**<0.001**	**>100**
Pre- to post COVID 19 lockdown change cannabis use (days per month): *Final model F (5,97) = 14.37, adjuster R^2 = 0.40, p < 0.001*							
Cannabis use, days months, pre-lockdown	**- 0.31**	**- 0.45 – - 0.18**	**0.07**	**- 0.38**	**4.80**	**<0.001**	**>100**
DSM-5 CUD, change	**0.93**	**0.23 – 1.81**	**0.39**	**0.21**	**2.67**	**0.009**	**6.03**
Expansion motives, change	**0.83**	**0.32 – 1.33**	**0.25**	**0.29**	**3.67**	**<0.001**	**88.90**
Social motives, change	**0.35**	**0.03 – 0.66**	**0.16**	**0.21**	**2.61**	**0.011**	**5.20**
Loneliness, change	1.47	0.15 – 2.80	0.67	0.17	2.18	0.031	2.11

DSM-5: Diagnostic and Statistical Manual of Mental Disorders; CUD: Cannabis Use Disorder; Motives were measured with the Marijuana Motives Measure; CCSM: Cross-Cutting Symptom Measure; CI bca: Confidence Interval bias corrected accelerated; SE: Standard Error); 95% CI based on bootstrapping 5000 replications. BS_{10}: Bayes factor likelihood H1 relative to H01 with default priors of including all other measures to the null model. Bold regression results refer to significant effects with at least moderate Bayesian evidence support.

Cannabis users versus controls

Age (W = 3129.00, p = 0.11, BF_{10} = 0.36) did not differ between groups, but there were more women (cannabis users = 43%; controls = 75%; $\chi^2(2) = 17.8$, p < 0.001, BF_{10} > 100), more students (cannabis users = 55%; controls = 73%; $\chi^2(1) = 5.6$, p = 0.017, BF_{10} = 3.0) and less cigarette smokers (cannabis users = 55%, controls = 10% at baseline; $\chi^2(1) = 23.8$, p < 0.001, BF_{10} > 100) in the control group. Alcohol use did not change and did not differ between groups (see Table 1). Illicit substance use did not change, but there was strong evidence for higher baseline (W = 5091.0, p < 0.001, BF_{10} = 16.1) and anecdotal evidence for higher pre-lockdown (W = 4742.5, p = 0.003, BF_{10} = 2.01) use in cannabis users.

Regarding mental wellbeing, cannabis users scored significantly higher on DSM-5-CCSM total, depression and sleep problems (Table 2), however, Bayesian evidence only supported a group difference on pre-lockdown DSM-5-CCSM total (W = 5287.5, p < 0.001, BF_{10} = 62.9) and depression (W = 5287.5, p < 0.001, BF_{10} = 62.9) scores. COVID-19 related worries did not differ between groups (p's > 0.06, BF_{10} < 0.54). Like in cannabis users, only loneliness significantly increased pre-to-post lockdown in the control group (W = 846.50, p < 0.001, BF_{10} > 100), but change in loneliness did not differ between groups.

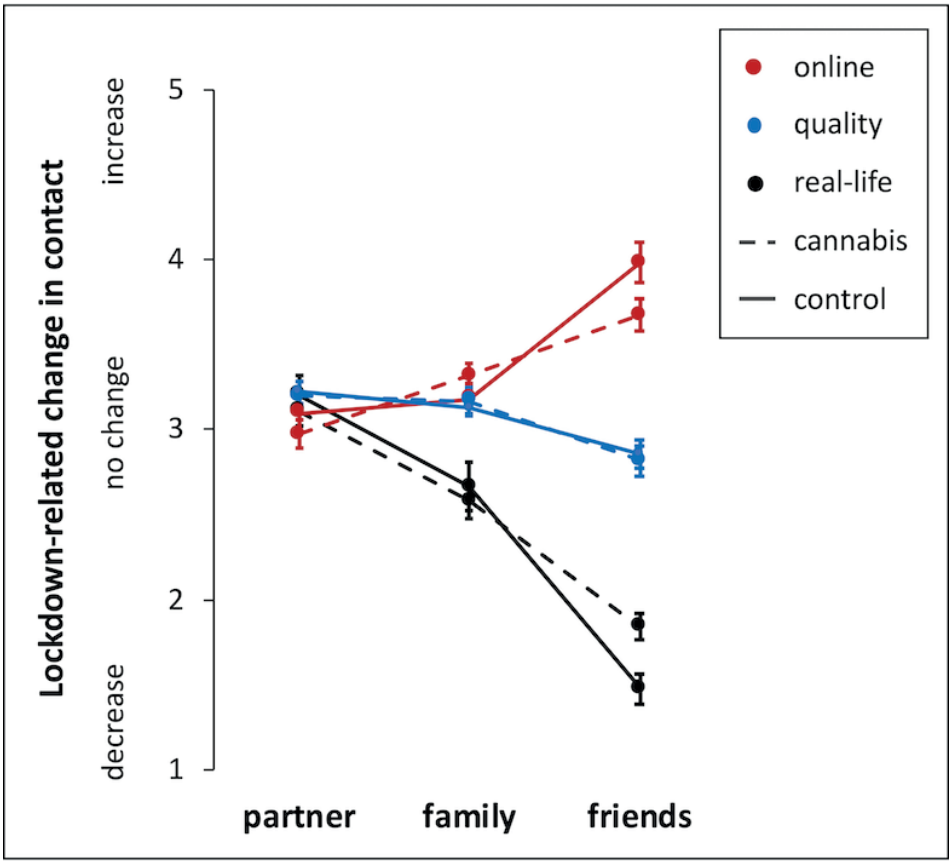


Figure 1. COVID-19 lockdown-related change in in-person, online and quality of contact with partners, family and friends (3 = no change). Means and standard error are reported. A decrease in in-person contact paralleled an increase in online contact with family and friends. Quality increased for partners and family and decreased for friends. Compared to cannabis users, controls showed a larger reduction in in-person contact with friends.

The percentage of individuals that lost their job during the COVID-19 lockdown did not differ between groups ($\chi^2(1) = 0.4$, $p = 0.51$, $BF_{10} = 0.23$). Pre-to-post lockdown change in social contact was similar between cannabis users and controls (no main or interaction effects with group, Figure 1), except for frequency of in-person contact (group interaction; $\chi^2(2) = 6.31$, $p = .04$). Post-hoc analysis showed that in-person contact with friends, but not partners of family, was reduced more in controls ($W = 4690.50$, $p = 0.003$, $BF_{10} = 5.98$), with moderate evidence strength.

Discussion

The COVID-19 pandemic and lockdown measures substantially impact daily life, highlighting the importance of monitoring the wellbeing of vulnerable populations, including cannabis users. The cannabis users included in this explorative study used on average 4-5 days per week and 57% had a moderate to severe CUD before lockdown. Our longitudinal survey data showed a significant increase in cannabis use during the first months of lockdown. There was no evidence for a change in CUD symptom severity, but during lockdown, time was weakly associated with reductions in CUD. The increase in use related to an increase in motives to use cannabis for expansion of thoughts and experiences. Moreover, while feelings of loneliness generally increased, both cannabis users and controls reported improved contact with partners and family and no change in symptoms of depression, anxiety, or sleep problems, despite ~30% losing their job. These results suggest a minimal impact of the lockdown on mental well-being in cannabis users. However, there were substantial individual differences that need to be taken into account, and increased anxiety and worries about the impact of COVID-19 on personal health did relate to increased CUD symptoms.

Which cannabis users are at risk for increasing cannabis use and CUD severity is an important question. We expected lockdown-related worsening of social relationships (Boman & Heck, 2017; Mason et al., 2017), job loss (Henkel, 2011; Poulton et al., 1997) and increases in mental health problems to relate to increases in cannabis use and CUD symptoms. Our results reflect changes during the first two months after the start of the lockdown and the explorative and partly retrospective nature of this study prevents us from drawing conclusions about causality. Nevertheless, as expected, changes in mental wellbeing covaried with changes in CUD symptom severity, with anxiety explaining unique variance with moderate evidence strength. This relationship is probably bidirectional, with anxiety being both a risk factor for and a consequence of CUD (Richardson, 2010). Unexpectedly, job loss did not affect CUD severity or cannabis use and better contact with family predicted an increase in CUD severity. It could be that worries expressed by family members and the feeling of positive family support increased awareness and reporting of the severity of their cannabis use (Templeton et al., 2010), warranting a more long-term and in-depth assessment of lockdown impact on cannabis users' wellbeing.

The strongest evidence was observed between change in CUD symptom severity and COVID-19 specific worries. Interestingly, in a small US sample Rogers et al. (2020) showed that individuals who initiated cannabis use during the pandemic had higher COVID-19 related worries than non-users and pre-pandemic users, supporting the inclusion of COVID-19 related worries in future studies. We observed strong evidence for a positive correlation between contamination worries and change in CUD severity.

However, we also observed extremely strong evidence for lower worries about personal economic consequences and higher worries about personal health uniquely predicting increasing CUD severity (on top of baseline CUD severity, change in anxiety and quality of family contact). In both cannabis users and controls, these worries were lower than worries about contamination and societal consequences. The relatively low worries about personal economic consequences, but also the 55% student sample (with perhaps other means of financial support) might explain the lack of an effect of job loss on cannabis use. The link between worry about mental and physical health and increased reported CUD severity may be indicative of self-awareness of cannabis use severity. Compromised self-awareness has been linked to poor addiction prognosis (Moeller & Goldstein, 2014), highlighting the need to investigate the impact of the lockdown in more severe clinical populations with CUD.

Regarding cannabis use motives, we observed a reduction in social motives that uniquely explained variance in change of cannabis use, such that a larger reduction in social motives was related to a larger reduction in cannabis use frequency. This intuitively follows the implemented social distancing measures and the significant decrease in in-person contact with friends. We also expected increased in coping motives (Benschop et al., 2015), but our data provides insufficient evidence to support or refute associations with change in cannabis use and CUD symptom severity. In contrast, evidence was very strong for increasing expansion motives predicting increasing use, suggestive of use as a result of lockdown induced boredom and the need for a 'mental breakout'. Like in previous studies, expansion motives correlated with use, but endorsement is generally low compared to enhancement motives (Bonar et al., 2017; Buckner et al., 2012).

Our longitudinal data on cannabis use and CUD severity, including assessments prior and during the first months of the Dutch lockdown is a clear strength. The negative association between time and change in CUD symptom severity during the lockdown (but no main effect of lockdown), may suggest less change in severity the further away from lockdown onset, or even a potential reduction. This highlights the need for studies that assess the long-term impact of the pandemic in vulnerable populations. Importantly, while cannabis outlets remained open in the Netherlands, the lockdown may have significantly impacted the cannabis market in other countries (Groshkova et al., 2020). It is therefore recommended that future studies take potentially restricted access and other cultural factors into account. Moreover, given the impact of the lockdown on social and work life, and the fact that severity of CUD is in part measured by the negative impact of cannabis use on social functioning, the lockdown may fundamentally affect CUD pathology. That is, social distancing and work from home may change CUD symptoms in a way not captured by the MINI 7.0.0

DSM-5 CUD section, warranting future qualitative and quantitative investigations of lockdown related changes in CUD pathology and its underlying mechanisms.

Some limitations should be considered. Although internal consistency of our measures was generally good, the restricted timeframe of the post-lockdown assessment (i.e., self-reported changes over a period of 2 months) and online nature of this study may have impacted the validity of our assessments. Moreover, the online nature of this study may have introduced a sampling bias, missing the most problematic users (Pierce et al., 2020), and a larger, matched, reference group is needed for more fine-grained investigations between cannabis users and controls. While in-person research is currently very limited, research via a video connection may be an option, taking issues with poor non-verbal communication, access, and privacy into account (Dodds & Hess, 2020).

In conclusion, our study provides important first insights into psychosocial consequences of the COVID-19 lockdown on cannabis users. Generally, the lockdown was related to increased cannabis use in cannabis users, and increased loneliness and 30% job loss in both cannabis users and control. However, the impact on CUD severity and mental health problems seemed minimal and quality of contact with partners and family improved. Pre-lockdown severity of cannabis use, COVID-19 related worries, increases in anxiety, more expansion and social motives, and quality of family contact all uniquely related to increases in cannabis use or CUD. These findings highlight the importance of studying individual differences and long-term effects of the lockdown.

Chapter 12

Development and validation of the Dutch social attunement questionnaire (SAQ)

This chapter is based on:
Kroon, E., Mies, G., Wiers, R. W., & Cousijn, J. (2023). Development and validation of the Dutch social attunement questionnaire (SAQ). *Social Development, 32*(2), 546-565. https://doi.org/10.1111/sode.12652

Abstract

The social plasticity hypothesis proposes that social attunement, i.e., the adaptation to and harmonization with one's environment, plays a crucial role in the risk for developing alcohol use disorders (AUDs) during adolescence, whereas in adulthood it paradoxically may make individuals more sensitive to the social pull to reduce drinking. This study aimed to develop a valid measure of social attunement: the social attunement questionnaire (SAQ). A total of 26-items were developed, and the questionnaire was completed by 576 Dutch mid to late adolescents and adults over three rounds of online data collection. Using exploratory factor analysis in part of the sample (N = 373), the final questionnaire was reduced to two subscales with a total of 11 items. This structure was confirmed using confirmatory factor analysis in the second part of the sample (N = 203). Results showed that the SAQ has acceptable internal consistency, good measurement invariance to gender, and subscales assess both cognitive as well as behavioral components of social attunement. In line with expectations in alcohol use settings, SAQ scores were not directly associated with alcohol use, but they were predictive of alcohol use when taking into account the interaction between perceived peer drinking and age. The SAQ appears suitable for the assessment of social attunement in (young) adult men and women, particularly assessing the role of social attunement in alcohol use settings. Further research is needed to confirm the utility of the SAQ in older adults and a broader variety of social settings.

Introduction

Adolescent development is of great interest to multiple fields of research, including addiction research. It is characterized by major physical and social changes, and high social learning and brain plasticity make that adolescents are generally very flexible in adjusting to those changes (Cousijn, Luijten et al., 2018). At the same time, adolescents often show increased risk-taking (Crone & Dahl, 2012). This attraction to risky behavior is thought to be guided by a relative imbalance between the heightened sensitivity of fronto-limbic brain areas involved in affective learning and reward processing, and more protracted development of frontal areas guiding control over our actions (Casey et al., 2008; Gladwin et al., 2011). As reward sensitivity is high and cognitive control suboptimal, immediate reward is preferred, whereas the long-term consequences of (risky) actions are largely ignored. Although seen in a variety of situations requiring social decision making, this imbalance appears to be particularly important in the often-seen excessive alcohol use in social situations during mid to late adolescence, which increases the risk of developing alcohol use disorders (AUDs; MacPherson et al., 2010). Nonetheless, most mid to late adolescents and young adults who drink excessively, and meet criteria for an AUD, go through a phase of natural reduction of use when maturing (Chassin et al., 2004; Vergés et al., 2013). This natural reduction, sometimes referred to as 'maturing out of addiction', might be caused partly by increased behavioral control, but this development does not explain fully why some adolescents maintain AUDs in adulthood but most naturally reduce use (Heyman, 2009).

Paradoxically, the same neuro-social mechanisms that place mid to late adolescents at initial risk for developing AUDs also might result in a unique resilience to the maintenance of alcohol-related problems (Cousijn, Luijten et al., 2018; Orford, 2001). More specifically, the *social plasticity hypothesis* describes how changing interactions between 1) (social) learning and (brain) plasticity, 2) behavioral control, and 3) social attunement could explain this increase and subsequent decrease in alcohol use seen in the transition from adolescence to adulthood (Cousijn, Luijten et al., 2018). Social attunement, one of the concepts central to this *social plasticity hypothesis*, can be defined as the degree to which one adapts and harmonizes with one's social environment (Cousijn, Luijten et al., 2018). During adolescence, parental influence diminishes, whereas the need to attune socially to one's peers seems to increase (Marshal & Chassin, 2000; Sebastian et al., 2008). Attuning to one's peers also can affect adolescent alcohol use through perceived alcohol use norms within the peer group (e.g., Brooks-Russell et al., 2014; Teunissen et al., 2012). Hence, adolescents prone to social attunement, who spend most of their time with an excessively drinking peer group, are hypothesized to show more excessive drinking behavior, even in the absence of explicit peer pressure.

Likewise, in a peer group with limited alcohol consumption, adolescents who are attuned highly to their environment are less likely to drink excessively.

The transition to adulthood involves major events like finishing studies, starting a job, finding a partner, and having children. During this maturation phase, group attitudes regarding alcohol use often change, resulting in social devaluation of alcohol use (Jackson et al., 2001). It is hypothesized that individuals prone to social attunement, who were at risk for excessive drinking at first, will adapt to this change in alcohol's social value and reduce their alcohol use accordingly (Cousijn, Luijten et al., 2018). Social attunement to the changing group norms might therefore be an important factor in the process of "maturing out of addiction" (e.g., Dawson et al., 2006; Lee et al., 2015). Due to relatively high brain plasticity and learning flexibility compared to adults, adolescents and young adults are thought to be particularly good at attuning to those new group standards, even after periods of excessive use.

Although questionnaires on more negative reinforcement motives of behavior change, such as social conformity (e.g., Mehrabian & Stefl, 1995), have been developed over the years, there is no measure to assess social attunement yet. The difference in reinforcement motives guiding the behavior makes it crucial to distinguish social attunement from social conformity behavior. Where social conformity could be described as behavioral adaptation to avoid negative feedback from the social environment (peer pressure/obedience), social attunement specifically explains behavioral adaptation to optimize and increase positive social feedback from this environment (positive reinforcement). Furthermore, this process might occur more implicitly and gradually than conformity: as a result, over time one's behavior will start to resemble that of the individuals with whom one spends the most time, creating social harmony within the group. This behavior will potentially be affected by the sensitivity of an individual toward the behavior of others, and social attunement tendencies also depend on the differences between one's behavior and the behavior of the environment to which to attune. Depending on the extent to which one values the behavior of others, one will attune more or less to the behavior of these individuals within the social group. This results in social harmony and increasingly positive socially rewarding outcomes (See Figure 1).

To test the *social plasticity hypothesis* (Cousijn, Luijten et al., 2018), a valid instrument to measure social attunement is key. For this purpose, we developed and validated the social attunement questionnaire (SAQ). Although the questionnaire was developed in the context of alcohol use and related problems because initiation and escalation of alcohol use is a clear example hypothesized to be affected by social attunement, we aimed to develop a questionnaire that could also be used in other contexts (e.g., other substance use and social risk-taking behaviors). We then assessed convergent and divergent validity

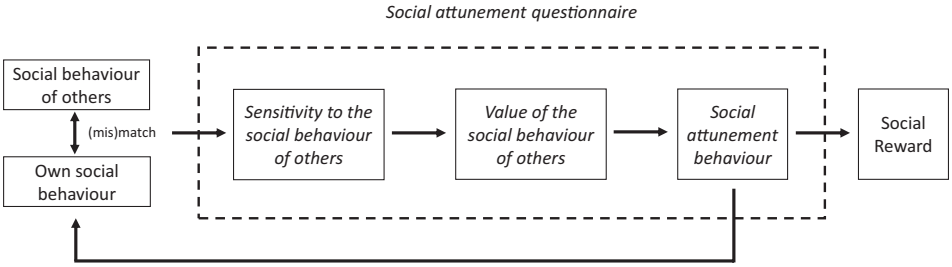


Figure 1. Overview of the conceptualisation of social attunement. The figure displays how individuals reflect on their own social behavior in relation to the behavior of others. Dependent on the mismatch between those behaviors, individuals might socially attune. The extent to which this happens depends on the individuals' sensitivity to the social behavior of others and the extent to which one values the behavior of the other. Over time, a continuous cycle of this social attunement process will result in increasingly socially rewarding outcomes.

of the SAQ and assessed measurement invariance to gender. SAQ scores were expected to be associated positively, but not one-on-one, with social conformity (Mehrabian & Stefl, 1995), as similar responses to items that reflect behavioral outcome (change of behavior and social reward) were expected, whereas social attunement and social conformity are supposed to diverge on items that reflect the motives and circumstances in which these behavioral outcomes occur. In addition, the social reward questionnaire (Foulkes et al., 2014) was included to assess how social attunement – with the goal of receiving social reward – relates to the pro-social interaction (good reciprocal relationships), admiration (gaining positive attention), sociability (engaging with the social group), passivity (giving control to others), and negative social potency (being cruel) subscales of this measure. Social attunement was expected to be associated positively with the pro-social interaction, admiration, and sociability subscale of the social reward questionnaire as these reflect values that would facilitate social attunement. No association was expected between social attunement and more non-social behaviors such as the passivity and negative social potency subscales of the social reward questionnaire. Similarly, assessing divergent validity, we expected social attunement to not be associated with the need for cognition scale (Cacioppo & Petty, 1982) as this scale is a commonly used scale of reflective of non-social decision making and interests.

Regarding the role of social attunement in alcohol consumption, we expected stronger social drinking motives (social and conformity) to relate to higher social attunement. Furthermore, we expected social attunement to decrease with age in our group of mid to late adolescents and adults (Cousijn, Luijten et al., 2018). As such, we expected social attunement to predict higher alcohol use especially in relatively younger participants and those who report relatively higher levels of peer alcohol use.

Method

The development of the SAQ consisted of multiple phases including 1) item generation, 2) assessment of content and face validity, and 3) online data collection for psychometric validation of the SAQ. In this third phase, we used exploratory factor analysis for item reduction and structure evaluation before assessing the internal consistency of the scale. Then, confirmatory factor analysis was performed to confirm the structure, internal consistency, and measurement invariance. Furthermore, convergent, and divergent validity was evaluated and the association between social attunement, perceived peer drinking, and alcohol consumption was assessed. Methods were approved by the ethics committee of the psychology department of the University of Amsterdam (round 1 and 3: 2018-DP-8768, round 2: 2018-DP-9891), and participants in each phase were fully informed about the procedure and gave (online) consent before participation.

Item generation

The following questionnaires, assessing constructs related to social attunement, were reviewed for initial item generation: Social Monitoring Scale (Lennox & Wolfe, 1984; Snyder & Gangestad, 1986), Concern for Appropriateness Scale (Lennox & Wolfe, 1984), Need to Belong Scale (Leary et al., 2013), and the Peer Pressure, Popularity, and Conformity Scale (Santor et al., 2000). A total of 23 items that, after adjustments, could fit the conceptualization of social attunement (Figure 1) were selected from the above-mentioned questionnaires (selected by EK, selection checked by GM). After adjustment of the items (EK), all items were reviewed again (GM & JC) to combine or delete items with overlapping content and the selection was supplemented with new items to make sure the included items covered all stages of our conceptualization, resulting in a total of 24 items.

Content and face validity

The first 24-item version of the SAQ was reviewed by 6 external experts in a relevant field (e.g., social learning or peer relations). These experts were provided with an explanation of our conceptualization of social attunement and asked to give their assessment of the relevance of each of the items item to the concept ("This item is relevant for the construct") and the clarity of each item ("This item is formulated clearly") on 7-point Likert scales (1 = completely disagree, 7 = completely agree), and to provide general feedback on the items. The average content validity index (CVI) for relevance, i.e., the percentage of positive (4 or higher) evaluations per item, was .88 (good; Polit & Beck, 2006). Two items with a CVI below .78 (sufficient; lowest CVI = .67; Polit & Beck, 2006) were adjusted based on the provided feedback (EK) and

re-assessed (GM & JC). In addition to our group of experts, a group of 8 non-experts (variable age, sex, and educational level) were asked to answer the clarity question for all items. Clarity was assessed by averaging the scores per item across both experts and non-experts. Eight items (33.3%) with an average score below 4 were adjusted based on provided feedback (EK) and re-assessed (GM & JC). After re-evaluation of all items, two additional items were developed (EK) and reviewed (GM & JC) with the aim of capturing the socially rewarding outcome (Figure 1) of social attunement.

Table 1 Sample characteristics

Measure	Sample 1	Sample 2	Statistics	Effect size	p-value
N	373	203	-	-	-
Age, Med (range)	20.00 (16:35)	30.00 (16:78)	*U* = 23960.00	.37	<.001
Gender, (Male/Female/Other%)	55.23/44.24/0.54	29.56/70.44/0.00	X^2(2, N = 576) = 36.73	-	<.001
Education level, med	3.00	2.00	X^2(2, N = 576) = 158.09	-	<.001
Low (%)	3.75	33.99	-	-	-
Middle (%)	10.46	29.56	-	-	-
High (%)	85.79	36.45	-	-	-
SAQ Full, M (SD)	46.80 (8.42)	43.02 (8.27)	*t*(574) = 5.19	.46	<.001
SAQ – Cognitions - subscale 1, M (SD)	18.62 (4.98)	16.56 (4.78)	*t*(574) = 4.81	.42	<.001
SAQ – Behaviour - subscale 2, M (SD)	28.19 (5.17)	26.46 (5.53)	*t*(574) = 3.74	.33	<.001
Need for Cognition, M (SD)†	63.79 (9.28)	-	-	-	-
SR-Admiration, Med (range)†	21.00 (8:28)	-	-	-	-
SR-Negative Social Potency, Med (range)†	14.00 (7:35)	-	-	-	-
SR-Passivity, Med (range)†	8.00 (3:21)	-	-	-	-
SR-Pro-social interaction, Med (range)†	31.00 (21:35)	-	-	-	-
SR-Sociability, Med (range)†	14.00 (7:21)	-	-	-	-
Conformity, Med(range)	-	0.00 (-31:22)	-	-	-
Perceived peer drinking, Med (range)	6.00 (0:11)	5.00 (1:12)	*U* = 47800.00	.29	<.001
AUDIT, Med (range)	9.00 (0:26)	6.00 (1:26)	*U* = 39621.00	.25	<.001
DM-Conformity, Med (range)	5.00 (5:25)	5.00 (5:15)	*U* = 37222.50	.24	<.001
DM-Social, Med (range)	17.00 (5:25)	13.00 (5:25)	*U* = 41464.50	.38	<.001
DM-Coping, Med (range)	7.00 (5:25)	6.00 (5:19)	*U* = 33947.50	.13	.016
DM-Enhancement, Med (range)	15.00 (5:25)	11.00 (5:21)	*U* = 41751.50	.39	<.001

Note. AUDIT: alcohol use disorder identification test; DM: drinking motives; Education: low = primary school - Dutch pre-vocational training secondary school (VMBO/MAVO) - vocational training (MBO), medium = Dutch pre-university of applied sciences secondary school (HAVO) – university of applied sciences (HBO), high: = Dutch pre-university secondary school (VWO) – university (WO) ;M: mean (reported when data was normally distributed); Med: median (reported when data was not normally distributed); SAQ: social attunement questionnaire; SD: standard deviation; SR: social reward; †Questionnaires only completed by part of the sample (N = 196).

Psychometric evaluation of the SAQ

Participants

A total of 589 responses on the SAQ were collected during 3 rounds of data collection (round 1: N = 196, round 2: N = 182, round 3: N = 211). Participants were recruited through social media (rounds 1 & 3), the lab website of the University of Amsterdam (rounds 1 & 3) or during the first-year psychology student test sessions held at the University of Amsterdam (round 2) and were all fluent in Dutch and lived in the Netherlands while participating in the study. Participants were compensated by receiving research credits (students in rounds 1, 2 and 3), or the opportunity to participate in a raffle for online gift cards (both students and non-students in rounds 1 and 3). Inclusion in each round was based on age (round 1: 16-35, round 2: no limit, round 3: 16-80) to ensure the inclusion of participants from mid adolescence to adulthood. Exclusion only applied to those who already participated in earlier rounds of the study. Sample characteristics are provided in Table 1.

Measures

Item reduction and structure assessment. The 26-item SAQ (Appendix I - Table S1) was used to assess social attunement on a 7-point Likert scale (1 = completely disagree, 2 = disagree, 3 = more or less disagree, 4 = neutral, 5 = more or less agree, 6 = agree, 7 = completely agree; see Appendix I - Table S1 for Dutch scale). Potential scores varied between 26 and 182 with higher scores indicating higher social attunement.

Sample characteristics and measurement invariance. Participants were asked to report on their age, gender (Round 1 and 3: male/female/other; Round 2: male/female), country of birth, and highest completed level of education (low = primary education, pre-vocational secondary education, or vocational education; middle = higher secondary education or higher professional education; high = pre-university secondary education or university) to be able to compare samples and assess measurement invariance.

Convergent and divergent validity. The need for cognition questionnaire (Round 1; Cacioppo & Petty, 1982; Verplanken et al., 1992), social reward questionnaire (Round 1; Foulkes et al., 2014; items from the sexual reward subscale were omitted), and social conformity questionnaire (Round 3; Mehrabian & Stefl, 1995) were included to assess convergent and divergent validity.

Age, social attunement, and alcohol consumption. Participants completed the alcohol use disorder identification test (AUDIT; Saunders et al., 1993) to assess alcohol use and related problems, the Cooper's Drinking motives questionnaire (DMQ; Cooper, 1994) to assess drinking motives (i.e., social, conformity, coping, and enhancement), and a three-item adaptation of the first three items of the AUDIT to assess perceived peer drinking (PPD; See Appendix I - Table S2).

Procedure

After providing consent, participants completed basic demographic questions, followed by the 26-item SAQ, additional questionnaires to assess convergent and divergent validity, as well as questionnaires to assess the association between social attunement, perceived peer drinking, and alcohol use. In round 2, participants were compensated with research credit after participation as our questionnaires were included in a larger test session organized by the department of psychology of the University of Amsterdam. In rounds 1 and 3, all participants had the choice to leave their email address to participate in a raffle of six (three per round) 20-euro online gift cards. The raffle was performed after finishing data collection per round.

Data analysis

Item reduction and structure assessment. The data from rounds 1 and 2 were combined into sample 1 (N = 378) and the data from round 3 was used as sample 2 (N = 211), to create two sufficiently large samples for the planned analyses (Table 1). Sample 1 was used for exploratory factor analysis (EFA) and sample 2 for confirmatory factor analysis (CFA). Outliers, i.e., participants with SAQ sum scores ± 2.5 SD from the mean were excluded from analyses. Using sample 1, EFA was performed for item reduction and to assess the factor structure of the SAQ. The EFA was performed in JASP (JASP Team, 2020) using parallel analysis, principal axis factoring (accounting for violation of multivariate normality), and Promax rotation (because of the expected correlation between factors). Item reduction was guided by factor loadings (> .35 minimal accepted loading), uniqueness, Kaiser-Meyer-Olkin (KMO) criteria (> .70 = good), improved model fit and increased explained variance after item reduction, and additional conceptual considerations (see results section). Then, using the final factor structure, internal consistency for the full scale, as well as each subscale separately, was assessed using Cronbach's alpha (> .70 acceptable for scales with 10 or more items) and McDonald's omega (> .70 acceptable). Using sample 2, CFA was performed to confirm the factor structure in an independent sample that differed from the original sample. Model fit was assessed using a chi-square test (significance indicating poor fit), Tucker-Lewis index (TLI; good fit > .90), Root Mean Square Error of Approximation (RMSEA; acceptable fit < .08, good fit < .05) as well as the comparative fit index (CFI; good fit > .90;). Again, internal consistency for the full scale as well as each factor was assessed using Cronbach's alpha and McDonald's omega (Hayes & Coutts, 2020).

Measurement invariance. To assess measurement invariance to gender, we ran the CFA again for both genders separately to check structure fit. Then, group CFA was performed assessing configural invariance, metric invariance, scalar invariance, and strict factorial invariance to gender. Gender differences in SAQ scores were assessed using an

independent sample t-test (or Mann-Whitney U test in case of violation of assumptions).

Convergent and divergent validity. To assess convergent and divergent validity, we performed Pearson correlations (or Spearman correlations in case of violation of assumptions) between total SAQ as well as SAQ subscale scores, and the need for cognition questionnaire, social reward questionnaire, social conformity questionnaire, and age.

Age, social attunement, and alcohol consumption. Additional analyses were conducted to assess whether social attunement was associated with drinking motives, perceived peer drinking and alcohol use. First, Pearson correlations (or Spearman correlations in case of violation of assumptions) between total SAQ scores and the four subscales of the DMQ, as well as age, PPD, and AUDIT score were assessed. Second, regression analyses were performed to assess whether SAQ score was predictive of AUDIT score and whether PPD, age, and their interactions explained additional variance in this association.

Results

Sample characteristics

Sample 1 (including rounds 1 and 2) and sample 2 (including round 3) significantly differed on most demographics, with higher age, a higher percentage of females, and lower median completed education in sample 2 (Table 1). Looking at alcohol-related measures, perceived peer drinking and AUDIT score were higher in sample 1, and the samples differed on all drinking motives (Table 1).

Exploratory factor analysis

Exploratory factor analysis (EFA) was used for item reduction and the assessment of the structure of the SAQ. Before running the first EFA, items 2, 8 and 19 were deleted for conceptual reasons. These items targeted social attunement in alcohol drinking situations specifically and, while originally included because of our interest in social alcohol drinking situations, were deleted to increase the generalizability of the measure for use in other social situations. Assessment of KMO (Full scale = .79) and the significance of Bartlett's test of sphericity ($X^2 = 1486.63$, df = 148, $p < .001$) indicated adequacy of the data for EFA.

Item reduction

Initial EFA, using parallel analysis, indicated a 5-factor structure (Appendix I - Table S3 - step 1). Based on the initial EFA, items 7, 10, 15, 23 and 25 were deleted because of a lack of loading (all < .3) on any of the factors and items 5 and 26 were deleted because of low KMO (KMO < .6; Appendix I - Table S3). This resulted in a 2-factor structure (Appendix I - Table S3 - step 2) from which items 1, 11, 16, 18, and 24 were omitted because of a lack of loading on any of the factors (all < .3). The final item set included 11 items divided over two factors (Appendix I - Table S3 - step 3; Tables 2 & 3).

Table 2 Overview of Factor Structure and Item Properties Resulting from Final Exploratory Factor Analysis

Item # 11-item	Item # 26-item	Factor 1	Factor 2	KMO	Uniqueness	Mean	SD	Median	Range
2	4	.55	-.10	.79	.74	2.86	1.32	3.00	1:7
3	6	.53	-.02	.82	.73	3.20	1.54	3.00	1:7
5	12	.63	.13	.74	.51	5.00	1.37	5.00	1:7
6	13	.39	.03	.89	.83	3.26	1.48	3.00	1:7
8	17	.78	-.07	.71	.44	4.31	1.63	5.00	1:7
1	3	.15	.56	.79	.58	4.20	1.55	5.00	1:7
4	9	-.07	.43	.76	.84	4.31	1.49	5.00	1:7
7	14	-.00	.68	.77	.54	4.62	1.52	5.00	1:7
9	20	.15	.38	.84	.77	4.61	1.39	5.00	1:7
10	21	-.14	.47	.76	.83	5.17	1.42	6.00	1:7
11	22	.14	.35	.87	.81	5.28	1.05	5.00	2:7
Subscale 1 – Cognitions	-	-	-	-	-	18.62	4.98	19.00	6:30
Subscale 2 – Behaviour	-	-	-	-	-	28.19	5.17	29.00	12:40
Full scale	-	-	-	.78	-	46.80	8.42	47.00	22:67

Note. rotation method applied is promax. Only factor loading > .30 are presented. N = 373

Table 3 Final Dutch 11-item Social Attunement Questionnaire

Item # 11-item	Item	Item # 26-item	Factor
1	Ik gedraag mij weleens op een manier die niet echt bij mij past omdat dit beter aansluit op de situatie.	3	2
ENG	*I sometimes behave differently from how I normally would, because it suits the situation better.*		
2	Ik heb er geen probleem mee om anders te zijn dan de mensen in de groep waarin ik me bevind. (R)	4	1
ENG	*I do not have a problem with being different from the people in the group I am in.*		
3	Ik probeer te voorkomen dat anderen denken dat ik anders ben.	6	1
ENG	*I try to prevent people from thinking that I am different.*		
4	Ik neem vaak woorden van een ander over.	9	2
ENG	*I often adopt words into my vocabulary that I hear others using.*		
5	Ik hecht veel waarde aan hoe mensen over mij denken.	12	1
ENG	*It really matters to me what people think of me.*		
6	Als de meerderheid van een groep een bepaalde mening heeft, ga ik daar meestal in mee.	13	1
ENG	*When the majority of a group has a certain opinion, I usually agree.*		
7	In verschillende situaties met verschillende mensen gedraag ik mij anders.	14	2
ENG	*In different situations with different people, I often behave very differently.*		
8	Het kan mij weinig schelen wat anderen van mij vinden. (R)	17	1
ENG	*I do not care much about what others think of me.*		
9	Als ik niet goed weet hoe ik me moet gedragen, kijk ik naar wat anderen doen.	20	2
ENG	*When I do not know how to behave, I look at what others do.*		
10	Ik pas mijn taalgebruik aan aan mijn gezelschap.	21	2
ENG	*I adjust my language to who I am with.*		
11	Ik probeer zo goed mogelijk aansluiting te vinden bij de groep waarin ik mij bevind.	22	2
ENG	*I try to align myself as good as possible to the group I'm with.*		

Note. Participants were asked to answer using a 7-point likert scale (English: 1 = Completely disagree, 2 = disagree, 3 = more or less disagree, 4 = neutral;, 5 = more or less agree, 6 = agree, 7 = Completely agree; Dutch: 1 = helemaal mee oneens, 2 = oneens, 3 = een beetje mee oneens, 4 = neutral, 5 = een beetje mee eens, 6 = mee eens, 7 = helemaal mee eens) and all items followed by (R) are reverse coded items; ENG = English translation (included here for clarification purposes only).

Final structure

Although the chi-square test of model fit was significant ($X^2(34, N = 373) = 92.991$, $p < .001$), additional fit indices indicated an acceptable to good fit (RMSEA = .069; TLI: .86). As expected, there was a substantial correlation between the subscales (r = .62), but the items included in both subscales seemed conceptually distinct. Items of subscale 1 reflect social attunement related Cognitions, that is, the extent to which you think about your own behavior and how others perceive your behavior. Items of subscale 2, on the other hand, reflect actual social attunement related Behavior, that is, the extent to which you adjust your behavior to attune to the behavior of others (Table 2 and 3).

Internal consistency

Both factors showed acceptable internal consistency for the Cognitions scale (McDonald's ω = .71, Cronbach's α = .71) and moderate internal consistency for Behavior scale (McDonald's ω = .67, Cronbach's α = .66). Although higher internal consistency would be preferable, the limited number of items might affect internal consistency negatively (e.g., Taber, 2018). Looking at the full scale, internal consistency was acceptable (McDonald's ω = .75, Cronbach's α = .75).

Table 4 Confirmatory Factor Analysis Results

Item # 11-item	Item # 26-item	Factor	Estimate	SE	Z-value	p-value	Mean	SD	Median	Range
2	4	1	.40	.09	4.31	<.001	2.52	1.22	2.00	1:7
3	6	1	.59	.13	4.70	<.001	2.97	1.66	2.00	1:7
5	12	1	.31	.12	11.33	<.001	4.43	1.53	5.00	1:7
6	13	1	.39	.11	3.63	<.001	2.86	1.40	2.00	1:7
8	17	1	.14	.12	9.48	<.001	3.78	1.62	4.00	1:7
1	3	2	.81	.14	5.84	<.001	4.07	1.73	5.00	1:7
4	9	2	.48	.13	3.77	<.001	3.74	1.56	4.00	1:7
7	14	2	.93	.12	7.90	<.001	4.62	1.49	5.00	1:7
9	20	2	.95	.13	7.57	<.001	4.15	1.58	5.00	1:6
10	21	2	.65	.13	5.18	<.001	4.98	1.54	5.00	1:7
11	22	2	.61	.10	5.92	<.001	4.90	1.29	5.00	2:7
Subscale 1 – Cognitions	-	-	-	-	-	-	16.56	4.78	17.00	5:29
Subscale 2 – Behaviour	-	-	-	-	-	-	26.46	5.53	28.00	12:39
Full scale	-	-	-	-	-	-	44.59	8.82	46.00	20:69

Note. SE: standard error, SD: standard deviation; N = 203

Confirmatory factor analysis

Confirmatory factor analysis (CFA) was used to assess the consistency of the 11-item two-factor questionnaire structure in another sample (Sample 2; Table 1). The chi-square test of model fit was not significant ($X^2(43, N = 203) = 58.781$, $p = .055$), fit

indices indicate that model fit was acceptable to good (RMSEA = .04, TLI = .93) and factor covariance (cov = .41, SE = .08, p < .001) showed sufficient discriminant validity between the factors (Table 4).

Internal consistency

Assessment of the internal consistency of both subscales in sample 2, showed moderate internal consistency for the Cognitions subscale (McDonald's ω = .67, Cronbach's α = .64), the Behavior subscale (McDonald's ω = .65, Cronbach's α = .64), and the full scale (McDonald's ω = .67, Cronbach's α = .69).

Table 5. Measurement Invariance

Subgroup	X^2	*df*	**p-value**	**RMSEA**	**90% CI**	**Δ RMSEA**	**p-value[1]**	**CFI**	**Δ CFI**
Men	78.68	43	<.001	.06	.04 - .08	-	.29	.93	-
Women	105.35	43	<.001	.07	.05 - .09	-	.03	.88	-
Configural	X^2	*df*	**p-value**	**RMSEA**	**90% CI**	**Δ RMSEA**	**p-value[1]**	**CFI**	**Δ CFI**
	184.03	86	<.001	.06	.05 - .08	-	.05	.91	-
Metric	X^2	*df*	**p-value**	**RMSEA**	**90% CI**	**Δ RMSEA**	**p-value[1]**	**CFI**	**Δ CFI**
	195.58	95	<.001	.06	.05 - .07	.002	.07	.90	.003
Scalar	X^2	*df*	**p-value**	**RMSEA**	**90% CI**	**Δ RMSEA**	**p-value[1]**	**CFI**	**Δ CFI**
	206.97	104	<.001	.06	.05 - .07	.002	.11	.90	.002
Strict	X^2	*df*	**p-value**	**RMSEA**	**90% CI**	**Δ RMSEA**	**p-value[1]**	**CFI**	**Δ CFI**
	215.12	115	<.001	.06	.04 - .07	.004	.22	.91	.003

Note. RMSEA < .05 = good fit; RMSEA < .08 = acceptable fit; CFI > .9 = acceptable fit; ΔCFI < .010 = non-significant worsening of fit; ΔRMSEA < .015 = non-significant worsening of fit; [1] p-value assessing close fit (RMSEA <.05)

Measurement invariance

Measurement invariance to gender. First, the fit of the 11-item 2-factor structure was assessed for both subgroups (men and women). Confirmatory factor analysis (CFA) showed that this structure fit similarly well in both groups, with the chi-square test being significant in both groups, but other fit indices indicating acceptable to good fit (Table 5). Second, configural invariance was assessed using group CFA in which the number of factors and their pattern was kept equal across groups (Table 5). Although the chi-square test was significant, other indices of model fit indicated acceptable to good fit and all factor loadings were significant. Third, metric invariance was assessed using group CFA in which the factor loadings were also kept equal across groups (Table 5). Results showed that the fit did not worsen significantly (ΔCFI < .010 & ΔRMSEA < .015), indicative of acceptable metric invariance. Similar results were found for scalar invariance, in which intercepts were also kept equal across groups, and strict factorial invariance, in which residual variances were also kept equal across groups (Table 5).

Gender differences in social attunement. Including all individuals who identified as either a man (N = 266) or woman (N = 308), results showed no significant difference between men (Cognitions subscale: M = 18.05, SD = 4.98; Full scale: M = 41.89, SD = 8.08)

and women (Cognitions subscale: M = 17.72, SD = 5.03; Full scale: M = 40.85, SD = 7.89) on the Cognitions subscale (t(572) = .78, p = .44, d = .065) and the full scale (t(572) = 1.56, p = .12, d = .078). However, there was a small but significant difference between men and women on the behavior subscale (t(572) = 2.44, p =.02), with men (M = 28.15, SD = 5.45) scoring higher than women (M = 27.06, SD = 5.24, d = .122).

Table 6 Correlational Analysis to Assess Convergent and Divergent Validity

Scale			*Subscale 1 - Cognitions*			*Subscale 2 - Behaviour*			*Full SAQ*			*Internal consistency*	
Need for cognition	***Exp***	***df***	***r***	***p***	***Results***	***r_s***	***P***	***Results***	***r***	***p***	***Results***	***ω***	***α***
Need for cognition	ns	193	-.27	<.001	-	-.06	.40	ns	-.20	<.01	-	.86	.86
Social reward	***Exp***	***df***	***r_s***	***p***	***Results***	***r_s***	***P***	***Results***	***r_s***	***p***	***Results***	***ω***	***α***
Admiration	+	193	.06	.38	ns	.32	<.001	+	.24	<.001	+	.79	.73
Non-social potency	ns	193	-.03	.65	ns	.14	.05	ns	.08	.26	ns	.67	.63
Passivity	ns	193	.29	<.001	+	.26	<.001	+	.34	<.001	+	.83	.83
Pro-social interaction	+	193	-.08	.28	ns	-.01	.94	ns	-.06	.43	ns	.69	.68
Social	+	193	.05	.47	ns	.22	<.01	+	.18	.01	+	.40	.29
Conformity	***Exp***	***df***	***r_s***	***p***	***Results***	***r_s***	***P***	***Results***	***r_s***	***p***	***Results***	***ω***	***α***
Conformity	+	201	.16	.02	+	.31	<.001	+	.30	<.001	+	.43	.41

Note: df: degrees of freedom; exp: expectations; na; not applicable; ns: not significant; p: p-value; r: pearson correlation coefficient; r_s : spearman correlation coefficient; ω: McDonald's Omega; α: Cronbach's Alpha; +: positive association; -: negative association

Convergent and divergent validity

In line with expectations, we found either no association or a negative association between social attunement scores and the need for cognition (Table 6). Also, there was no association between the social attunement scores and non-social potency. However, conformity was associated positively with the social attunement scales. The pattern of the association between social attunement and the other social reward scales did not fully match our expectations. For the admiration and social scales, the Cognitions subscale did not match our expectations, but the Behavior subscale and the full scale did. Against expectations, SAQ scores were associated positively with the passivity scale (no association was expected) and SAQ scores were not associated with the pro-social interaction scale (positive association expected).

Age, social attunement, and alcohol consumption

Correlation analyses were performed to assess how PPD, age, SAQ, and AUDIT were associated with each other. Results show that age was associated negatively with AUDIT (r_s = -.10, p = .02; Internal consistency: ω = .83, α = .79) and SAQ (r_s = -.21, p < .001; Internal consistency: ω = .74, α = .74): older individuals showed less alcohol use and related problems as well as less social attunement. Furthermore, AUDIT related positively with PPD (r_s = .57, p < .001; Internal consistency: ω = .83, α = .66), showing

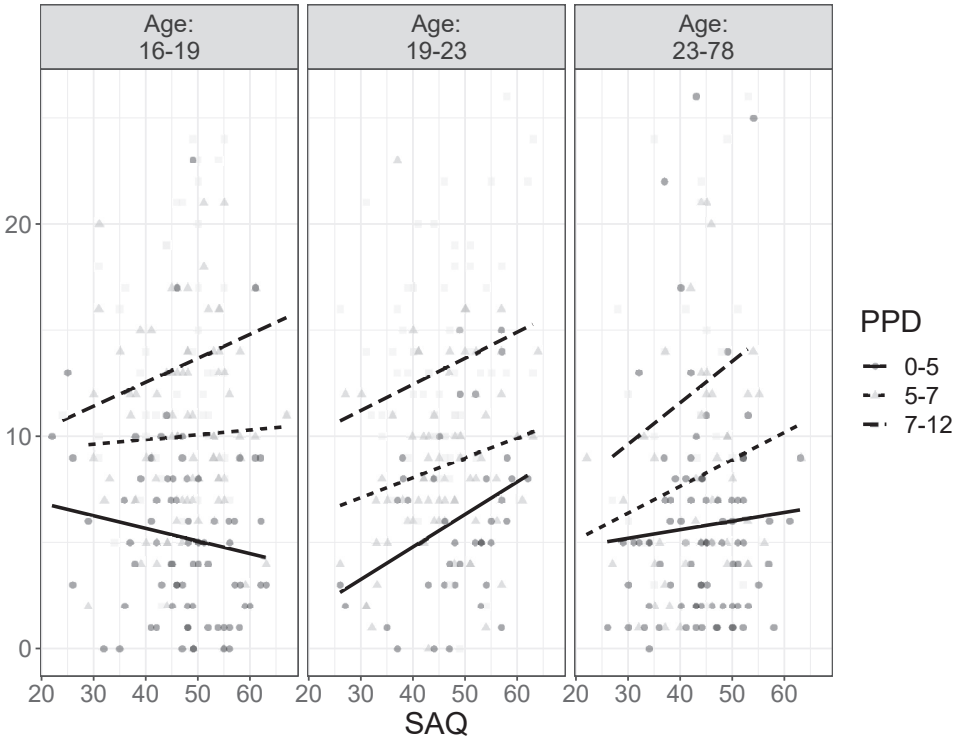


Figure 2. The relationship between age, social attunement score (SAQ) and perceived peer drinking (PPD) in their Association with Alcohol Use (AUDIT). The association between SAQ and AUDIT, displayed in three panels that represent age groups (tertiary split for visualisation purposes) with three lines representing differing levels of perceived peer drinking (tertiary split for visualisation purposes). Results suggest that the association between AUDIT and SAQ depends on the interaction between age and PPD. There is amore distinct effect of PPD on the association between SAQ and AUDIT in the relatively younger mid-late adolescent age group (panel 1). Also, it becomes clear that AUDIT score is associated with perceived peer dinking in all age groups (all panels, different lines in same order).

an association between perceived peer drinking and own drinking behavior. Regression analyses were performed to assess how age, PPD and SAQ were associated and interacted in their association with AUDIT. Results showed that both SAQ score (B = .09, p = .02) and the interaction between age and PPD (B = -.34, p = .002) were predictive of AUDIT scores ($F(4, 537) = 60.35$, $p < .001$; $R^2 = .31$; $N = 541$). Using tertiary splits for the age and PPD variables to visualize these interactions, Figure 2 shows that the association between SAQ and AUDIT is dependent on PPD and age: higher SAQ appears related to lower AUDIT only in relatively younger (Age: 16-19) individuals who reported relatively lower levels of peer drinking (PPD: 0-5). Furthermore, we found positive associations between SAQ score and all four motives for alcohol consumption

measured with the DMQ: social (r_s = .24, p < .001; Internal consistency: ω = .88, α = .86), conformity (r_s = .36, p <.001; Internal consistency: ω = .81, α = .80), coping (r_s = .26, p < .001; Internal consistency: ω = .80, α = .79), and enhancement (rs = .13, p = .002; Internal consistency: ω = .84, α = .82). Exploratory additional regression models were run to assess whether social and conformity drinking motives (separately) would explain additional variance in the regression model presented above. Results showed that, when adding conformity motives to the model (F(5, 525) = 45.11, p < .001; R^2 = .30; N = 525), the interaction between PPD and age remained a significant predictor of AUDIT (B = -.32, p = .004), but that this was not the case for SAQ (B = .07, p = .07) and conformity (B = .05, p = .21). When adding social motives to the model (F(5, 525) = 58.57, p < .001; R^2 = .35; N = 525), the interaction between PPD and age also remained a significant predictor of AUDIT (B = -.25, p = .02), although this was not the case for SAQ (B = .03, p = .37). However, social motives were a significant predictor of AUDIT (B = .28, p < .001) in this model.

Discussion

The social attunement questionnaire (SAQ) was developed to be able to assess social attunement, the extent to which one adapts to and harmonizes behavior with the social environment (Cousijn, Luijten et al., 2018) in different social situations. The resulting 11-item SAQ contained two subscales capturing the *Cognitions* (subscale 1) and Behavior (subscale 2) related to social attunement, showing good psychometric properties that were consistent over genders. Furthermore, results largely confirmed our expectations on how SAQ scores, together with perceived peer drinking and age could predict alcohol use in a sample of mid to late adolescents and adults. The pattern of results from the analyses assessing convergent and divergent validity generally confirmed a good fit between the 11-item SAQ and our conceptual framework of social attunement but also provided novel insights to be tested in future studies. Below we will first discuss the structure and psychometric properties of the SAQ, followed by an in-depth discussion of theoretical and practical research implications.

The five items included in the *Cognitions* subscale assess the extent to which individuals think about their own behavior and about how others perceive that behavior. The six items included in the Behavior subscale assess the actual behavior someone performs in response to their environment to adapt to and harmonize with this environment. The 15 deleted items primarily included examples of cognitions and behaviors that also are reflected in the remaining items, suggesting that these items did not generalize well enough over individuals to be included in the SAQ. The structure that resulted from our exploratory factor analysis (EFA) was confirmed using confirmatory factor analysis (CFA) in another sample, that varied from the first

sample on all included variables (Table 1). Although additional replication of these CFA results in a sample that matches the EFA sample would be highly recommended, the factor structure confirmation in a sample that is dissimilar increases the likelihood of generalizability of the measure in a variety of Dutch samples. Notably, the EFA showed a significant chi-square test, which indicates poor fit (Sun, 2005). However, it is well-known that chi-square tests of fit can be overly sensitive when the sample size is relatively large (e.g., Bollen, 1989; Miles & Shevlin, 2007; Tucker & Lewis, 1973), and other fit indices indicated acceptable to good fit (Sun, 2005). In addition, the assessment of different measures of measurement invariance confirmed invariance to gender in this sample. In both samples separately, the internal consistency of the SAQ was moderate-acceptable, and in the samples combined, internal consistency was acceptable-good (Lance et al., 2006; Tavakol & Dennick, 2011). Although internal consistency was lower than anticipated, it is in line with the nature of the SAQ, which assesses complex human behavior and the limited number of items per subscale (5-6 items each), lowering internal consistency levels which one may expect to be in the .65-.80 range in case of Cronbach's alpha (Vaske et al., 2017). This latter point is supported by the fact that the full scale (11 items) showed higher internal consistency. Furthermore, the factor analytic evidence of unidirectionality of the items provide additional confidence in the psychometric properties of the SAQ. However, future studies using the SAQ should evaluate the internal consistency of the subscales carefully to confirm these results.

In line with our conceptional framework of social attunement, the *Cognitions* but not the *Behavior* subscale correlated negatively with the need for cognition scale, suggesting a cognitive component that differentiates between more subjective social cognition (e.g., "I try to prevent people from thinking that I am different.") and the more objective cognitive processes as assessed with the need for cognition questionnaire (e.g., "I really enjoy a task that involves coming up with new solutions to problems"; Cacioppo & Petty, 1982; Verplanken et al., 1992). Furthermore, the *Behavior* but not the *Cognitions* subscale correlated positively with the social and admiration scale of the social reward questionnaire. The behavior assessed by the social and admiration scales of the social reward questionnaire might indeed be similar to some of the behaviors assessed by the 'Behavior' scale of the SAQ (e.g., "I try to align myself as good as possible to the group I'm with."). However, the cognitive process behind these behaviors might be very dissimilar, explaining the differences in associations and highlighting the importance of the *Cognitions* scale to capture the full social attunement process. As expected, conformity (peer pressure/obedience) and social attunement (positive reinforcement) correlated positively, but substantial SAQ variance cannot be explained by conformity (highest r = .31 for the *Behavior* subscale).

In contrast to our expectations, the SAQ correlated positively with passivity ("giving others control and allowing them to make decisions"; Foulkes et al., 2014) but not with pro-social interaction ("having kind, reciprocal relations"; Foulkes et al., 2014) of the social reward questionnaire. However, speculatively, more passive individuals may score higher on social attunement because they more often adapt to others rather than deciding for themselves. The lack of association between the SAQ and pro-social interaction subscale of the social reward questionnaire, was also unexpected. This latter subscale focuses on the nature and type of relationships. Although we expected that individuals with relatively more "kind, reciprocal relationships" would score higher on social attunement, our results suggest that the nature/type of relationships does not affect social attunement directly to the individuals within this relationship.

We assessed how the SAQ related to drinking motives. Unexpectedly, the SAQ correlated positively with all drinking motives, a result that could not be explained by general higher alcohol consumption in individuals with higher social attunement scores. Importantly, although social and conformity drinking motives are intuitively more 'social' than enhancement and coping motives, the drinking motives questionnaire does not distinguish between the (social) settings in which drinking occurs (Cooper, 1994). Social factors could play a role in all drinking motives. For example, some may specifically drink to enhance positive affect in social settings (e.g., party) or to cope with negative affect during social situations, whereas others would drink to enhance positive affect or cope with negative affect in non-social settings (e.g., drinking alone). The positive association between the SAQ and all drinking motives, supported by the general notion that trajectories of alcohol use are more problematic in non-social versus social drinkers (e.g., Crutzen et al., 2013; Kuntsche et al., 2006; Mann et al., 1987), suggest that it could also be useful to develop a drinking motives questionnaire that distinguishes between drinking in social and non-social settings. We hypothesize that specifically non-social coping and enhancement will be associated negatively with social attunement and be a risk factor for long term problems, whereas social coping and enhancement would be associated positively with social attunement and could be indicative of a higher chance of maturing out.

In line with the general theories of social development (Steinberg, 2005), social attunement was highest in the mid to late adolescent age range and significantly decreased with age. Also, those with higher perceived peer drinking consumed more alcohol themselves, whereas no direct association between social attunement and alcohol use was found. However, further analysis revealed that perceived peer drinking and age interacted and, together with social attunement, were predictive of alcohol use. These results indicate that higher social attunement is associated with higher alcohol use in those individuals who perceive high peer drinking, but that the effect

of peer drinking decreases with increasing age. This result is in line with the idea that peers could be particularly influential during adolescence (e.g., Gardner & Steinberg, 2005) and thereby affect alcohol use initiation and escalation during mid to late adolescence specifically. However, it is important to note that the age distribution was skewed towards younger participants (i.e., very limited number of participants over 40 years old), and longitudinal data is needed to investigate the development of social attunement with age, and its effect, as well as the effect of perceived peer drinking, on alcohol use across multiple age groups.

As there were positive associations between SAQ and both social drinking motives (social and conformity), we assessed whether the predictive effects of SAQ, peer drinking and age on alcohol use remained similar when including these drinking motives as predictors. Results showed that social drinking motives explained variance in alcohol use while accounting for the interaction between age and perceived peer drinking, whereas social attunement was not a significant predictor in this model. Adding conformity drinking motives to the model resulted in the interaction between age and perceived peer drinking to be the only significant predictor of alcohol use. However, it should be noted that the relatively high correlation of SAQ scores with both motives warrant careful interpretation. So, although social drinking motives also appear to explain additional variance in the association of age and perceived peer drinking with alcohol use, the strength of the SAQ is that it has the potential to be used to assess social attunement in both alcohol-use-related as well as more general settings, whereas this is not the case for the measures of drinking motives. Future studies are needed to assess the utility of the SAQ beyond alcohol use. For example, the SAQ might be a useful tool to assess one's general tendency to attune to adaptive (e.g., prosocial behavior) and maladaptive peer behaviors (e.g., delinquency, unsafe sex, or unsafe driving) across different life stages and social settings (e.g., school, work, family).

Aside from studying applicability of the SAQ across developmental trajectories and a range of social settings, several additional steps should be taken to assess the validity of the SAQ. The current study only collected limited demographic data from participants and future studies should collect a wider range of variables to assess measurement invariance to for example SES, ethnicity, and more detailed measures of educational level. An English translation of the SAQ is available which will – once validated - enable us and others to assess how fundamental differences between countries and cultures might affect both social attunement and its association with perceived peer drinking and alcohol use in different age groups. In line with this, future studies are encouraged to assess how social attunement is associated with descriptive and injunctive norms (Krieger et al., 2016) and how an individual's inter and intra group assertiveness (Korem et al., 2012) and autonomy (Helwig, 2006) affects social

attunement over one's development, depending on the cultural background. Moreover, assessments of test-retest reliability are needed to assess within person stability of social attunement through development.

In conclusion, the two subscales of the SAQ appear to capture both the *Cognitions* and *Behavior* components of social attunement, showing good measurement invariance to gender. Our newly developed instrument appears to be suitable to gain important insights into the role of social attunement in development and substance use, however, more studies are needed to test the SAQ's utility in broader samples and situations.

Chapter 13

General discussion

Over the past decades, cannabis research has evolved from a small field, with little attention to the potentially addictive effects of cannabis, towards a growing field employing a variety of methods to investigate and explore the complexity of cannabis use, from initiation to dependence. This thesis contributes to the field of cannabis research by generating knowledge on underexplored topics, but also by uncovering important research gaps that will need to be addressed in the coming years. First, an integrated overview of the results will be presented (Figure 1). Second, the highlights and challenges that arose from the described studies will be discussed, integrating these into our initial neurocognitive model of cannabis use and CUD. Third, I will provide a checklist with important considerations for cannabis research moving forward.

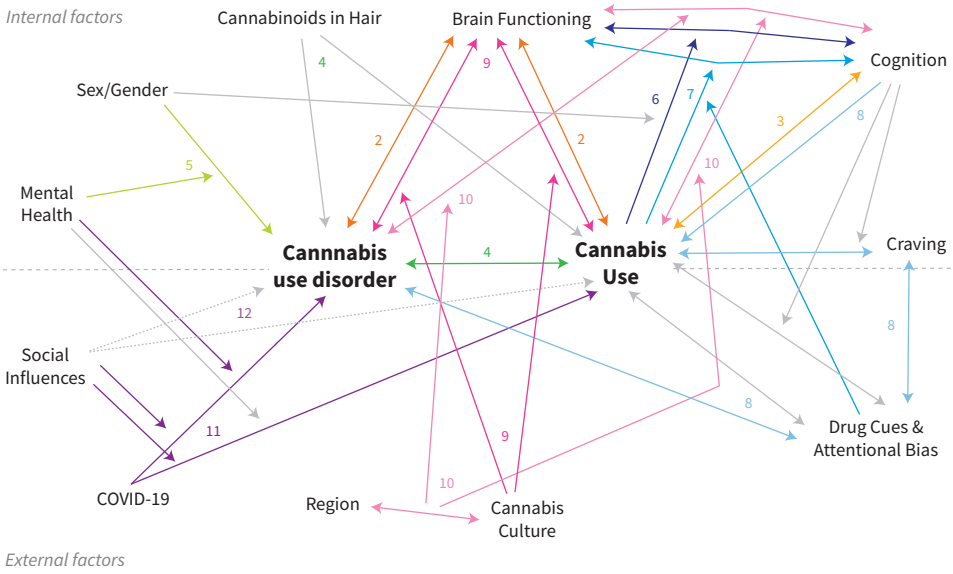


Figure 1. Overview of the results. An updated overview of the most important direct associations and interactions between internal and external factors involved in cannabis use and cannabis use disorder as assessed in this thesis. Each chapter is colored and numbered, with colored lines representing the confirmed associations or interactions as presented in chapter 1 (Figure 1) and grey lines representing originally proposed associations that were not confirmed.

As described in **chapter 2**, most individuals with CUD do not receive treatment and remission rates are low for those who enter treatment (24-35% still abstinent after 6 months; Denis et al., 2006; Hoch et al., 2014), with cognitive deficits and comorbid mental health problems likely to negatively affect treatment outcomes (EMCDDA, 2015). Furthermore, **chapter 2 and chapter 3** concluded that there is

substantial evidence that cannabis use can affect brain structure and brain function as well as the associated cognitive processes but that results are far from conclusive. Most importantly, it appears that individual differences – like heaviness of use, CUD severity, sex/gender, and comorbid psychopathology – might play a large role in the effects of heavy cannabis use, the development of CUD, and the effectiveness of treatment outcomes. Hence, it is crucial to look beyond dichotomous labels of heavy use or CUD and incorporate internal and external factors that could affect cannabis use trajectories to work towards a more complete neurocognitive model of cannabis use and CUD. **Chapters 4-12** described the search for and exploration of the complex interactions that 1) could explain part of the current inconsistency in the literature, 2) increase our understanding of the fundamental processes underlying heavy use and CUD, and 3) could, in turn, help improve prevention and treatment efforts.

Measuring cannabis use and CUD

The measurement of cannabis use is often reliant on retrospective self-report measures that might not always provide reliable estimates of use (Harrison, 1995). Furthermore, measures vary across and within different clinical and research settings, hampering the integration of results. Recently, Lorenzetti et al. proposed the three-layer International Cannabis Toolkit (iCannToolkit) as a multidisciplinary consensus for the measurement of cannabis use (Lorenzetti et al., 2022). The base layer includes three universal questions assessing the presence of lifetime use, last use, and days of use within the last month, the mid-layer includes more detailed self-report measurements (e.g., timeline follow back (TLFB), Robinson et al., 2014), while the top layer includes biological measures of use (i.e., cannabinoid quantification in urine or blood/plasma). The feasibility of including the mid- and top-layer measurements is largely dependent on the available research time and financial resources. Hence, there are limited studies that compare self-report with biological measures of use. Furthermore, the ICannToolkit and other efforts to align measurement largely focus on the quantification of cannabis use, omitting the potential associations with use-related problems that might be crucial to predict clinical outcomes. **Chapter 4** described our efforts to quantify cannabinoid exposure using hair analyses and to assess associations between hair-derived cannabinoid concentrations and a variety of self-report measures of use and use-related problems (e.g., CUD symptoms) in the same sample of near-daily cannabis users with CUD. The results showed a large overlap between the presence (yes/no) of THC in urine and hair. However, hair-derived cannabinoid (THC, CBD and CBN) concentrations were not associated with self-reported cannabis use or use-related problems, highlighting the importance of research into more reliable cannabinoid quantification methods.

In **chapter 4, 6, 7, 8, 9, 10 and 11** I used a variety of measures to assess cannabis use and related problems, primarily including self-reported grams per week, and frequently used measures of cannabis use-related problems such as the cannabis use disorder identification test (CUDIT-R, Adamson et al., 2010), Marijuana Problem Scale (MPS; Stephens et al., 2000), and DSM-5 CUD symptoms (American Psychiatric Association, 2013a; MINI CUD, Sheehan et al., 1997). While **chapter 4** showed moderate to extremely strong evidence for positive correlations between these measures, the way they interact with different internal and external factors associated with cannabis use and CUD differed across studies. This suggests that different measures may explain different aspects of the etiology of cannabis use and CUD. For example, WM-related brain activity only related to cannabis use-related problems (CUD and MPS) in dependent users (**chapter 10**), but not in a more heterogenous sample of regular-to-dependent users (**chapters 6 and 7**). Furthermore, associations between measures of brain functioning and cannabis use and related problems varied with site (**chapter 10**; WM-related brain activity) and cultural attitudes (chapter 9; resting state functional connectivity). Moreover, in **chapter 8**, poorer interference control was only associated with heaviness of use (gram/week) but not use related problems – indicating potential sub-acute effects of use. In **chapter 11**, the COVID-19 lockdown was associated with an increase in cannabis use (gram/week) but not CUD scores and different factors (e.g., anxiety and sleep problems and changes in use motives) were associated with changes in cannabis use (gram/week) and CUD during the lockdown.

In our quest to understand CUD pathology, it is important to include different measures of use and problems, but also to study how different problems may interact. As treatment efforts are largely unsuccessful (only 24-35% still abstinent after 6 months; Denis et al., 2006; Hoch et al., 2014), a shift towards a 'symptom network approach' – treating symptoms as entities that interact in causal ways rather than all originating from a common cause (Borsboom, 2017) - might provide insights into common patterns and individual differences that could impact treatment success. In **chapter 5** I applied a network approach, showing that the DSM-5 CUD symptoms are highly connected, with only risky use and tolerance being relatively less connected to the other symptoms in the network. Currently, the clinical utility of psychopathology networks like ours remains unclear as replicability is debated (e.g., Borsboom et al., 2017; Forbes et al., 2017). Most studies are constrained by their use of convenience samples (Contreras et al., 2019) and it is unclear to what extent network density might either increase (i.e., targeting one symptom might affect all other symptoms) or decrease (i.e. needing to target a large group of symptoms to reduce the chance of their direct associations affecting effectiveness) potential treatment success (e.g., using idiographic network models, Mansueto et al., 2022). Looking at gender

differences, I showed that while men endorse about half of the CUD symptoms more often than women do, the associations between symptoms appear similar. However, a comorbid anxiety and/or mood disorder diagnosis was differentially associated with CUD symptoms in men compared to women. In men, mood disorders were strongly associated with anxiety disorders, but only the presence of an anxiety disorder was associated with the CUD symptoms network through *unsuccessful attempts to reduce or quit use*, which could indicate an important role of anxiety in efforts to reduce and quit in men. In women, anxiety disorders were strongly associated with mood disorders, but only the presence of a mood disorder was associated with the CUD symptoms network through *craving* and *withdrawal*, potentially indicative of self-medication mechanisms in women. These results indicate that while men and women might present with similar CUD symptoms, comorbid mental health problems might interact with CUD symptoms differently depending on sex/gender.

The role of cognition and related brain activity in cannabis use and CUD

Cognitive functioning is thought to play an important role in the ability to control the motivational urges to use cannabis in heavy users and individuals with CUD (e.g., Bickel et al., 2018). However, as described in **chapters 2 and 3**, the reported associations between cognitive performance and cannabis use are inconsistent and differences in brain activity between users and controls are regularly observed in the absence of performance differences (e.g., Hatchard et al., 2020). One of the domains with particularly inconsistent results is working memory (WM). Nonetheless, the N-back WM task is a task that consistently activates the executive control network – including frontal and parietal regions - known to be crucial for cognitive control (e.g., Owen et al., 2005). In **chapters 6, 7 and 10** I used similar letter N-back tasks to assess performance and brain activity differences in large samples of heavy and dependent cannabis users as well as controls. While no performance differences were observed in **chapter 7** (total N = 69; heavy and dependent users N = 36), controls outperformed cannabis users on the trials with the highest memory load (2-back) in **chapter 6** (total N = 189; heavy and dependent users N = 104) and **chapter 10** (total N = 184; dependent users N = 100). As sample sizes in these papers are substantially larger than most fMRI studies using similar tasks (e.g., Cousijn, Wiers et al., 2014; Hatchard et al., 2020; Smith et al., 2010) and effect sizes of the simple group comparisons on 2-back performance are relatively low (small to medium effect size in **chapter 6** (cohen's d = 0.30) and **chapter 10** (cohen's d = .35)), these results suggest that most studies to date are underpowered to detect group differences on this task. This immediately relates to one of the weak points of the N-back task: while performance is relatively high

on the 2-back trials (close to 90% correct in **chapters 6 and 10**), reducing variability in the outcome, adding a 3-back condition to the task tends to result in individuals performing close to chance (e.g., Jaeggi et al., 2010), limiting the ability to distinguish low task performance from low task motivation.

Associations between cognition and motivation

In **chapter 7** I adopted another approach to increase cognitive demand during the N-back task by assessing how the presence of cannabis-related (controlled for neutral) task-irrelevant flankers might affect performance and brain activity in heavy users. Unexpectedly, task performance was not affected by adding the cannabis flankers, with accuracy as reported in **chapter 7** (cannabis flanker trials mean accuracy = 88.57%) being similar to accuracy in **chapter 6** (no-flanker trials mean accuracy = 88.42%). However, fMRI results showed that when the task got more cognitively demanding, cannabis users showed cannabis flanker specific reductions in activity in areas associated with salience and motivational behavior (insula and thalamus; James et al., 2021; Menon & Uddin, 2010) as well as cognition (SPL and SMG; Stoeckel et al., 2009; Wolpert et al., 1998). Although replication is crucial, these results indicate that substance specific cues might interfere with control related brain processes, specifically when cognitive demand increases.

Taking a behavioral approach to assess the effects of the same cannabis cues as used in the N-back flanker task, **chapter 8** assessed attentional bias (AB) to cannabis cues in a large group of cannabis users with variable cannabis use frequency and dependence status. Only those individuals in treatment for CUD showed an AB (larger than zero) to cannabis cues. Furthermore, group differences in AB were only observed when comparing those in treatment for CUD with the other end of the use spectrum (never-sporadic users). This indicates that large group contrasts in use and large samples (due to small-medium effect sizes, i.e. one-sample t-test for presence of AB in CUD group: Cohen's d = .25, independent sample t-test between CUD and never-sporadic users: Cohen's d = .43) might be crucial to observe AB and group differences and might therefore also have affected the behavioral effects of the flankers on N-back performance in **chapter 7**.

Chapter 8 also revealed that craving (average over the session) mediated the association between AB and cannabis use measures. Although causality cannot be inferred from this study, these results might indicate that an increase in AB might increase craving through higher cue exposure, rather than the presence of craving increasing AB towards cannabis cues. As several theories of addiction (e.g., Bickel et al., 2018) highlight the importance of interactions between motivational processes - such as craving and AB - and cognitive control as important factors in escalation of use and

CUD, I also assessed the role of interference control (IC) in the association between motivational measures and use. Unexpectedly, IC did not moderate the association between motivational measures and use. However, IC was directly associated with grams per week of cannabis use but not cannabis use related problems: those that used more cannabis showed lower IC performance. As this association was not observed in the abstinent individuals in treatment for CUD, these results highlight the importance of considering the potential sub-acute effects of cannabis use on performance on cognitive tasks.

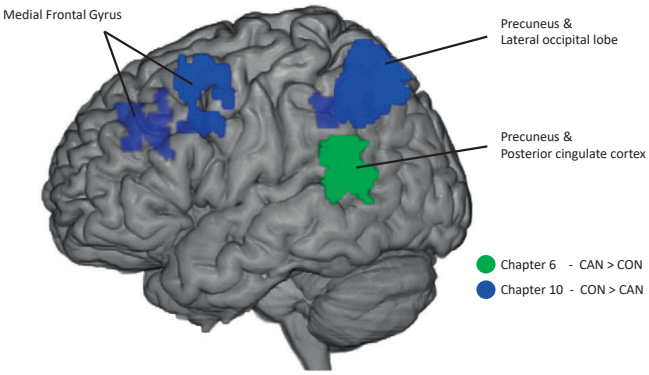


Figure 2. Comparison of results from chapter 6 and chapter 10. Direct comparison of the results from chapter 6 (green) and chapter 10 (blue) show that conflicting results from the precuneus arise from distinct clusters. Results from chapter 6 (green) result from more ventral portions of the precuneus and include the posterior cingulate cortex. Results from chapter 10 (blue) arise from more dorsal portions of the precuneus and include the lateral occipital lobe (and medial frontal gyrus regions).

WM-related brain activity in cannabis users

In general, when looking at the N-back MRI results, our results do not align with the notion that heavy cannabis users might compensate their performance deficits by over-recruiting executive control regions during the task, as proposed by several earlier studies that showed brain activity differences without observing any behavioral differences (e.g., Hatchard et al., 2020). Focusing on results from the regular N-back tasks (without flankers) used in **chapters 6 and 10**, the results may initially seem to contradict each other. As can be seen in Figure 2, these results arise from distinct brain clusters that include portions of the ventral (**chapter 6**) and dorsal (**chapter 10**) precuneus. While the precuneus is regularly discussed as a single entity - being an important node in the default mode network – the dorsal regions extending into the superior parietal lobe have been primarily associated with cognition and shifting from

default mode to cognitive processes (Cavanna & Trimble, 2006), while the ventral regions are functionally connected to the posterior cingulate cortex (Zhang & Li, 2012) and thought to be involved in interoceptive default mode processes (Vatansever et al., 2017). In summary, this would indicate that there was a relatively smaller increase in activity in cognition related regions in one study (**chapter 10**) and a relatively smaller reduction in activity in default mode related regions in the other study (**chapter 6**) in cannabis users compared to controls when task complexity increased.

Resting state functional connectivity

Using a resting state approach, **chapter 9** explored resting state functional connectivity (RSFC) in the executive control and default mode network as well as the salience network that is known to be associated with attribution of salience to drug related cues and associated compulsive behavior (Zilverstand et al., 2018). Looking at within and between network RSFC, I observed higher RSFC of a small parietal cluster (lateral occipital lobe, precuneus, and superior parietal lobe) with the rest of the dorsal salience network in controls compared to cannabis users. While this cannot be directly tested with this design, this increased RSFC (**chapter 9**) in dorsal salience network regions might enable controls to have relatively higher responsiveness of these regions during cognitive tasks (**chapter 10**).

External factors affecting cannabis use and CUD

The role of cultural attitudes

Cultural neuroscience is a growing field that explores how culture affects brain processes and associated daily life behaviors (e.g., Chiao et al., 2013; Kim & Sasaki, 2014). Substance use is one field in which cultural differences and norms clearly affect use (Resnicow et al., 2000; Trucco, 2020); but how these behavioral differences relate to the brain processes underlying substance use has largely been unexplored. This is particularly relevant for cannabis, as cultural cannabis attitudes – including perceived benefits and harms of use – appear to be changing with the ongoing changes in cannabis legislation (UNODC, 2021).

In **chapter 10**, I assessed perceived harms and perceived benefits of cannabis use in cannabis users with CUD and controls from Texas, USA and The Netherlands. In terms of jurisdiction, these two sites are on the opposite ends of the legalization spectrum, with recreational cannabis use still being illegal in Texas while cannabis use has been decriminalized in The Netherlands since 1976. While cannabis users, in general, appeared more positive and less negative towards cannabis use than controls, the results showed that attitudes do not necessarily align with legislation: Texan cannabis users reported more perceived benefits and lower perceived harms than

Dutch cannabis users and reported a similar pattern regarding the perceived attitudes of their close friends and family. Furthermore, perceived attitudes of the country/state were similar between Dutch and Texan participants. This misalignment of site differences in legislation and individual differences in cultural attitudes pleads for using an individual differences approach rather than focusing on group differences.

Results from **chapter 6 and 10** also showed that site differences and individual differences in cultural attitudes are differentially associated with brain activity and RSFC. **Chapter 10** showed interactions between cannabis attitudes and site with grams of use per week in the association with WM related brain activity. However, not all interactions with site could be explained by differences in cannabis attitudes and vice versa, highlighting the importance of distinguishing between site effects and the individuals' attitudes towards cannabis. In addition to **chapter 10**, results of **chapter 6** showed interactions of cannabis attitudes with measures of use as well as CUD and related problems in the association with RSFC. Most associations were observed in the frontal and parietal regions that are part of the default mode network. Furthermore, interactions with CUD appeared primarily with country/state attitudes, while interactions with grams per week appeared primarily with personal attitudes, indicating potential differences between levels of cannabis attitude assessments. While these results indicate widespread associations between cannabis culture and brain functioning, causality of these associations is unclear and replication is crucial to assess reliability of the measures, also across different regions. However, it must be noted that while incorporating individual differences in cannabis attitudes into the broader neurocognitive model of cannabis use and CUD can provide insights into the associations between attitudes and use patterns, looking at the interactions between cannabis attitudes and brain functioning substantially increases the complexity of the results, limiting the potential clinical utility at this stage.

Social factors

Aside from cultural factors, social and interpersonal factors are known to be important external factors contributing to substance use (e.g., Eisenberg et al., 2014; Newcomb & Harlow, 1986). One of the biggest life changing events of this generation has been the COVID-19 pandemic and the associated lockdowns that had tremendous impact on social interaction and interpersonal relationships. In **chapter 11**, I investigated the effects of the first COVID-19 lockdown on cannabis use and CUD symptoms, but also assessed changes in use motives, social contact, loneliness, mental wellbeing, and COVID specific worries that might affect cannabis use and CUD symptomology. The lockdown was associated with an increase in cannabis use in monthly-daily cannabis users but not in CUD severity. However, during the lockdown,

time was negatively associated with CUD scores, indicating a decrease, stabilization, or blunted increase in CUD scores in those that participated further into the lockdown. Although not assessed by COVID-19 related studies on cannabis use (Bonnet et al., 2023), it could be that the COVID-19 lockdown related social isolation reduced the presence of social symptoms (i.e., problems with social responsibilities might be less likely reported during the lockdown), causing a reduction of reported CUD symptoms in the long run. During the lockdown (pre-lockdown to during lockdown change), social motives for use became less common, and loneliness increased, while general mental health symptoms were stable in these early weeks of the lockdown.

Although under unique circumstances, these results highlight the importance of social and interpersonal factors in cannabis use. However, like cultural factors, social factors can be difficult to measure, and existing measures used in substance use research tend to focus on the effects of explicit peer norms or peer pressure. **Chapter 12** described the development of a new social attunement questionnaire (SAQ), assessing an individual's tendency to adapt to and harmonize with the social environment in the absence of explicit norms or peer pressure. The final 11-item questionnaire includes a cognitive (the extent to which you think about your own behavior and how others perceive this) and behavioral (the extent to which you adjust your behavior to attune with your environment) subscale. Data from this validation study was also used to pilot how SAQ scores related to age, peer drinking and alcohol use behaviors – one of the substances most commonly consumed in social settings and known to be affected by peer consumption (e.g., Voogt et al., 2013) - in a sample of adolescents and adults. Results showed that younger individuals scored higher on the SAQ, in line with the particularly large influence of peers during adolescence (e.g., Ciranka & van den Bos, 2019). Furthermore, SAQ scores and the interaction between perceived peer drinking and age were predictive of alcohol use and related problems: particularly in adolescents, social attunement in the direction of perceived peer drinking was associated with one's own alcohol use. The SAQ has been developed to be able to assess social attunement to a variety of behaviors, including other substance use, but has so far only been tested in relation to alcohol use. In line with the effect of changes in cannabis use motives and CUD symptoms during the lockdown, social attunement might also play a role in cannabis use depending on peer behaviors. As research into the effects of peers on cannabis use largely focused on explicit norms and patterns of peer cannabis use in adolescents and young adults (e.g., Agrawal, Lynskey, Bucholz, Madden et al., 2007; Leadbeater et al., 2022), studies should explore the potential role of social attunement in trajectories of cannabis use over the lifespan.

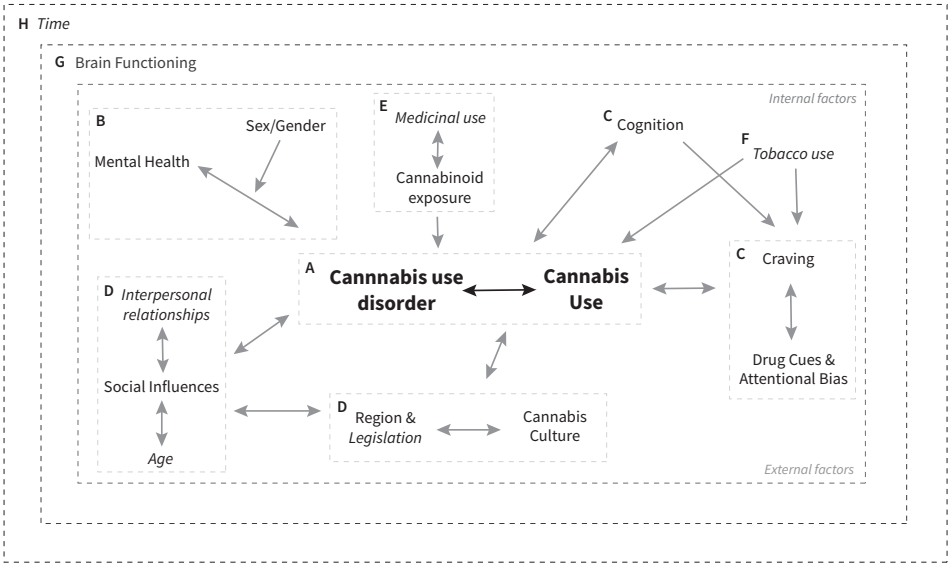


Figure 3. Initial neurocognitive model of cannabis use and CUD. Letters indicate different highlight themes and challenges for future research as discussed in this chapter. Grey lines represent the - often potentially bidirectional - associations that are crucial for future research to explore. The italic items represent novel factors that - although not directly assessed in my studies - appear to be important additions to this model. Additional layers have been added to indicate the overarching importance of brain functioning in the etiology of cannabis use and CUD and the importance of assessing those processes over time to assess developmental processes and causality.

Highlights, challenges & future directions

The multimethod studies I conducted in different samples of cannabis users can contribute to the development of a more comprehensive neurocognitive model of cannabis use and CUD. I consider this thesis an important step in the right direction, but a large and complex puzzle remains to be solved in the years ahead. Below, I discuss the key highlights and challenges that arose from our studies - proposing an initial neurocognitive model of cannabis use and CUD (Figure 3) that can be used as a starting point for future research - before presenting a cannabis research checklist that includes important considerations and crucial assessments that should be included to establish the increased study comparability that is needed to move this field forward.

Heavy use versus dependence (A)

Only about 30 percent of weekly-to-daily cannabis users will develop a CUD (Leung et al., 2020), but with the growing number of daily users, considering the interactions between risk factors for CUD is crucial to better understand use trajectories and to distinguish who will become dependent and who will not. However, while increasingly

common in recent years, most studies do still not consider the differential processes underlying cannabis use (e.g., in grams per week) and symptoms of dependence (e.g., CUD symptoms or experienced cannabis use related problems). From the results presented in this thesis, it is clear that while there are strong associations between heaviness of use and CUD (e.g., **chapter 4**), they can and should not be used interchangeably: heavy use does not equal dependence. For example, use and dependence are differentially associated with cognition (e.g., **chapter 8**) and brain functioning (e.g., **chapter 9 and 10**). Furthermore, CUD is multifaceted and different symptoms might be differentially associated with each other depending on age, sex/gender, or comorbid mental health symptoms (e.g., **chapter 5**). Researchers should be encouraged to include measures of frequency and quantity of use as well as severity of CUD and assess these in individuals with variable levels of cannabis use and CUD to further elucidate the processes of CUD development and the associated (neuro) cognitive profiles and moderators (Figure 3-A).

Mental health & understanding gender and sex differences (B)

Most studies only include cannabis users with few mental health problems to produce clean comparisons with the included control groups. While this helps us filter out the effects of cannabis use itself more easily, this approach does not acknowledge the high prevalence of mental health problems in heavy and dependent cannabis users (e.g., **chapter 2 and chapter 5**) and might produce less ecologically valid results. Furthermore, it might undermine the inherent associations between substance use disorders and other mental health problems that could affect treatment outcomes (Lees et al., 2021) and obscure important interactions with sex/gender, for example (e.g., **chapter 5**). While sex/gender differences are underexplored in general – and efforts distinguishing sex from gender effects are fully lacking – the potential impact of sex/gender on the interaction between CUD and mental health problems is an important factor to consider in the efforts to improve treatment outcomes (Figure 3-B).

The interactions of motivation and control related processes (C)

For decades, theories of substance use disorders have focused on the importance of cognitive control-related processes (e.g., inhibition) in the control of motivational urges to use (e.g., craving) to remain abstinent (e.g., Bickel et al., 2018). However, in the cannabis research field, motivational and control-related processes are often investigated in isolation (e.g., **chapter 6 and 10**) and the number of studies investigating *how* these processes interact remain limited. We should challenge ourselves more to create paradigms that allow us to study how the effects of cannabis cues and related attentional processes change depending on the cognitive demands, for example

(e.g., **chapter 7**). In addition, longitudinal designs are crucial to investigate causal associations between cannabis use and cognitive problems, and the role of cognition in overcoming motivational urges and in limiting the interference from motivational stimuli should be further explored (Figure 3-C).

Cultural attitudes and social processes (D)

Symptoms of CUD do not solely include items indicating physical dependence such as craving, tolerance, and withdrawal; social and interpersonal problems arising from persistent use are crucially important in CUD. The development of social and interpersonal problems dependent on the individual's environment, both in terms of use (e.g., cannabis use by peers), daily life responsibilities (e.g., family, work), and the attitudes of the social environment towards the potential benefits and harms of (persistent) cannabis use. From my studies it has become clear that differences in legislation between sites as well as individual differences in cannabis attitudes interact with measures of cannabis use and dependence in their association with brain functioning (**chapter 9 and 10**). Furthermore, results showed that a more progressive cannabis legislation is not necessarily associated with more positive and less negative attitudes towards cannabis use, and that differences in legislation are not always accompanied by differences in perceived cannabis attitudes. Hence, it remains crucial to assess both differences and similarities across sites to learn about the cultural mechanisms affecting use. Furthermore, more fine-grained measures of social and interpersonal problems related to cannabis use are currently lacking, complicating assessments of the effects of culture and social use on CUD. Efforts should be made to 1) assess the role of social influence and social attunement on cannabis use across the life span, 2) assess how cultural attitudes are affected by changing legislation and how this might affect the brain processes underlying CUD, and 3) how cultural attitudes affect the experience of interpersonal problems associated with CUD using newly validated measurements of these problems (Figure 3-D).

Medicinal use and cannabinoid exposure (E)

While the studies in this thesis primarily focus on recreational cannabis use – with only 9 out of 81 (11.11%) Dutch and 9 out of 58 (15,52%) Texan daily cannabis users with CUD reporting use for primarily medicinal purposes (cross-cultural sample used in **chapter 9 and 10**) - medicinal cannabis use is increasingly common (Boehnke et al., 2022; Rhee & Rosenheck, 2023). Cannabis has been suggested to be beneficial for chronic pain (e.g., associated with MS or cancer (treatment), Boyaji et al., 2020), mental health (Khan et al., 2020), and sleep problems (Babson et al., 2017), but evidence remains limited. Furthermore, when the legalization of recreational use parallels the legalization of medicinal use, one might not visit doctors for a cannabis prescription

but opt to self-medicate in countries where cannabis is available for recreational use. One of the problems with self-medication is that the regulation of cannabis products in limited in most countries making it hard for individuals to choose products with known THC/CBD concentration from distributors. In line with this, research on cannabinoid exposure and potency in both medicinal and recreational users is very limited, also due to the methodological and legal difficulties in measuring cannabinoid exposure and cannabis potency (e.g., **chapter 4**). Investments in the methods to assess cumulative cannabinoid exposure and potency are crucial to further this field and to be able to explore the potential benefits and harms of the use of different cannabinoids by (self-reported) medical and recreational users (Figure 3-E).

Tobacco co-use (F)

Tobacco co-use is one of the biggest challenges for cannabis researchers. First, combining cannabis with tobacco is very common in Europe but less so in other regions like the United States (Hindocha et al., 2016), making it difficult to compare representative samples from different locations. Looking at the cross-cultural sample used in **chapter 9 and 10**, the percentage of daily tobacco users was substantially higher in the Dutch (42 out of 81, 51.85%) than in the Texan (7 out of 58, 12.07%) cannabis users, even after targeted recruitment efforts to match tobacco use across sites. Second, tobacco use – like most other drug use - is more common in cannabis users than in the general population often used as control groups (Hindocha et al., 2021), making it difficult to match groups. Third, the lack of easily accessible measurements of cannabis exposure makes it difficult to explore the potential interactions between cannabinoids and nicotine in their effects on the brain (Viveros et al., 2006). In general, the measurement of tobacco use is crucial in any study on cannabis use, and tobacco use should ideally be measured in sufficient detail (e.g., using TLFB measurements with visual tools separating tobacco used with and without cannabis) to enable follow-up assessment of its effects on the central study outcomes (e.g., through sensitivity analyses). However, studies specifically focusing on the interaction between tobacco and cannabinoid use – rather than only the evaluation of shared effects – are needed to confirm initial results that tobacco use could affect the effects of cannabis on the brain (e.g., Kuhns et al., 2021), and could negatively impact clinical outcomes through higher dependence symptoms, higher rates of comorbid psychopathology, increased withdrawal symptoms, and increased chances of cue-associated relapse when not quitting tobacco and cannabis use simultaneously (Lemyre et al., 2019).

Brain functioning (G)

The processes and interactions described earlier are all assumed to arise from

individual differences in brain functioning. However, the more complex the interactions and behaviors, the more complex the underlying brain patterns, and the more difficult it becomes to explain how these interactions and behaviors might arise from these patterns (e.g., **chapter 9 and 10**). While fMRI research has taken large steps over the last two decades - and human in-vivo measurement of the brain is crucial to bridge the gap between both animal research and in-vitro research and the study of human behavior - it has not proven to be the holy grail some might have expected it to be at the start of the MRI era. Results in the field of addiction have provided us insight into potential fundamental processes underlying addictive behaviors and the direct effects of some substances on brain structure and function, but steps are often incremental and there is a long road ahead to understand how brain functioning translates to complex behaviors. Hence, I believe brain functioning should be considered an important fundamental layer in the field of addiction, but that we should prioritize increasing our understanding of individual differences on a behavioral level to inform treatment and improve treatment outcomes.

The effects of time (H)

The question of causality remains one of the biggest unanswered questions in the addiction field, largely due to the ethical constraints on experimental research establishing causality, the inherent limitations of often-conducted cross-sectional study designs, and the lack of longitudinal studies. Large cohort studies are being conducted (e.g., Chan et al., 2021), but due to the nature of the study and the included sample, these studies do often only include a small percentage of individuals with substance use disorders and often include self-report measures with limited detail. Longitudinal studies are being conducted in more specific samples of users (e.g., de Haan et al., 2013), often including more detailed measures but smaller samples and shorter follow-up periods. Recently, more effort has been put into the development of more data-intensive shorter-term measurements such as experience sampling methods (e.g., Sznitman et al., 2020) to assess likely causal associations between symptoms on a shorter time scale. In general, longitudinal studies require large budgets and time investments to complete, but at the same time can have large impact on the understanding of (likely) causality of problems and thereby inform the focus of future studies. Investing in longitudinal studies – assessing changes over time – remains crucial to further understand the development of CUD and other substance use disorders, investing in a broad range of measures including changes in use and symptomology, mental health, changing cultural attitudes and interpersonal relationships, as well as motivation, control, and the underlying brain processes (Figure 3-H).

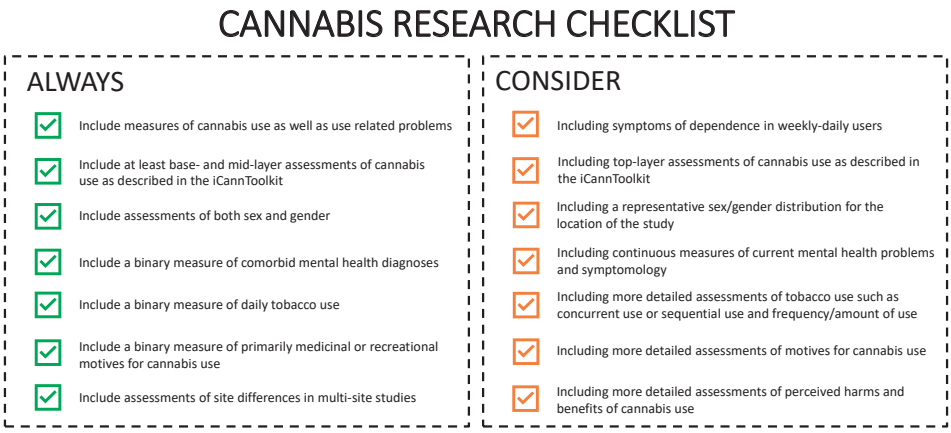


Figure 4. Cannabis research checklist. A proposal for a comprehensive field-wide cannabis research checklist, including measurements that should always be included to increase comparability of studies and measurements that should be considered based on the goals, budget, and time constraints of the study.

Conclusion

As can be seen in Figure 1, there is evidence for a variety of interactions between internal and external factors associated with cannabis use and CUD. Together, these results provide small but important pieces of the puzzle that will guide future research to work towards a more complete neurocognitive model of cannabis use and CUD of which an initial version is presented in Figure 2. However, to establish this goal, measurement is key; we need to work towards a consensus on what constitutes crucial assessments in cannabis research. Based on my experience with multimethod cross-cultural cannabis research over the last years, I would like to propose a starting point for the discussion to reach this consensus. Figure 4 presents a *cannabis research checklist* including measurements that I believe should *always* be included when conducting cannabis research, as well as additional measures that should be *considered* based on the goals, budget, and time constraints of the study. Embracing, field-wide standards cannot only help starting cannabis researchers navigate the complex study design process but might also encourage experienced researchers to consider including measures they usually omit from their studies. Furthermore, I believe standards that go beyond the measurement of cannabis use and CUD itself can aid study comparison and might encourage researchers to look beyond group differences, taking into account individual differences to better inform prevention and treatment efforts.

Appendices

Appendix A

Supplementary materials chapter 4

Price per gram

How much does the cannabis you typically consume cost? Please state per gram.

…… per gram

Relative potency

When comparing it to other types of cannabis you have used, how potent is the cannabis you typically use?

0----------100

Perceived 'high'

How strong is the 'high' you get from the cannabis you typically use?

(not strong at all) 1 ---------- 5 (very strong)

Potency category

Please categorize the potency of the cannabis that you typically use.

- Very mild
- Mild
- Average
- Strong
- Very Strong

THC percentage category

How much THC does the cannabis you typically use contain?

- 0-5%
- 5-10%
- 10-15%
- 15-20%
- 20-25%
- 25-30%
- More than 30%

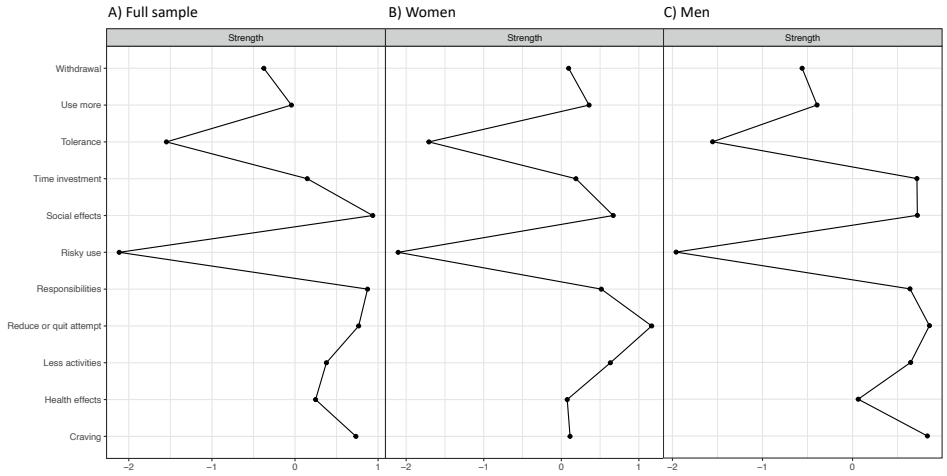
Figure S1. Overview of self-report measures of potency

Appendix B

Supplementary materials chapter 5

Figure S1

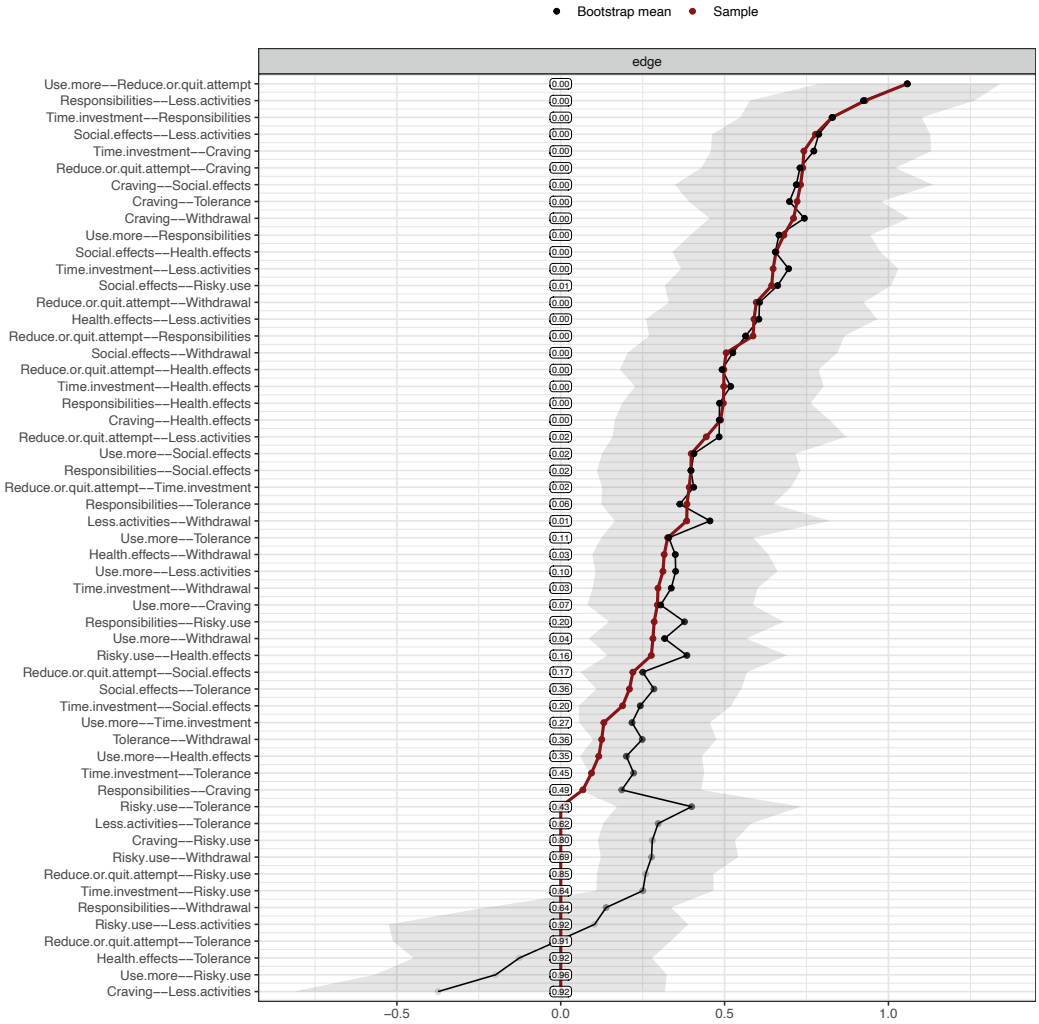
Strength Centrality of the 11 MINI CUD Symptoms in the CUD Symptom Network



Note: A) Full sample. B) Women. C) Men. Z-scores are shown on the x-axis.

Figure S2

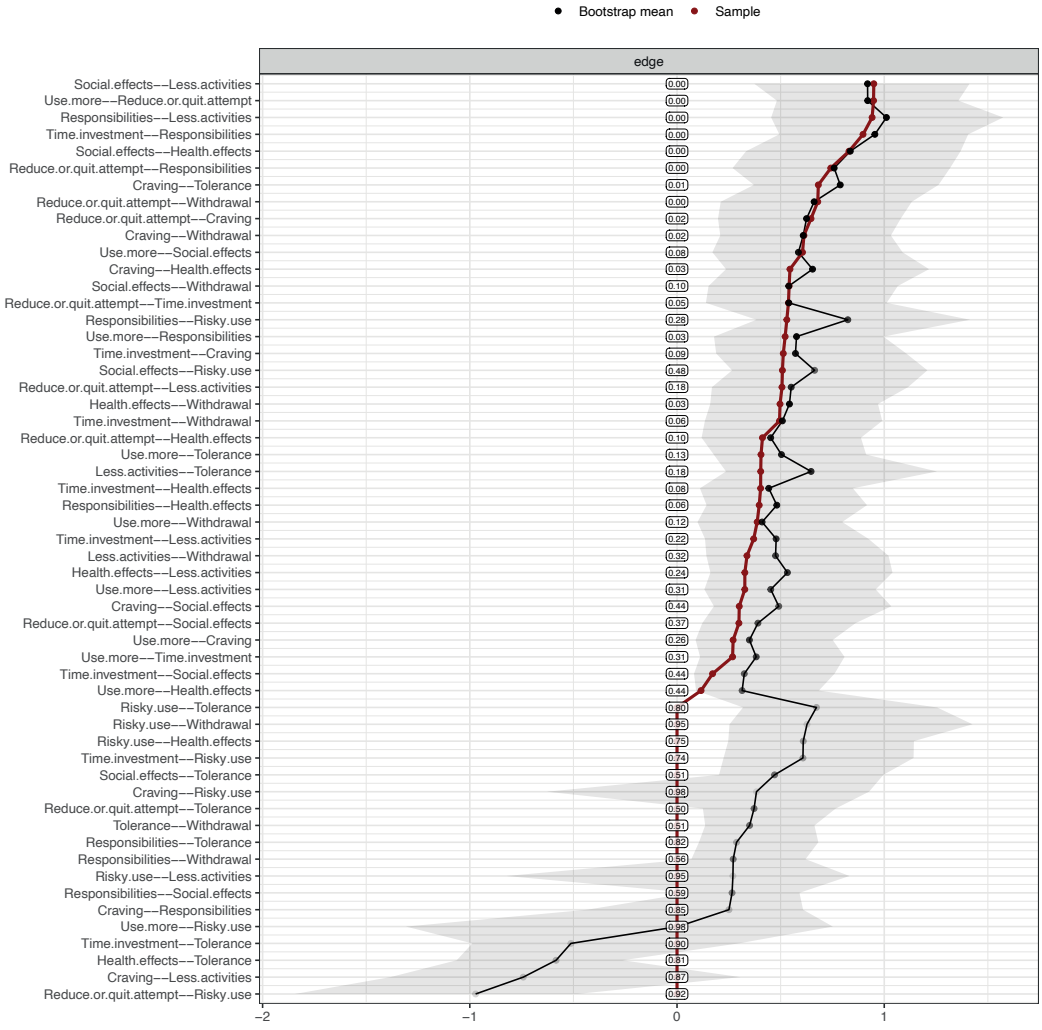
Edge Bootstraps of the CUD Symptom Network in the Full Sample



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S3

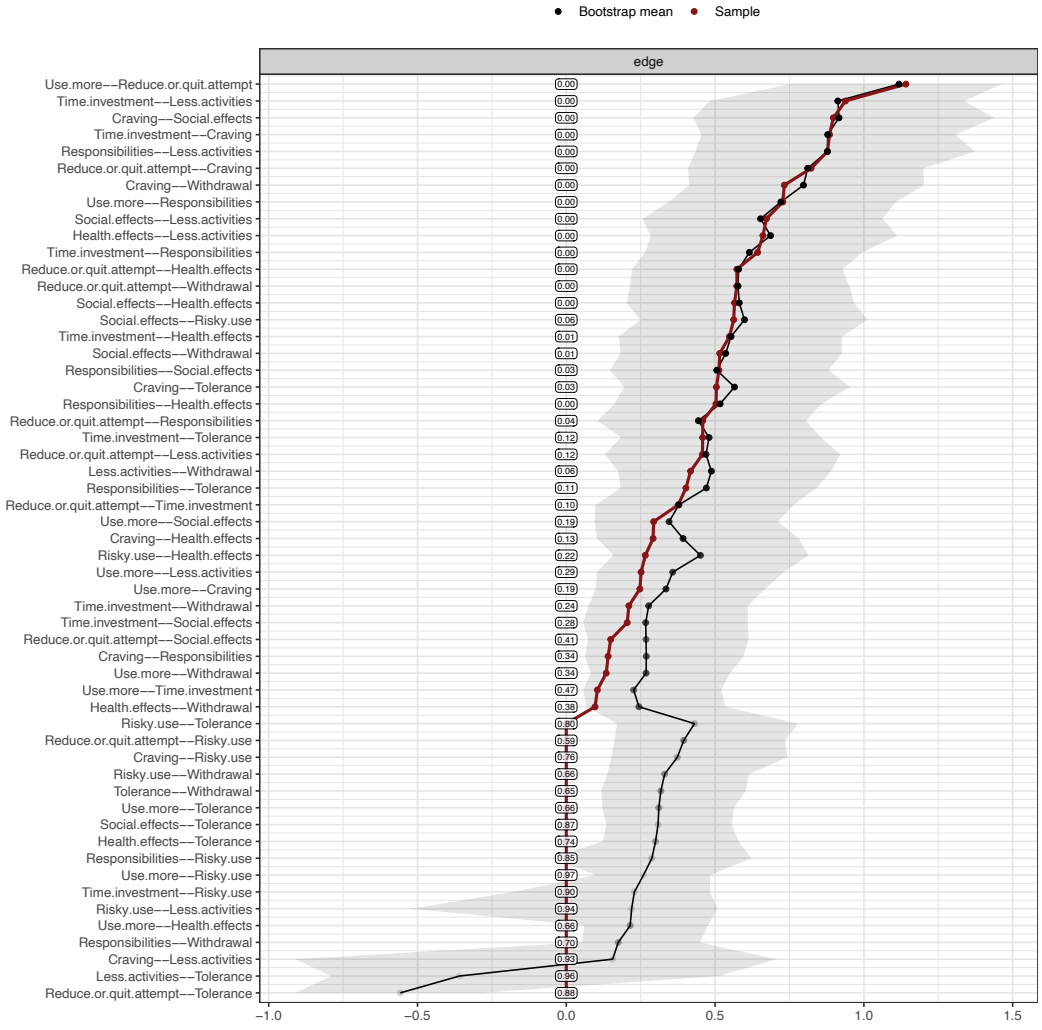
Edge Bootstraps of the CUD Symptom Network in Women



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S4

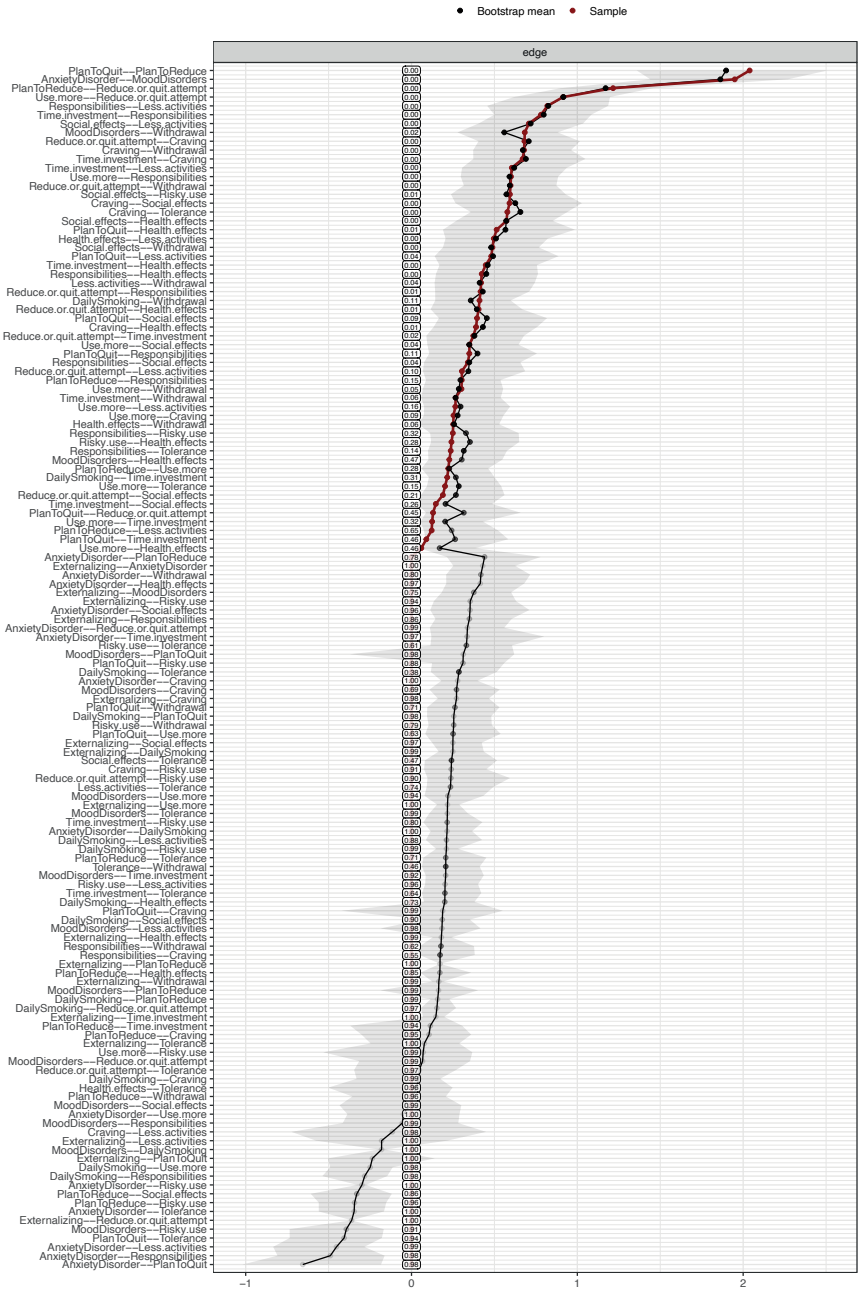
Edge Bootstraps of the CUD Symptom Network in Men



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S5

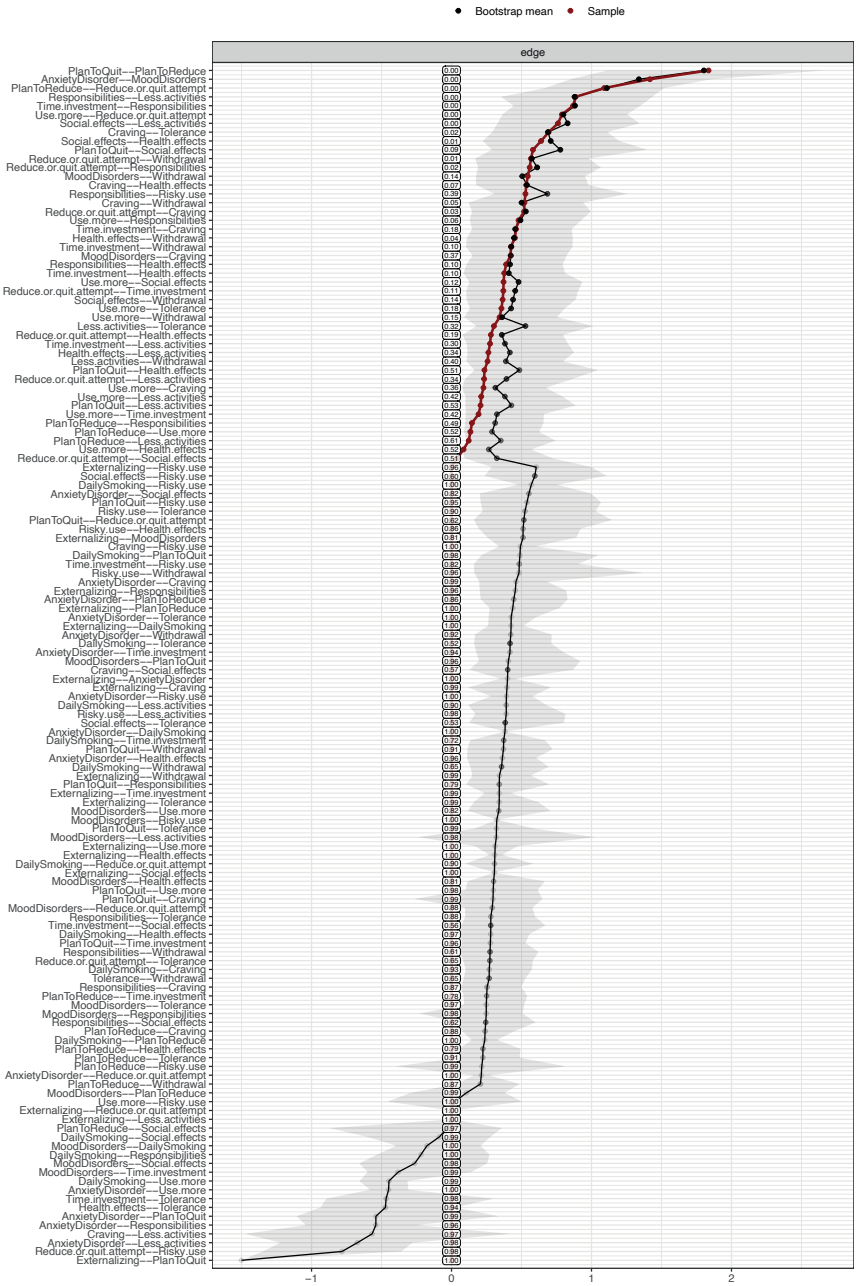
Edge Bootstraps of the CUD Symptoms Plus Exploratory Variables Network in the Full Sample



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S6

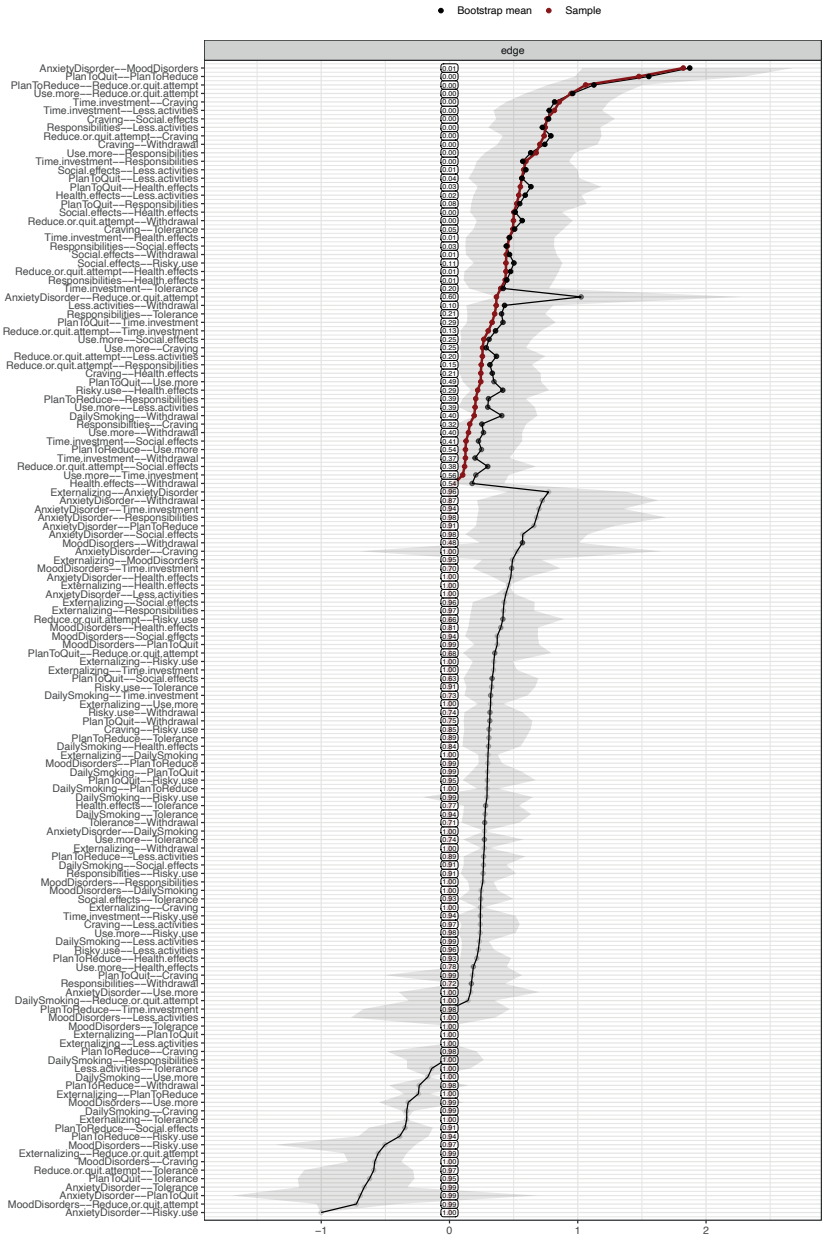
Edge Bootstraps of the CUD Symptoms Plus Exploratory Variables Network in Women



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S7

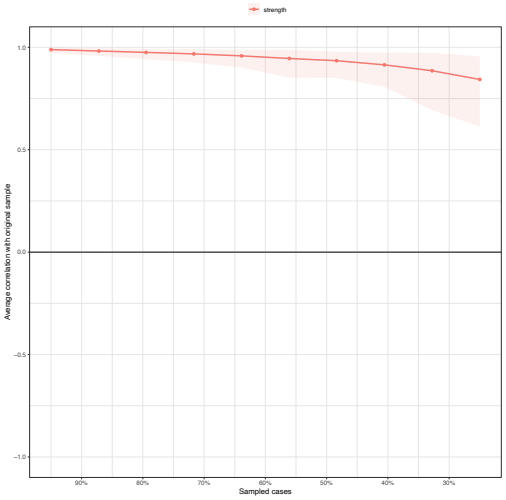
Edge Bootstraps of the CUD Symptoms Plus Exploratory Variables Network in Men



Note: Bootstrapped confidence region derived from occasions when edges were not estimated to be zero (1000 bootstrapped samples). The boxes show the number of times when that edge was estimated to be zero.

Figure S8

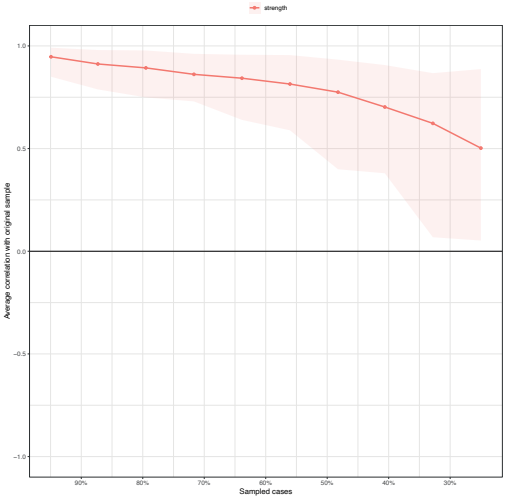
Strength Centrality Case-dropping Bootstraps for the CUD Symptom Network in the Full Sample



Note: The figure shows the correlation of strength between the original and case-dropping sample based on 1000 bootstrapped samples. The correlation is always large, indicating that strength centrality is stable.

Figure S9

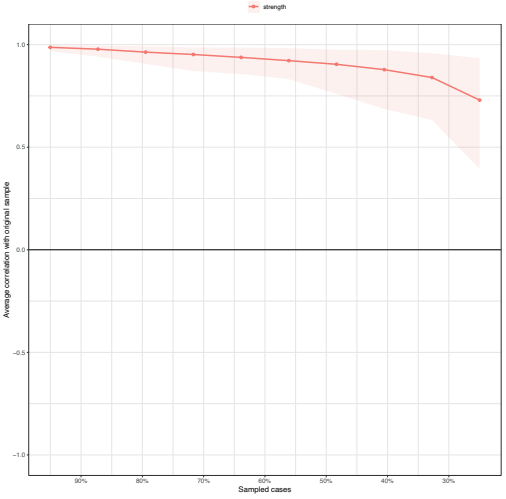
Strength Centrality Case-dropping Bootstraps for the CUD Symptom Network in Women



Note: The figure shows the correlation of strength between the original and case-dropping sample based on 1000 bootstrapped samples. The correlation is large except with a very small number of sampled cases, indicating that strength centrality is stable.

Figure S10

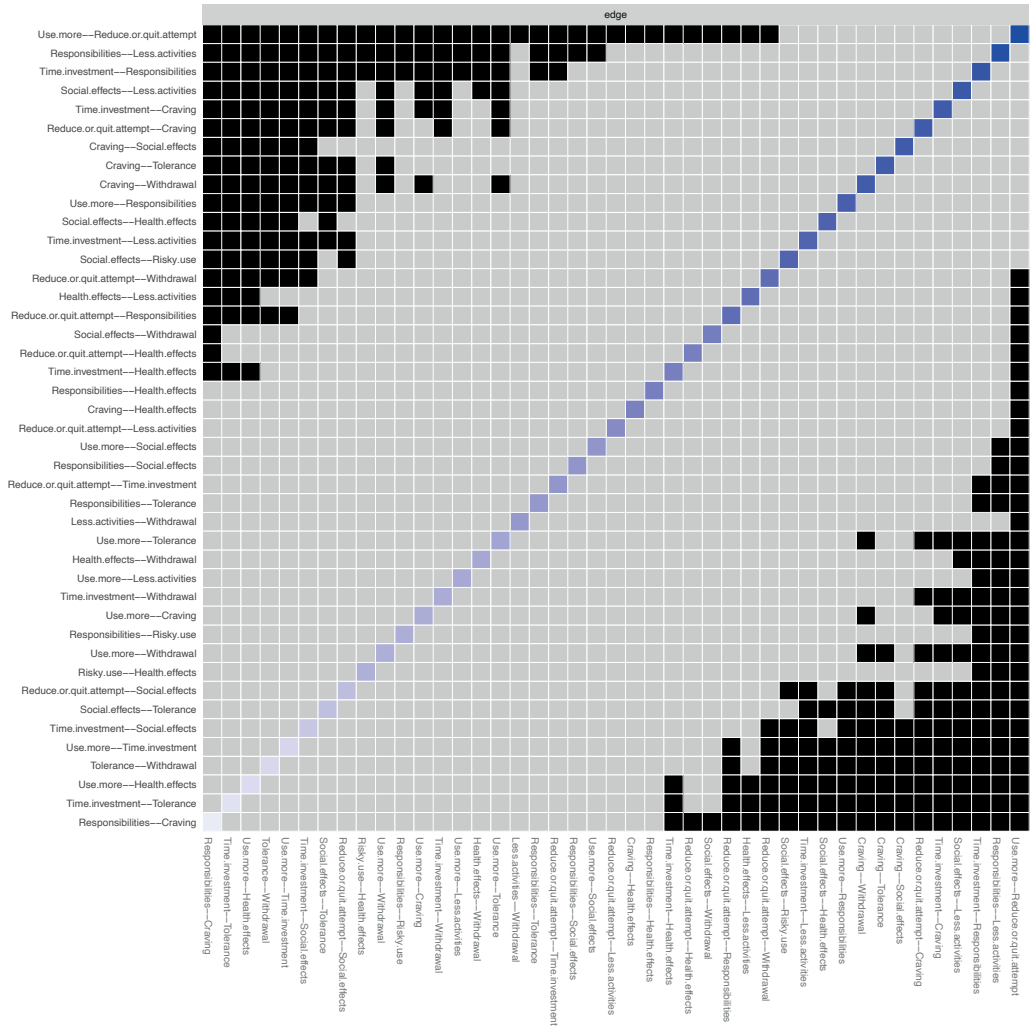
Strength Centrality Case-dropping Bootstraps for the CUD Symptom Network in Men



Note: The figure shows the correlation of strength between the original and case-dropping sample based on 1000 bootstrapped samples. The correlation is always large, indicating that strength centrality is stable.

Figure S11

Bootstrapped Difference Tests to Test for Significant Differences Between Edges Within the CUD Symptom Network in the Full Sample



Note: The figure, based on 1000 bootstrapped difference tests, shows a black square for pairs of edges that are significantly different within the CUD symptom network in the full sample. For example, the edge between craving and time investment is significantly larger than the one between craving and responsibilities. Please zoom in the picture if interested in a specific edge difference. Note that this figure does not represent differences in the edges between genders, but how edges differ within the full sample network.

Table S1

Edge Weights for the CUD Symptom Networks of Women and Men

Node	Use more	Reduce or quit attempt	Time investment	Craving	Responsibilities	Social effects	Risky use	Health effects	Less activities	Tolerance	Withdrawal
Use more	0.00	1.14	0.10	0.25	0.73	0.29	0.00	0.00	0.25	0.00	0.13
Reduce or quit attempt	0.95	0.00	0.38	0.82	0.46	0.15	0.00	0.57	0.46	0.00	0.57
Time investment	0.27	0.54	0.00	0.88	0.64	0.20	0.00	0.55	0.94	**0.46**	0.21
Craving	0.27	0.65	0.51	0.00	0.14	0.90	0.00	0.29	0.00	0.50	0.73
Responsibilities	0.52	0.74	0.90	0.00	0.00	0.51	0.00	0.50	0.88	0.40	0.00
Social effects	0.61	0.30	0.17	0.30	0.00	0.00	0.56	0.57	0.67	0.00	0.52
Risky use	0.00	0.00	0.00	0.00	0.53	0.51	0.00	0.27	0.00	0.00	0.00
Health effects	0.12	0.41	0.40	0.55	0.40	0.83	0.00	0.00	0.66	0.00	0.10
Less activities	0.33	0.51	0.37	0.00	0.94	0.95	0.00	0.33	0.00	0.00	0.42
Tolerance	0.41	0.00	**0.00**	0.68	0.00	0.00	0.00	0.00	0.40	0.00	0.00
Withdrawal	0.39	0.68	0.49	0.61	0.00	0.54	0.00	0.50	0.34	0.00	0.00

Note: Edge weights for women are in the lower triangle, while edge weights for men are in the upper triangle. Bold text indicates edges that were significantly different between genders without controlling for multiple comparisons.

Table S2

Edge Weights for the CUD Symptom and Exploratory Variable Networks of Women and Men

Node	Externalizing diagnosis	Anxiety diagnosis	Mood diagnosis	Daily cigarette	Plan to quit	Plan to reduce	Use more	Reduce or quit attempt	Time investment	Responsi-bilities	Craving	Social effects	Risky use	Health effects	Less activities	Tolerance	Withdrawal
Externalizing diagnosis	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Anxiety diagnosis	0.00	0.00	1.82	0.00	0.00	0.00	0.00	**0.37**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mood diagnosis	0.00	1.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	0.00
Daily cigarette	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.19
Plan to quit	0.00	0.00	0.00	0.00	0.00	1.48	0.24	0.00	0.33	0.52	0.00	0.00	0.00	0.55	0.56	0.00	0.00
Plan to reduce	0.00	0.00	0.00	0.00	1.84	0.00	0.12	1.06	0.00	0.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Use more	0.00	0.00	0.00	0.00	0.00	0.14	0.00	0.95	0.10	0.68	0.26	0.27	0.00	0.00	0.20	0.00	0.15
Reduce or quit attempt	0.00	**0.00**	0.00	0.00	0.00	1.09	0.79	0.00	0.30	0.25	0.74	0.12	0.00	0.44	0.26	0.00	0.50
Time investment	0.00	0.00	0.00	0.00	0.00	0.00	0.19	0.37	0.00	0.60	0.86	0.13	0.00	0.47	0.82	**0.40**	0.12
Responsibilities	0.00	0.00	0.00	0.00	0.00	0.15	0.48	0.56	0.87	0.00	0.16	0.45	**0.00**	0.43	0.75	0.35	0.00
Craving	0.00	0.00	**0.42**	0.00	0.00	0.00	0.23	0.52	0.46	0.00	0.00	**0.76**	0.00	0.24	0.00	0.49	0.70
Social effects	0.00	0.00	0.00	0.00	0.58	0.00	0.37	0.04	0.00	0.00	**0.00**	0.00	0.44	0.50	0.58	0.00	0.44
Risky use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.53**	0.00	0.00	0.00	0.22	0.00	0.00	0.00
Health effects	0.00	0.00	0.00	0.00	0.24	0.00	0.09	0.28	0.38	0.39	0.53	0.64	0.00	0.00	0.54	0.00	0.04
Less activities	0.00	0.00	0.00	0.00	0.21	0.12	0.21	0.23	0.28	0.89	0.00	0.76	0.00	0.26	0.00	**0.00**	0.36
Tolerance	0.00	0.00	0.00	0.00	0.00	0.00	0.36	0.00	**0.00**	0.00	0.69	0.00	0.00	0.00	**0.30**	0.00	0.00
Withdrawal	0.00	0.00	0.54	0.00	0.00	0.00	0.34	0.57	0.42	0.00	0.52	0.37	0.00	0.45	0.26	0.00	0.00

Note: Edge weights for women are in the lower triangle, while edge weights for men are in the upper triangle. Bold text indicates edges that were significantly different between genders without controlling for multiple comparisons.

Appendix C

Supplementary materials chapter 6

Study 1

A total of 25 cannabis users and 24 controls between 18 and 25 years old participated in the study. The data included was collected during a 3-year follow-up session of the original project and inclusion criteria described applied on the baseline session. Cannabis users were included if they used cannabis a minimum of 10 times per month for at least the previous 18 months, while controls were not allowed to have used cannabis over 50 times in their life and not during the last year. Exclusion criteria were substance use other than cannabis over a hundred times, excessive alcohol use, smoking over 20 cigarettes a day, history of major psychological or medical problems. Included participants were requested to abstain from using drugs or alcohol 24 hours before the start of the session. A urine screening was conducted to assess recent drug use and all that tested positive for a drug other than THC in the cannabis group (i.e. alcohol, amphetamines, benzodiazepines, cocaine, or opiates) were excluded.

Study 2

A total of 34 cannabis users and 31 controls between 18 and 25 years old participated in the study. Cannabis users were included if they used cannabis a minimum of 10 times per month for at least the last 2 years, while controls were not allowed to have used cannabis over 50 times in their life and not during the last year. Exclusion criteria were substance use other than cannabis over a hundred times, excessive alcohol use, smoking over 20 cigarettes a day, current use of prescription or illicit psychoactive drugs besides cannabis, history of major psychological or medical problems, leaving school before age 16, and treatment for cannabis use disorder. Included participants were requested to abstain from using drugs or alcohol 24 hours before the start of the session. A urine screening was conducted to assess recent drug use and all that tested positive for a drug other than THC in the cannabis group (i.e. amphetamines, benzodiazepines, cocaine, methamphetamines, or opiates) were excluded.

Study 3

A total of 45 cannabis users and 30 controls between 18 and 30 years old participated in the study. Cannabis users were included if they used cannabis a minimum of 6 times a week for at least the past year, while controls were not allowed to have used cannabis over 25 times in their life and not more than 5 times during the last year. Exclusion criteria were regular use of substances other than cannabis, excessive alcohol use, current use of prescription or illicit psychoactive drugs besides cannabis, history of major psychological or medical problems, and treatment for cannabis use disorder. Included participants were requested to abstain from using drugs or alcohol 24 hours before the start of the session. A urine screening was conducted to assess recent drug use and all that tested positive for a drug other than THC in the cannabis group (i.e. amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy (MDMA), methamphetamines, methadone, morphine/opiates, phencyclidine (PCP), oxycodone) were excluded.

Figure S1. Study specific information and exclusion criteria.

Table S1. Overview of linear mixed model results assessing the effect of group, sex and their interaction on the included continuous outcome variables						
Model	**Model coefficients**					
	Fixed effects					**Random effects**
Measure	***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***
Age						
Intercept	21.74	20.76 – 22.71	0.50	43.48	<0.001	
Group	0.84	-0.52 – 2.20	0.70	1.20	0.23	1.72
Sex	0.49	-0.73 – 1.72	0.63	0.78	0.44	
Group x Sex	-0.69	-2.48 – 1.10	0.92	-0.75	0.45	-
Estimated IQ[1]						
Intercept	-0.21	-0.52 – 0.10	0.16	-1.31	0.19	
Group	0.27	-0.16 – 0.71	0.22	1.22	0.22	0.55
Sex	0.08	-0.31 – 0.47	0.20	0.41	0.68	
Group x Sex	0.16	-0.41 – 0.73	0.29	0.54	0.59	-
Depression (BDI)						
Intercept	8.24	6.08 – 10.40	1.11	7.44	<0.001	
Group	-2.39	-5.40 – 0.63	1.55	-1.54	0.12	3.81
Sex	0.16	-2.55 – 2.87	1.39	0.11	0.91	
Group x Sex	-1.65	-5.62 – 2.31	2.03	-0.81	0.42	-
State Anxiety (STAI)[2]						
Intercept	34.26	31.45 – 37.06	1.44	23.80	<0.001	
Group	-1.52	-5.53 – 2.48	2.05	-0.74	0.46	4.46
Sex	-1.34	-4.94 – 2.26	1.85	-0.73	0.47	
Group x Sex	-0.30	-5.68 – 5.09	2.76	-0.11	0.92	-
Trait Anxiety (STAI)[2]						
Intercept	38.97	35.87 – 42.07	1.59	24.52	<0.001	
Group	-4.87	-9.29 – -0.45	2.27	-2.15	**0.03**	4.92
Sex	-2.10	-6.09 – 1.90	2.05	-1.02	0.31	
Group x Sex	1.29	-4.67 – 7.24	3.06	0.42	0.67	-
Alcohol use and related problems (AUDIT)						
Intercept	5.42	4.32 – 6.52	0.57	9.59	<0.001	
Group	-0.85	-2.39 – 0.70	0.79	-1.07	0.29	1.95
Sex	1.38	-0.00 – 2.77	0.71	1.95	0.05	
Group x Sex	0.04	-1.98 – 2.07	1.04	0.04	0.97	-

Nicotine Dependence (FTND)						
Intercept	2.43	1.65 – 3.20	0.40	6.09	<0.001	1.17
Group	-0.90	-2.16 – 0.36	0.65	-1.39	0.17	
Sex	-0.29	-1.29 – 0.71	0.51	-0.56	0.57	
Group x Sex	-0.14	-1.67 – 1.95	0.93	-0.16	0.88	-
Cigarettes/Day						
Intercept	10.15	7.62 – 12.68	1.31	7.78	<0.001	3.21
Group	-2.36	-6.49 – 1.78	2.13	-1.11	0.27	
Sex	-1.45	-4.64 – 1.74	1.65	-0.88	0.38	
Group x Sex	1.86	-3.94 – 7.67	2.99	0.62	0.54	-
Other substance use						
Intercept	24.68	12.04 – 37.32	6.48	3.81	<0.001	22.29
Group	-21.63	-39.29 – -3.98	9.04	-2.39	**0.02**	
Sex	10.85	-5.02 – 26.71	8.13	1.33	0.18	
Group x Sex	-8.83	-32.04 – 14.38	11.89	-0.74	0.46	-
Cannabis use and related problems (CUDIT-R)						
Intercept	13.68	11.80 – 15.57	0.96	14.23	<0.001	3.31
Sex	-0.20	-2.57 – 2.17	1.21	-0.17	0.87	
CUD symptoms – Study 2[3]						
Intercept	5.60	4.46 – 6.74	0.58	9.67	<0.001	1.24
Sex	-0.50	-1.90 – 0.90	0.71	-0.70	0.48	
CUD symptoms – Study 3[3]						
Intercept	3.38	2.57 – 4.18	0.41	8.32	<0.001	0.89
Sex	0.18	-0.92 – 1.28	0.56	0.32	0.75	
Gram/Week						
Intercept	3.30	1.92 – 4.68	0.70	4.69	<0.001	2.43
Sex	1.69	-0.05 – 3.44	-0.89	1.91	0.06	
Age of Onset						
Intercept	15.47	14.91 – 16.03	0.29	54.26	<0.001	0.98
Sex	-0.40	-1.10 - 0.31	0.36	-1.11	0.27	
Days Since Last Use						
Intercept	18.76	-9.85 – 47.36	14.56	1.29	0.20	49.48
Sex	-3.51	-39.34 – 32.32	18.24	-0.19	0.85	

Note: AUDIT: alcohol use disorder identification test; BDI: Beck's depression inventory; CUD: cannabis use disorder; CUDIT-R: cannabis use disorder identification test; FTND: Fagerström test for nicotine dependence; STAI: state trait anxiety inventory; [1] Using standardized (Z) scores to compare studies; [2] STAI State & STAI Trait only assessed in study 2 and 3; [3] CUD scores separate for study 2 (SCID) and 3 (MINI) due to different measures used to assess DSM-5 CUD symptoms, study 1 did not assess CUD; Significant results are presented in bold.

Table S2. Overview of model selection to assess accuracy during the N-back task as a function of working memory (WM)-load, group, sex and their interaction

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Accuracy		*B*	95% *CI* (*B*)	*SE* (B)	*t*	*p*	*SD*	AIC	*χ2*	*p*
BM	(Intercept)	94.42	93.93 – 94.90	0.25	381.92	0.00	4.74	3379.58	-	-
1	(Intercept)	96.32	95.30 – 97.34	0.52	184.64	<0.001	2.36	3221.90	165.67	**<.001**
	WM-load: 0-back - 1-back	-1.97	-2.80 – - 1.15	0.42	-4.69	**<0.001**	3.74			
	WM-load: 0-back - 2-back	-5.88	-6.71 – -5.06	0.42	-13.97	**<0.001**				
	Group	0.53	-0.45 – 1.50	0.50	1.06	0.289	-			
	Sex	0.80	-0.19 – 1.78	0.50	1.58	0.115	-			
2	*(Intercept)*	*96.58*	*95.48 – 97.69*	*0.57*	*170.85*	*<0.001*	*2.38*	3217.01	*8.90*	***.01***
	WM-load: 0-back - 1-back	*-1.85*	*-2.95 – -0.75*	*0.56*	*-3.28*	***0.001***	*3.69*			
	WM-load: 0-back - 2-back	*-6.80*	*-7.90 – -5.70*	*0.56*	*-12.04*	***<0.001***				
	Group	*-0.05*	*-1.40 – 1.31*	*0.69*	*-0.07*	*0.95*	-			
	Sex	*0.79*	*-0.19 – 1.78*	*0.50*	*1.58*	*0.12*	-			
	WM-load: 0-back - 1-back x Group	*-0.28*	*-1.91 – 1.35*	*0.84*	*-0.34*	*0.74*	-			
	WM-load: 0-back - 2-back x Group	*2.01*	*0.37 –3.64*	*0.84*	*2.40*	***0.02***	-			
3	(Intercept)	96.84	95.58 – 98.10	0.65	149.48	<0.001	2.39	3220.34	.67	.72
	WM-load: 0-back - 1-back	-2.23	-3.76 – -.70	0.78	-2.85	**0.01**	3.67			
	WM-load: 0-back - 2-back	-7.18	-8.71 – -5.65	0.78	-9.15	**<0.001**				
	Group	-0.09	-1.45 – 1.27	0.70	-0.13	0.90	-			
	Sex	0.39	-0.98 – 1.77	0.70	0.56	0.58	-			
	WM-load: 0-back - 1-back x Group	-0.21	-1.86 – 1.43	0.84	-0.24	0.80	-			
	WM-load: 0-back - 2-back x Group	2.07	0.43 – 3.72	0.84	2.46	**0.01**	-			
	WM-load: 0-back - 1-back x Sex	0.60	-1.06 – 2.27	0.85	0.71	0.48	-			
	WM-load: 0-back - 2-back x Sex	0.59	-1.07 – 1.26	0.85	0.70	0.49	-			
4	(Intercept)	96.55	95.15 – 97.94	0.72	134.88	<0.001	2.38	3221.42	.92	.34
	WM-load: 0-back - 1-back	-2.23	-3.76 – -.70	0.79	-2.84	**0.01**	3.69			
	WM-load: 0-back - 2-back	-7.18	-8.71 – -5.65	0.79	-9.14	**<0.001**				
	Group	0.47	-0.31 – 2.25	0.91	0.51	0.60	-			
	Sex	0.85	-0.81 – 2.51	0.85	1.00	0.32	-			
	WM-load: 0-back - 1-back x Group	-0.21	-1.86 – 1.43	0.84	-0.25	0.80	-			
	WM-load: 0-back - 2-back x Group	2.07	0.43 – 3.72	0.84	2.46	**0.02**	-			
	WM-load: 0-back - 1-back x Sex	0.60	-1.06 – 2.27	0.85	0.71	0.48	-			
	WM-load: 0-back - 2-back x Sex	0.59	-1.07 – 2.26	0.85	0.70	0.49	-			
	Group x Sex	-0.96	-2.93 – 1.01	1.01	-0.95	0.34	-			
5	(Intercept)	96.84	95.34 – 98.35	0.77	125.02	<0.001	2.39	3220.68	4.74	.09
	WM-load: 0-back - 1-back	-2.18	-4.00 – -0.36	0.94	-2.33	**0.02**	3.66			
	WM-load: 0-back - 2-back	-8.11	-9.93 – -6.29	0.94	-8.67	**<0.001**				
	Group	-0.09	-2.19 – 2.00	1.07	-0.09	0.93	-			
	Sex	0.39	–1.50 – 2.28	0.97	0.40	0.69	-			
	WM-load: 0-back - 1-back x Group	-0.32	-2.85 – 1.10	1.30	-0.25	0.80	-			
	WM-load: 0-back - 2-back x Group	3.87	1.34 – 6.39	1.20	2.98	**0.00**	-			
	WM-load: 0-back - 1-back x Sex	0.52	-1.75 – 2.79	1.17	0.44	0.66	-			
	WM-load: 0-back - 2-back x Sex	2.06	–0.22 – 4.34	1.17	1.76	0.08	-			
	Group x Sex	0.01	-2.74 – 2.76	1.41	0.01	1.00	-			
	WM-load: 0-back - 1-back x Group x Sex	0.18	-3.12 – 3.49	1.70	0.11	0.91	-			
	WM-load: 0-back - 2-back x Group x Sex	-3.09	-6.40 – 0.22	1.70	-1.82	0.07	-			

Linear mixed model results using random intercept and maximum likelihood estimation; BM: baseline model; CI: Confidence Interval; SE: Standard Error; SD: Standard deviation; AIC: Akaike information criterion. Note: final models as presented in the manuscript are presented in italic and significant results are presented in bold.

Table S3. Overview of model selection to assess reaction time during the N-back task as a function of working memory (WM)-load, group, sex and their interaction

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Reaction Time		B	95% CI (B)	SE (B)	*t*	*p*	*SD*	AIC	*χ2*	*P*
BM	(Intercept)	549.31	535.67 – 562.96	6.94	79.11	0.00	90.22	6910.46	-	-
1	(Intercept)	492.12	465.28 – 518.96	13.71	35.89	<0.001	89.18	6593.68	324.78	<0.001
	WM-load: 0-back - 1-back	51.81	39.03 – 64.59	6.53	7.94	**<0.001**	56.25			
	WM-load: 0-back - 2-back	146.23	133.47 – 158.98	6.52	22.44	**<0.001**				
	Group	-4.53	-32.50 – 23.43	14.24	-0.02	0.75	-			
	Sex	-10.42	-38.69 – 17.84	14.39	-0.72	0.47	-			
2	*(Intercept)*	*483.94*	*456.38 – 511.51*	*14.11*	*34.30*	*<0.001*	*89.10*	*6591.09*	*6.59*	***0.04***
	WM-load: 0-back - 1-back	*61.94*	*44.78 – 79.11*	*8.78*	*7.05*	***<0.001***	*55.78*			
	WM-load: 0-back - 2-back	*160.96*	*143.86 – 178.07*	*8.75*	*18.39*	***<0.001***				
	Group	*13.61*	*-17.89 – 45.10*	*16.07*	*0.85*	*0.40*	-			
	Sex	*-10.49*	*-38.70 – 17.72*	*14.39*	*-0.73*	*0.47*	-			
	WM-load: 0-back - 1-back x Group	*-22.35*	*-47.81 – 3.12*	*13.03*	*-1.71*	*0.09*	-			
	WM-load: 0-back - 2-back x Group	*-32.55*	*-57.98 – -7.13*	*13.01*	*-2.50*	***0.01***	-			
3	(Intercept)	486.17	456.99 – 515.34	14.96	32.50	<0.001	89.15	6594.88	0.21	0.90
	WM-load: 0-back - 1-back	58.78	34.93 – 82.63	12.23	4.81	**<0.001**	55.75			
	WM-load: 0-back - 2-back	157.40	133.56 – 181.24	12.23	12.88	**<0.001**				
	Group	13.21	-18.33 – 44.76	16.12	0.82	0.41	-			
	Sex	-13.95	-45.85 – 17.95	16.30	-0.86	0.39	-			
	WM-load: 0-back - 1-back x Group	-21.77	-47.39 – 3.86	13.14	-1.66	0.10	-			
	WM-load: 0-back - 2-back x Group	-31.90	-57.49 – -6.30	13.12	-2.43	**0.02**	-			
	WM-load: 0-back - 1-back x Sex	4.92	-21.00 – 30.83	13.29	0.37	0.71	-			
	WM-load: 0-back - 2-back x Sex	5.54	-21.35 – 31.43	13.27	0.42	0.68	-			
4	(Intercept)	487.62	453.96 – 521.28	17.27	28.23	<0.001	89.14	6596.85	0.03	0.87
	WM-load: 0-back - 1-back	58.78	34.93 – 82.63	12.24	4.80	**<0.001**	55.75			
	WM-load: 0-back - 2-back	157.40	133.56 – 181.24	12.23	12.87	**<0.001**				
	Group	10.38	-35.10 – 55.86	23.26	0.45	0.66	-			
	Sex	-16.24	-57.70 – 25.23	21.21	-0.77	0.45	-			
	WM-load: 0-back - 1-back x Group	-21.76	-47.39 – 3.86	13.15	-1.65	0.10	-			
	WM-load: 0-back - 2-back x Group	-31.89	-57.48 – -6.30	13.13	-2.43	**0.02**	-			
	WM-load: 0-back - 1-back x Sex	4.92	-21.00 – 30.83	13.30	0.37	0.71	-			
	WM-load: 0-back - 2-back x Sex	5.54	-20.35 – 31.43	13.28	0.42	0.68	-			
	Group x Sex	4.89	-51.67 – 61.44	28.93	0.17	0.87	-			
5	(Intercept)	488.94	454.10 – 523.78	17.91	27.30	<0.001	89.18	6599.31	1.55	.46
	WM-load: 0-back - 1-back	61.54	33.04 – 90.05	14.65	4.20	**<0.001**	55.62			
	WM-load: 0-back - 2-back	150.64	122.13 – 179.14	14.65	10.28	**<0.001**				
	Group	7.85	-40.81 – 56.52	24.94	0.31	0.75	-			
	Sex	-18.29	-62.07 – 25.49	22.43	-0.82	0.42	-			
	WM-load: 0-back - 1-back x Group	-27.12	-66.53 – 12.29	20.26	-1.34	0.18	-			
	WM-load: 0-back - 2-back x Group	-18.91	-58.32 – 20.51	20.26	-0.93	0.35	-			
	WM-load: 0-back - 1-back x Sex	0.48	-35.18 – 36.13	18.33	0.03	0.98	-			
	WM-load: 0-back - 2-back x Sex	16.14	-19.45 – 51.72	18.30	0.88	0.38	-			
	Group x Sex	9.22	-54.67 – 73.11	32.74	0.28	0.78	-			
	WM-load: 0-back - 1-back x Group x Sex	9.41	-42.38 – 61.21	26.63	0.35	0.72	-			
	WM-load: 0-back - 2-back x Group x Sex	-22.45	-74.20 – 29.29	26.60	-0.84	0.40	-			

Linear mixed model results using random intercept and maximum likelihood estimation; BM: baseline model; CI: Confidence Interval; SE: Standard Error; SD: Standard deviation; AIC: Akaike information criterion. Note: final models as presented in the manuscript are presented in italic and significant results are presented in bold.

Table S4. Activation overview for the effect of WM and WM-load

				MNI coordinates			
	Cluster size (voxels)	**Brain regions**	**Hemisphere**	**X**	**Y**	**Z**	**Zmax**
WM							
2 > 0	30508	Insula	Right	34	22	0	14.40
		Paracingulate cortex	Right	6	20	46	13.40
		SFG	Left	-4	18	52	12.80
		MFG	Right	30	4	54	12.60
	14499	SMG	Right	38	-46	42	12.90
		Angular gyrus	Right	46	-48	50	12.40
		SMG	Left	-38	-48	42	12.10
		Angular gyrus	Left	-40	-54	48	11.70
	1274	MTG	Right	66	-32	-10	7.68
		ITG	Right	56	-44	-12	6.80
0 > 2	43724	Precuneus	Left	-8	-54	18	13.70
		PCC	Left	-8	-54	24	12.90
		PCC	Right	2	-50	26	12.50
	479	Lateral occipital lobe	Left	-54	-68	34	7.22
		Angular gyrus	Left	-44	-60	28	4.33
WM-load							
2 > 1	34408	Paracingulate gyrus	Left	-6	22	48	11.80
		Insula	Left	-36	22	-2	11.80
		Paracingulate gyrus	Right	8	24	40	11.70
		Insula	Right	-32	22	0	11.40
		Frontal pole	Right	38	50	16	11.10
	17425	Sup. Lateral occipital lobe	Right	32	-76	54	9.78
		Sup. Lateral occipital lobe	Left	-34	-60	42	9.23
		SMG	Right	42	-46	44	9.19
		SPL	Left	-34	-54	40	9.16
	896	MTG	Right	64	-46	-10	6.33
1 > 2	1536	Central operculum	Left	-40	0	14	7.32
		Parietal operculum	Left	-42	-24	18	6.77
	1474	Parietal operculum	Right	54	-24	24	6.54
		Central operculum	Right	38	4	14	6.10
		Insula	Right	42	-12	20	5.77
	1016	ACC	Left	-12	34	-2	6.63
		Subcallosal area	Right	2	30	-2	6.18
		Subcallosal area	Left	-4	30	-2	5.90
		ACC	Right	10	36	2	4.70
		PCC	Left	-6	40	-10	4.32
	829	Precuneus	Left	-8	-52	18	5.38
	502	SMA	Right	6	-10	58	4.24
		SMA	Left	-2	-12	52	4.23
	479	PHG	Left	-20	-38	-12	5.78
		Hippocampus	Left	-26	-16	-14	5.08
		Pallidum	Left	-22	-8	-8	3.83
	314	CWM	Right	16	-30	26	5.23
	170	Precuneus	Right	16	-50	10	4.77
		PCC	Right	6	-50	24	3.78

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 3.1$); 1 = 1-back, 2 = 2-back; ACC: anterior cingulate cortex, CWM: cerebral white matter, ITG: inferior temporal gyrus, MFG: medial frontal gyrus, MTG: medial temporal gyrus, PCC: posterior cingulate cortex, SFG: superior frontal gyrus, SMG: supramarginal gyrus, Sup: superior, PHG: parahippocampal gyrus.

Appendix D

Supplementary materials chapter 7

Table S1. Overview of model selection to assess accuracy and reaction time during the N-back task as a function of working memory (WM)-load, group and flanker type

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Accuracy		*B*	95% *CI* (*B*)	*SE* (B)	*t*	*p*	*SD*	AIC	*χ2*	*p*
0	(Intercept)	92.50	91.58 : 93.43	.47	196.64	<.001	2.61	2646.391	-	-
	WM-load	-	-	-	-	-	3.98			
	Flanker Type	-	-	-	-	-	3.99			
1	*(Intercept)*	*92.28*	*94.03 : 96.52*	*.63*	*150.83*	*<.001*	*3.03*	*2604.738*	*45.62*	*<.001*
	WM-load: 1-back	*-3.00*	*-4.43 : -1.57*	*.73*	*-4.12*	*<.001*	*2.95*			
	WM-load: 2-back	*-5.32*	*-6.75 : -3.88*	*.73*	*-7.31*	*<.001*				
	Flanker Type	-	-	-	-	-	*4.04*			
2	(Intercept)	95.50	94.19 : 96.81	.67	143.01	<.001	3.03	2605.676	1.06	.30
	WM-load: 1-back	-3.00	-4.43 : -1.57	.73	-4.12	<.001	2.96			
	WM-load: 2-back	-5.31	-6.75 : -3.88	.73	-7.30	<.001				
	Flanker Type: neutral	-.44	-1.28 : 0.40	.43	-1.03	0.31	4.03			
3	(Intercept)	95.06	94.48 : 96.63	.80	118.27	<.001	3.00	2606.725	0.95	.33
	WM-load: 1-back	-3.00	-4.43 : -1.57	.73	-4.11	<.001	2.96			
	WM-load: 2-back	-5.32	-6.75 : -3.88	.73	-7.29	<.001				
	Flanker Type: neutral	-0.44	-1.28 : 0.40	.43	-1.03	.31	4.03			
	Group: control	0.91	-0.95 : 2.78	.94	0.97	.33	-			
4	(Intercept)	95.79	93.90 : 97.85	1.02	94.39	<.001	3.03	2614.568	6.16	.52
	WM-load: 1-back	-3.34	-5.76 : -0.92	1.24	-2.69	0.008	2.86			
	WM-load: 2-back	-7.35	-9.77 : -4.93	1.24	-5.93	<.001				
	Flanker type: neutral	-1.35	-3.36 : 0.66	1.03	-1.31	.19	4.02			
	Group: control	-0.34	-3.23 : 2.54	1.47	-0.23	.82	-			
	WM-load: 1-back * Flanker Type: neutral	0.96	-1.88 : 3.81	1.46	0.66	.51	-			
	WM-load: 2-back * Flanker Type: neutral	1.60	-1.24 : 4.45	1.46	1.10	.27	-			
	WM-load: 1-back * Group: control	0.10	-3.40 : 3.59	1.79	0.05	.96	-			
	WM-load: 2-back * Group: control	3.51	0.01 : 3.91	1.79	1.96	.05	-			
	Flanker type: neutral * Group: control	1.00	-1.90 : 3.91	1.50	0.67	.50	-			
	WM-load: 1-back * Flanker Type: neutral * Group: control	-0.79	-4.90 : 3.32	2.12	-0.37	.71	-			
	WM-load: 2-back * Flanker Type: neutral * Group: control	-1.88	-5.99 : 2.23	2.12	-0.89	.38	-			

Mixed model results using random intercept and maximum likelihood estimation; CI: Confidence Interval; SE: Standard Error; SD: Standard deviation; AIC: Akaike information criterion.
Note: final models as presented in the manuscript are presented in italic.

Table S1. Continued

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Reaction Time		**B**	**95% CI (B)**	**SE (B)**	***t***	***p***	***SD***	**AIC**	***χ2***	***P***
0	(Intercept)	505.70	483.16 : 528.24	11.45	44.18	<.001	82.11	4819.618	-	-
	WM-load	-	-	-	-	-	76.49			
	Flanker Type	-	-	-	-	-	37.75			
1	*(Intercept)*	*454.36*	*428.86 : 479.87*	*12.98*	*35.00*	*<.001*	*88.05*	*4742.542*	*81.08*	*<.001*
	WM-load: 1-back	*44.50*	*23.76 : 65.24*	*10.53*	*4.23*	*<.001*	*53.07*			
	WM-load: 2-back	*109.52*	*88.78 : 130.26*	*10.53*	*10.40*	*<.001*				
	Flanker Type	-	-	-	-	-	*38.66*			
2	(Intercept)	454.63	428.77 : 480.49	13.18	34.49	<.001	88.05	4744.526	0.02	.90
	WM-load: 1-back	44.50	23.76 : 76.24	10.54	4.22	<.001	53.07			
	WM-load: 2-back	109.52	88.78 : 130.26	10.54	10.39	<.001				
	Flanker Type: neutral	-0.54	-9.10 : 8.03	4.37	-0.12	.90	38.66			
3	(Intercept)	450.19	416.54 : 483.84	17.17	26.22	<.001	87.93	4746.362	0.16	.68
	WM-load: 1-back	44.50	23.76 : 65.24	10.55	4.22	<.001	53.07			
	WM-load: 2-back	109.52	88.78 : 130.26	10.55	10.38	<.001				
	Flanker Type: neutral	-0.54	-9.10 : 8.03	4.37	-0.12	.90	38.66			
	Group: control	9.29	-36.34 : 54.91	23.00	0.40	.69	-			
4	(Intercept)	458.64	421.96 : 495.33	18.88	24.29	<.001	87.99	4754.888	5.47	.60
	WM-load: 1-back	42.73	10.71 : 74.75	16.43	2.60	.01	52.94			
	WM-load: 2-back	94.52	62.50 : 126.55	16.43	5.75	<.001				
	Flanker type: neutral	-7.39	-27.73 : 12.95	10.47	-0.71	.48	38.23			
	Group: control	-12.18	-65.88 : 41.51	27.30	-0.45	.66	-			
	WM-load: 1-back * Flanker Type: neutral	-4.62	-33.39 : 24.14	14.80	-0.31	.76	-			
	WM-load: 2-back * Flanker Type: neutral	7.99	-20.78 : 36.75	14.80	0.54	.59	-			
	WM-load: 1-back * Group: control	15.73	-30.57 : 62.03	23.76	0.66	.51	-			
	WM-load: 2-back * Group: control	30.70	-15.60 : 77.00	23.76	1.29	.20	-			
	Flanker type: neutral * Group: control	21.91	-7.50 : 51.33	15.14	1.45	.15	-			
	WM-load: 1-back * Flanker Type: neutral * Group: control	-14.40	-55.99 : 27.20	21.41	-0.67	.50	-			
	WM-load: 2-back * Flanker Type: neutral * Group: control	-15.39	-56.99 : 26.20	21.41	-0.72	.47	-			

Mixed model results using random intercept and maximum likelihood estimation; CI: Confidence Interval; SE: Standard Error; SD: Standard deviation; AIC: Akaike information criterion.
Note: final models as presented in the manuscript are presented in italic.

Table S2. Activation overview for the flanker and working memory (WM) contrasts

				MNI coordinates			
	Cluster size (voxels)	**Brain regions**	**Hemisphere**	**X**	**Y**	**Z**	**Zmax**
Flanker							
c > n	469	IFG	Left	-50	26	12	4.17
n > c	44257	Intracalcerine cortex	Left	-18	-86	4	5.46
		Frontal pole	Right	36	58	-2	5.40
		Lingual gyrus	Right	10	-84	-4	5.36
		Lingual gyrus	Left	-6	-84	-6	5.34
		Occipital Pole	Left	-10	-94	2	5.21
	1363	Frontal pole	Left	-30	58	-10	4.57
WM							
2 > 1	38581	MFG	Left	-30	4	58	7.13
		Insula	Right	30	20	8	6.24
		SFG/Paracingulate gyrus	Left	-8	16	48	6.08
	13625	Precuneus	Left	-6	-68	50	6.37
		Lateral occipital	Left	-30	-70	34	6.36
		SPL	Left	-32	-50	42	5.89
		SMG	Left	-38	-48	40	5.86
1 > 2	10178	MFG/Paracingulate gyrus	Left	-8	40	-10	5.66
	1160	Central operculum	Right	42	-14	16	4.17
	1139	Cingulate gyrus	Left	-2	-48	30	5.62
	606	Central operculum	Left	-44	0	14	4.11

MNI = Montreal Neurological Institute; MNI coordinates and Z-scores of separate local maxima for each cluster (whole-brain cluster-corrected at $p < 0.05$, $Z > 2.3$); c = cannabis flanker, n = neutral flanker; 1 = 1-back, 2 = 2-back; IFG = Inferior Frontal Gyrus, MFG = Medial Frontal Gyrus, SFG = Superior Frontal Gyrus, SPL = Superior Parietal Lobe, SMG = Supramarginal Gyrus.

Appendix E

Supplementary materials chapter 8

Study 1 (N = 106)
This study included individuals that used cannabis on a near-daily basis but were not in treatment for CUD (Regular users) and a matched control group that used little or no cannabis and had not used recently (Never-sporadic and Occasional users) and was conducted over multiple years between 2019 and 2021. Craving was assessed using a visual analogue scale (VAS) at the start and the end of the session. Total session length was approximately 4 hours, including MRI procedures. Stroop data collected in this study was not published before due to recent completion of the study.

Study 2 (N = 68)
This study included individuals that used cannabis multiple times a week but were not in treatment for CUD (Regular users) and a matched control group that used little or no cannabis and had not used recently (Never-sporadic and Occasional users). Craving was assessed using the Marijuana Craving Questionnaire (MCQ; Heishman et al., 2001) at the start and the end of the session. Total session length was approximately 3 hours, including MRI procedures. Stroop data collected in this study was not published before due to the small sample size of the individual dataset.

Study 3 (N = 58, N = 55 included)
This study included individuals that used cannabis multiple times a week but were not in treatment for CUD (Regular users) and a matched control group that used little or no cannabis and had not used recently (Never-sporadic and Occasional users). Craving was assessed using the MCQ at the start and the end of the session. Total session length was approximately 3 hours, including MRI procedures. Stroop data collected in this study was published before (Cousijn, Watson, et al., 2013).

Study 4 (N = 40)
This study included individuals in treatment for CUD (CUD users). Craving was assessed using a VAS at the start and the end of the session. Total session length was approximately 45 minutes. Stroop data collected in this study was published before (van Kampen et al., 2020).

Study 5 (N = 57)
This study included individuals in treatment for CUD (CUD users) and was conducted over multiple years between 2012 and 2014. Craving was assessed using a VAS at the start and the end of the session. Total session length was less than 1 hour and took place in the addiction care facility. Stroop data collected in this study was published before (Cousijn et al., 2015).

Study 6 (N = 90, N = 86 included)
This study included individuals that used cannabis multiple times a week (some exceptions included, see Table S1) but were not in treatment for CUD (Regular users). Session induced craving was assessed using the MCQ at the start and the end of the session. Total session length was approximately 30 minutes and conducted within a Dutch cannabis dispensary. Stroop data collected in this study was published before (Cousijn, Snoek, et al., 2013).

Study 7 (N = 93, N = 90 included)
This study included individuals that used cannabis multiple times a week but were not in treatment for CUD (Regular users). Craving was assessed using the MCQ at the start and the end of the session. Total session length was approximately 45 minutes. Stroop data collected in this study was published before (Cousijn & van Duijvenvoorde, 2018).

Study 8 (N = 48)
This study included individuals that used cannabis multiple times a week but were not in treatment for CUD (Regular users) and a matched control group that used little to no cannabis (Never-sporadic users). Craving was assessed using a VAS at the start and the end of the session. Total session length was approximately 2 hours. Stroop data collected in this study was not published before due to the small sample size of the individual dataset. No AUDIT scores were recorded in this study.

Figure S1. Overview of included studies

Deviations from the pre-registration

All deviations from the pre-registration are referred to as exploratory analysis in the manuscript. Details on the deviations are provided below.

Additional Variables
In addition to the pre-registered session induced craving variable (the change between start of session and end of session craving), we have added a measure of average session craving (the average of start of session and end of session craving). While the session induced craving measure reflects the craving that builds over the time of the test session, potentially affected by drug cue exposure during the session, this increase or decrease does not reflect the absolute level of craving one experiences. Hence, we included a measure that better reflects the extent to which one craves cannabis at the moment of testing.
Additional Analyses
All correlational, simple regression, moderation, mediation, and moderated mediation models that included session induced craving (as pre-registered) were re-ran using average session craving instead.
Multiple comparison corrections
Unlike pre-registered, Bonferroni corrections for multiple comparison corrections were applied to the correlation and simple regression analyses. For these analyses, uncorrected and corrected p-values are provided in the manuscript.

Figure S2. Overview of deviations from the pre-registration

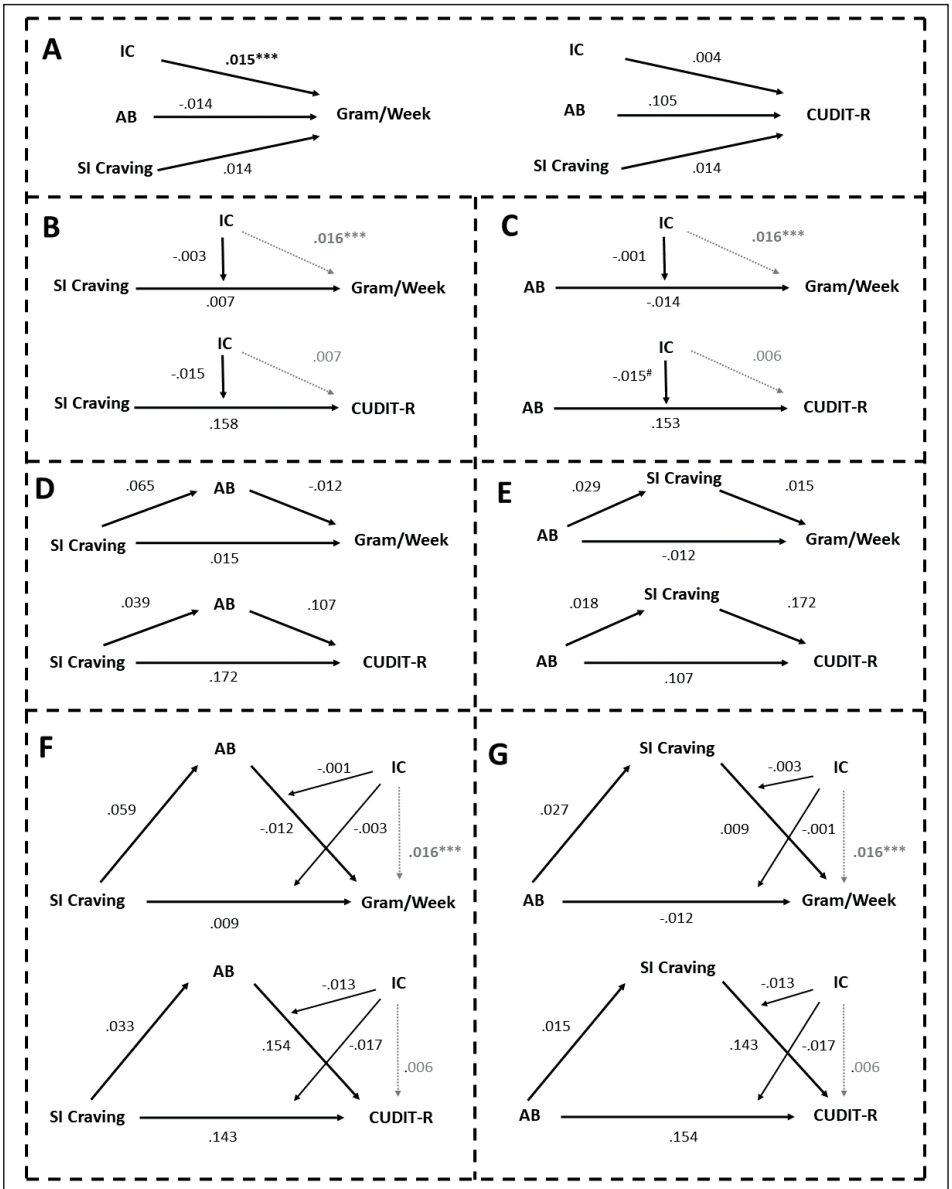


Figure S3. Regression, moderation, mediation, and moderated-mediation analysis results. The associations between session induced (SI) craving, attentional bias (AB), and interference control (IC) in their relationship with heaviness (gram/week) and severity of cannabis use (CUDIT-R). *** $p < .001$, see Table S2-S5 for exact p-values.

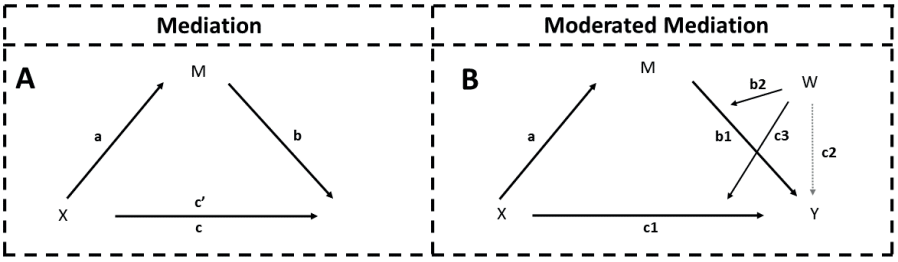


Figure S4. Overview of statistical models used to assess mediation and moderated mediation. A) direct effect: c'; indirect effect: ab; total effect: direct + indirect, **B)** direct effect: c1 + c3W; indirect effect: a(b1+b2W); total effect: direct + indirect; index of moderated mediation: ab2

Table S1. Overview of participants per included study

	Never-Sporadic	Occasional	In between	Regular	CUD	Total
Study 1	22	21	x	63	X	106
Study 2	28	5	x	35	X	68
Study 3	24	7	3	24	X	55 (58)
Study 4	x	x	x	x	40	40
Study 5	x	x	x	x	57	57
Study 6	x	2	4	84	X	86 (90)
Study 7	x	x	1	92	X	92 (93)
Study 8	23	x	x	25	X	48
Total	97	35	8	323	97	552 (560)

Note: all excluded participants and totals including those participants presented in grey, all included participants presented in black.

Table S2. Correlation table displaying within person (N = 40) correlation of different standardized measures of craving and their association with included measures of cannabis use

	MCQ craving average	MCQ craving change	VAS craving average	VAS craving change	CUDIT-R	Gram/Week
MCQ craving average	-	-	-	-	-	-
MCQ craving change	r = .436 p = .005	-	-	-	-	-
VAS craving average	r = .806 p <.001	r = .452 p = .003	-	-	-	-
VAS craving change	r = .149 p = .358	r = .500 p = .001	r = .257 p = .109	-	-	-
CUDIT-R	r = .364 p = .021	r = .131 p = .422	r = .293 p = .067	r = .122 p = .452	-	-
Gram/Week	r = .455 p = .003	r = .184 p = .255	r = .540 p < .001	r = -.119 p = .463	r = .420 p = .007	-

Note: CUDIT-R; cannabis use disorder identification tests – revised; MCQ: marijuana craving questionnaire, VAS: visual analogue scale

Table S3. Simple regression results							
Model	**Results**						
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	-.057	.346	-.737 - .624	.164	.870	1.0	$F(1,338) = 1.301$, $R^2 <$
SI Craving	.171	.150	-.124 - .467	1.141	.255	.765	.001, $p = .255$, $p_{bonf} = .765$
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	-.013	.341	-.684 - .659	.037	.970	1.0	$F(1,350) = .023$, $R^2 = -.003$,
Interference control	.004	.027	-.050 - .058	.150	.881	1.0	$p = .881$, $p_{bonf} = 1.0$
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	.015	.341	-.656 -0.685	.043	.966	1.0	$F(1,352) = 1.082$, $R^2 <$
Attentional bias	.104	.101	-.093 - .303	1.04	.299	.897	.001, $p = .299$, $p_{bonf} = .897$
Grams per week	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	.994	.052	.891 - 1.096	19.064	<.001	<.001	$F(1,330) = .383$, $R^2 = -.002$,
SI Craving	.014	.023	.031 - .060	.619	.536	1.0	$p = .536$, $p_{bonf} = 1.0$
Grams per week	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	1.004	.050	.905 - 1.103	20.025	<.001	<.001	$F(1,343 = 14.23$, $R^2 = .037$,
Interference control	.015	.004	.007 - .023	3.772	**<.001**	**<.001**	$p < .001$, $p_{bonf} < .001$
Grams per week	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	**p_{bonf}**	**F-test**
Intercept	.999	.051	.899 - 1.098	19.710	<.001	<.001	$F(1,347) = .807$, $R^2 < .001$,
Attentional bias	-.014	.015	-.043 - .016	-.899	.370	1.0	$p = .370$, $p_{bonf} = 1.0$

Note: CUDIT-R: cannabis use disorder identification test; p_{bonf} : Bonferroni corrected p-values; SI craving: session induced craving; SE: standard error; R^2: adjusted R-squared

Table S4. Moderation results						
Model	**Results**					
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	**p_{bonf}**
Intercept	-.055	.347	-.735 - .625	.158	.874	1.0
SI Craving	.158	.151	-.138 - .455	1.046	.295	.591
Interference control	.007	.028	-.048 - .061	.241	.810	1.0
SI Craving * Interference control	-.015	.013	-.041 - .011	1.137	.255	.511
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	**p_{bonf}**
Intercept	.040	.341	-.629 - .709	.117	.907	1.0
Attentional bias	.153	.104	.000 - .023	1.470	.141	.282
Interference control	.006	.027	-.103 - .143	.211	.833	1.0
Attentional bias * Interference control	-.015	.008	-.018 - .001	1.964	.050	.099
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	**p_{bonf}**
Intercept	.999	.051	.899 - 1.100	19.470	<.001	<.001
SI Craving	.007	.024	-.018 - .130	.296	.767	1.0
Interference control	.016	.004	.294 - .803	3.826	**<.001**	**<.001**
SI Craving * Interference control	-.003	.002	-.129 - .025	1.240	.215	.430
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***P***	**p_{bonf}**
Intercept	1.005	.050	.907 - 1.104	20.084	<.001	<.001
Attentional bias	-.014	.015	-.044 - .016	.904	.366	.732
Interference control	.016	.004	.008 - .024	3.936	**<.001**	**<.001**
Attentional bias * Interference control	-.001	.001	-.003 - .001	.810	.418	.836

Note: CUDIT-R: cannabis use disorder identification test; p_{bonf} : Bonferroni corrected p-values; SI craving: session induced craving; SE: standard error; Maximum likelihood estimation used in all models.

Table S5. Mediation results						
Model	**Results**					
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ SI Craving (c)	.172	.153	-.127 - .471	1.128	.259	.519
Attentional Bias ~ SI Craving (a)	.039	.081	-.120 - .199	.483	.629	1.0
CUDIT-R ~ Attentional Bias (b)	.107	.102	-.093 - .307	1.047	.295	.591
Indirect (ab)	.004	.010	-.015 - .023	.438	.661	1.0
Direct (c`)	.172	.153	-.127 - .471	1.128	.259	.519
Total (ab + c`)	.176	.153	-.123 - .476	1.154	.248	.497
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ Attentional bias (c)	.107	.102	-.002 - .006	1.047	.295	.591
SI Craving ~ Attentional bias (a)	.018	.036	-.028 - .042	.483	.629	1.0
CUDIT-R ~ SI Craving (b)	.172	.153	-.005 - .020	1.128	.259	.519
Indirect (ab)	.003	.007	.000 - .000	.444	.657	1.0
Direct (c`)	.107	.102	-.002 - .006	1.047	.295	.591
Total (ab + c`)	.110	.102	-.002 - .006	1.075	.283	.565
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Grams/Week ~ SI Craving (c)	.015	.023	-.030 - .061	.656	.512	1.0
Attentional Bias ~ SI Craving (a)	.065	.083	-.096 - .227	.793	.428	.856
Grams/Week ~ Attentional Bias (b)	-.012	.015	-.043 - .018	.806	.420	.841
Indirect (ab)	-.001	.001	-.004 - .002	.565	.572	1.0
Direct (c`)	.015	.023	-.030 - .061	.656	.512	1.0
Total (ab + c`)	.014	.023	-.032 - .060	.621	.535	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Grams/Week ~ Attentional bias (c)	-.012	.015	-.043 - .018	.806	.420	.841
SI Craving ~ Attentional bias (a)	.029	.036	-.043 - .100	.793	.428	.856
Grams/Week ~ SI Craving (b)	.015	.023	-.030 - .061	.656	.512	1.0
Indirect (ab)	.000	.001	-.001 - .002	.505	.613	1.0
Direct (c`)	-.012	.015	-.043 - .018	.806	.420	.840
Total (ab + c`)	-.012	.015	-.042 - .018	.778	.437	.874

Note: CUDIT-R: cannabis use disorder identification test; p_{bonf} *: Bonferroni corrected p-values; SI craving: session induced craving; SE: standard error; Maximum likelihood estimation used in all models.*

Table S6. Moderated-Mediation results						
Model	**Results**					
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ SI Craving (c1)	.143	.158	-.167 - .452	.904	.366	.732
Attentional Bias ~ SI Craving (a)	.033	.081	-.126 - .192	.407	.684	1.0
CUDIT-R ~ Attentional bias (b1)	.154	.103	-.048 - .355	1.496	.135	.269
CUDIT-R ~ Interference control (c2)	.006	.028	-.049 - .061	.219	.826	1.0
CUDIT-R ~ Attentional bias * Interference control (b2)	-.013	.008	-.029 - .002	1.732	.083	.167
CUDIT-R ~ SI Craving * Interference control (c3)	-.017	.015	-.047 - .013	1.111	.267	.533
Indirect (a(b + b2W))	.005	.013	-.021 - .031	.393	.694	1.0
Direct (c1+c3W)	.146	.158	-.163 - .455	.924	.356	.711
Total (direct+indirect)	.151	.158	-.159 - .461	.954	.340	.681
Index of moderated mediation (ab2)	-.000	.001	-.003 - .002	.397	.692	1.0
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ Attentional bias (c1)	.154	.106	-.054 - .361	1.453	.146	.292
SI Craving ~ Attentional bias (a)	.015	.037	-.057 - .088	.407	.684	1.0
CUDIT-R ~ SI Craving (b1)	.143	.152	-.155 - .441	.939	.348	.695
CUDIT-R ~ Interference control (c2)	.006	.028	-.049 - .062	.219	.826	1.0
CUDIT-R ~ SI Craving * Interference control (b2)	-.017	.015	-.046 - .012	1.153	.249	.498
CUDIT-R ~ Attentional bias * Interference control (c3)	-.013	.008	-.029 - .002	1.683	.092	.185
Indirect (a(b + b2W))	.002	.006	-.009 - .014	.375	.708	1.0
Direct (c1+c3W)	.156	.106	-.053 - .364	1.465	.143	.286
Total (direct+indirect)	.158	.107	-.051 - .367	1.483	.138	.276
Index of moderated mediation (ab2)	-.000	.001	-.002 - .001	.384	.701	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***P***	p_{bonf}
Gram/Week ~ SI Craving (c1)	.009	.024	-.038 - .055	.366	.715	1.0
Attentional Bias ~ SI Craving (a)	.059	.082	-.102 - .221	.720	.471	.943
Gram/Week ~ Attentional bias (b1)	-.012	.015	-.042 - .017	.814	.416	.832
Gram/Week ~ Interference control (c2)	.016	.004	.008 - .024	3.963	**<.001**	**<.001**
Gram/Week ~ Attentional bias * Interference control (b2)	-.001	.001	-.003 - .001	.774	.439	.878
Gram/Week ~ SI Craving * Interference control (c3)	-.003	.002	-.007 - .002	1.169	.242	.485
Indirect (a(b + b2W))	-.001	.001	-.003 - .002	.535	.593	1.0
Direct (c1+c3W)	.009	.024	-.037 - .056	.394	.694	1.0
Total (direct+indirect)	.009	.024	-.038 - .055	.363	.716	1.0
Index of moderated mediation (ab2)	-.000	.000	.000 - .000	.527	.598	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Gram/Week ~ Attentional bias (c1)	-.012	.016	-.043 – .018	.792	.428	.857
SI Craving ~ Attentional bias (a)	.027	.037	-.046 - .099	.720	.471	.943
Gram/Week ~ SI Craving (b1)	.009	.023	-.036 - .053	.384	.701	1.0
Gram/Week ~ Interference control (c2)	.016	.004	.008 - .024	3.963	**<.001**	**<.001**
Gram/Week ~ SI Craving * Interference control (b2)	-.003	.002	-.007 - .002	1.226	.220	.440
Gram/Week ~ Attentional bias * Interference control (c3)	-.001	.001	-.003 - .001	.754	.451	.901
Indirect (a(b + b2W))	.000	.001	-.001 - .002	.357	.721	1.0
Direct (c1+c3W)	-.012	.016	-.043 - .019	.775	.438	.877
Total (direct+indirect)	-.012	.016	-.043 - .019	.759	.448	.896
Index of moderated mediation (ab2)	-.000	.000	.000 - .000	.621	.535	1.0

Note: CUDIT-R: cannabis use disorder identification test; p_{bonf} *: Bonferroni corrected p-values; SI craving: session induced craving; SE: standard error; Maximum likelihood estimation used in all models; See Figure S2 & Figure S3 for additional information on the included models.*

Table S7. Results of exploratory simple regression analyses including average session (AS) craving instead of session induced (SI) craving

Model			Results				
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	p_{bonf}	**F-test**
Intercept	-.056	.333	-.711 - .599	.169	.866	1.0	$F(1,338) = 28.19$, $R^2 = .074$, $p < .001$, $p_{bonf} < .001$
AS Craving	1.755	.330	1.11 - 2.41	5.309	**<.001**	**<.001**	
Grams per week	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	p_{bonf}	**F-test**
Intercept	-.019	.214	-.440 - .401	.090	.928	1.0	$F(1,330) = 20.93$, $R^2 = .057$, $p < .001$, $p_{bonf} < .001$
AS Craving	.977	.214	.557 - 1.40	4.575	**<.001**	**<.001**	

Note: AS craving: average session craving; CUDIT-R: cannabis use disorder identification test; p_{bonf} *: Bonferroni corrected p-values; SE: standard error;* R^2*: adjusted R-squared*

Table S8. Results of exploratory moderation & mediation analyses including average session (AS) craving instead of session induced (SI) craving

Moderation						
Model	**Results**					
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Intercept	-.059	.336	-.717 - .599	-.175	.850	1.0
AS Craving	1.844	.330	1.197 – 2.490	5.595	**<.001**	**<.001**
Interference control	-.016	.027	-.068 - .037	.589	.556	1.0
AS Craving * Interference control	-.004	.024	-.051 - .042	.183	.855	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Intercept	.023	.213	-.394 - .440	.107	.915	1.0
AS Craving	.919	.211	.507 - 1.332	4.367	**<.001**	**<.001**
Interference control	.056	.017	.023-.089	3.313	**.001**	**.002**
AS Craving * Interference control	-.010	.015	-.040 - .019	.679	.497	.994
Mediation						
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ AS Craving (c)	1.733	.336	1.075 - 2.392	5.160	**<.001**	**<.001**
Attentional Bias ~ AS Craving (a)	.545	.181	.191 - .900	3.013	**.003**	**.005**
CUDIT-R ~ Attentional Bias (b)	.027	.100	-.169 - .222	.267	.790	1.0
Indirect (ab)	.014	.055	-.092 - .121	.266	.790	1.0
Direct (c`)	1.733	.336	1.075 - 2.392	5.160	**<.001**	**<.001**
Total (ab + c`)	1.748	.332	1.098 - 2.398	5.272	**<.001**	**<.001**
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ Attentional bias (c)	.027	.100	-.169 - .222	.267	.790	1.0
AS Craving ~ Attentional bias (a)	.048	.016	.017 - .079	3.013	**.003**	**.005**
CUDIT-R ~ AS Craving (b)	1.733	.336	1.075 - 2.392	5.160	**<.001**	**<.001**
Indirect (ab)	.083	.032	.021 - .146	2.602	**.009**	**.019**
Direct (c`)	.027	.100	-.169 - .222	.267	.790	1.0
Total (ab + c`)	.110	.102	-.090 - .310	1.075	.283	.567
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Grams/Week ~ AS Craving (c)	1.033	.215	.611 - 1.454	4.803	**<.001**	**<.001**
Attentional Bias ~ AS Craving (a)	.552	.183	.194 - .910	3.019	**.003**	**.005**
Grams/Week ~ Attentional Bias (b)	-.101	.064	-.225 - .024	1.578	.114	.229
Indirect (ab)	-.055	.040	-.133 - .022	1.399	.162	.324
Direct (c`)	1.033	.215	.611 - 1.454	4.803	**<.001**	**<.001**
Total (ab + c`)	.977	.213	.560 - 1.395	4.589	**<.001**	**<.001**
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
Grams/Week ~ Attentional bias (c)	-.101	.064	-.225 - .024	1.578	.114	.229
AS Craving ~ Attentional bias (a)	.048	.016	.017 - .080	3.019	**.003**	**.005**
Grams/Week ~ AS Craving (b)	1.033	.215	.611 - 1.454	4.803	**<.001**	**<.001**
Indirect (ab)	.050	.020	.012 - .088	2.556	**.011**	**.021**
Direct (c`)	-.101	.064	-.225 - .024	1.578	.114	.229
Total (ab + c`)	-.051	.065	-.178 - .077	.778	.437	.873

Note: AS craving: average session craving; CUDIT-R: cannabis use disorder identification test; p_{bonf} : Bonferroni corrected p-values; SE: standard error; R^2: adjusted R-squared; Maximum likelihood estimation used in all models.

Table S9. Results of exploratory moderated-mediation analyses including average session (AS) craving instead of session induced (SI) craving

Model	Results					
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ AS Craving (c1)	1.794	.335	1.137 - 2.450	5.353	**<.001**	**<.001**
Attentional Bias ~ AS Craving (a)	.552	.180	.198 - .906	3.059	**.002**	**.004**
CUDIT-R ~ Attentional bias (b1)	.064	.100	-.133 - .261	.637	.524	1.0
CUDIT-R ~ Interference control (c2)	-.012	.027	-.065 - .040	.458	.647	1.0
CUDIT-R ~ Attentional bias * Interference control (b2)	-.012	.008	-.027 - .003	1.512	.130	.260
CUDIT-R ~ AS Craving * Interference control (c3)	.007	.025	-.042 - .055	.262	.793	1.0
Indirect (a(b + b2W))	.036	.057	-.075 - .148	.641	.522	1.0
Direct (c1+c3W)	1.793	.335	1.136 - 2.449	5.350	**<.001**	**<.001**
Total (direct+indirect)	1.829	.331	1.181 - 2.477	5.532	**<.001**	**<.001**
Index of moderated mediation (ab2)	-.006	.005	-.016 - .003	1.356	.175	.350
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	p_{bonf}
CUDIT-R ~ Attentional bias (c1)	.064	.103	-.139 - .267	.618	.537	1.0
AS Craving ~ Attentional bias (a)	.050	.016	.018 - .081	3.059	**.002**	**.004**
CUDIT-R ~ AS Craving (b1)	1.794	.335	1.137 - 2.450	5.354	**<.001**	**<.001**
CUDIT-R ~ Interference control (c2)	-.012	.027	-.065 - .040	.458	.647	1.0
CUDIT-R ~ AS Craving * Interference control (b2)	.007	.025	-.042 - .055	.261	.794	1.0
CUDIT-R ~ Attentional bias * Interference control (c3)	-.012	.008	-.027 - .004	1.465	.143	.286
Indirect (a(b + b2W))	.089	.033	.023 - .154	2.655	**.008**	**.016**
Direct (c1+c3W)	.066	.104	-.138 - .270	.633	.527	1.0
Total (direct+indirect)	.155	.107	-.055 - .364	1.448	.147	.295
Index of moderated mediation (ab2)	.000	.001	-.002 - .003	.260	.795	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***P***	p_{bonf}
Gram/Week ~ AS Craving (c1)	.975	.213	.558 - 1.392	4.588	**<.001**	**<.001**
Attentional Bias ~ AS Craving (a)	.559	.182	.202 - .916	3.069	**.002**	**.004**
Gram/Week ~ Attentional bias (b1)	-.106	.064	-.231 - .018	1.672	.095	.189
Gram/Week ~ Interference control (c2)	.058	.017	.025 - .091	3.460	**.001**	**.001**
Gram/Week ~ Attentional bias * Interference control (b2)	-.002	.005	-.011 - .008	.360	.719	1.0
Gram/Week ~ AS Craving * Interference control (c3)	-.009	.016	-.040 - .022	.574	.566	1.0
Indirect (a(b + b2W))	-.059	.040	-.138 - .020	1.463	.143	.287
Direct (c1+c3W)	.977	.213	.561 - 1.394	4.598	**<.001**	**<.001**
Total (direct+indirect)	.918	.210	.506 - 1.330	4.362	**<.001**	**<.001**
Index of moderated mediation (ab2)	-.001	.003	-.006 - .004	.358	.720	1.0
Grams per week	***B***	***SE* (B)**	**95%*CI***	***z***	***p***	
Gram/Week ~ Attentional bias (c1)	-.106	.065	-.234 - .022	1.624	.104	.209
AS Craving ~ Attentional bias (a)	.050	.016	.018 - .082	3.069	**.002**	**.004**
Gram/Week ~ AS Craving (b1)	.975	.212	.559 - 1.391	4.591	**<.001**	**<.001**
Gram/Week ~ Interference control (c2)	.058	.017	.025 - .091	3.460	**.001**	**.001**
Gram/Week ~ AS Craving * Interference control (b2)	-.009	.016	-.040 - .022	-.572	.567	1.0
Gram/Week ~ Attentional bias * Interference control (c3)	-.002	.005	-.012 - .008	-.350	.726	1.0
Indirect (a(b + b2W))	.049	.019	.011 - .086	2.552	**.011**	**.021**
Direct (c1+c3W)	-.106	.066	-.235 - .023	1.610	.107	.215
Total (direct+indirect)	-.057	.067	-.188 - .074	.852	.394	.788
Index of moderated mediation (ab2)	-.000	.001	-.002 - .001	.563	.574	1.0

Note: AS craving: average session craving; CUDIT-R: cannabis use disorder identification test; p_{bonf} : Bonferroni corrected p-values; SE: standard error; Maximum likelihood estimation used in all models; See Figure S2 & Figure S3 for additional information on the included models.

Table S10. Results of regression analyses assessing the association between interference control and heaviness and severity of use in individuals in treatment for CUD.

Model	**Results**						
CUDIT-R	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	p_{bonf}	**F-test**
Intercept	-.121	.705	-.1.524 - 1.282	.172	.864	1.0	$F(1,84) < .001$, $R^2 = -.012$, $p = .978$, $p_{bonf} = 1.0$
Interference control	.001	.056	-.110 - .113	.027	.978	1.0	
Grams per week	***B***	***SE* (B)**	**95%*CI***	***t***	***p***	p_{bonf}	**F-test**
Intercept	-.252	.938	-2.126 - 1.620	.269	.788	1.0	$F(1,65) = 1.482$, $R^2 = .007$, $p = .228$, $p_{bonf} = .455$
Interference control	.091	.075	-.059 - .241	1.218	.228	.455	

Note: CUDIT-R: cannabis use disorder identification test; p_{bonf} : Bonferroni corrected p-values; SE: standard error; R^2: adjusted R-squared

Appendix F

Supplementary materials chapter 9

Table S1. Exclusion overview					
Reason for exclusion	**CUD**		**Control**		**Total**
	NL	**US**	**NL**	**US**	
Original sample	**74**	**51**	**50**	**36**	**211**
Data quality exclusion	6	4	2	3	**15**
Brain anomaly exclusion	0	0	1	0	**1**
Positive drug test exclusion	4	1	1	0	**6**
Total Excluded	10	5	4	3	**22**
Total Included	**64**	**46**	**46**	**33**	**189**
Note. CUD = cannabis use disorder					

Table S2. Sample characteristics split over sites

Measure	Unit	NL			TX			ANOVA result	Post-Hoc
		CUD (N=64)	Control (N=46)	Total (N=110)	CUD (N=46)	Control (N=33)	Total (N=79)		
Gender[1]	%m/f/o	31.25/68.75/0	52.17/47.83/0	60.00/40.00/0	58.70/39.13/2.17	63.64/36.36/0	37.98/60.76/1.27	-	1,4,6
Age	M(SD)	21.89(3.49)	22.20(3.19)	22.02(3.36)	24.46(2.52)	23.55(3.12)	24.08(2.81)	Site	4,5
Education years	M(SD)	16.45(2.82)	17.48(2.20)	16.88(2.58)	14.34(2.64)	15.29(2.50)	14.73(2.61)	Site, Group	4,5,3
Estimated IQ	M(SD)	8.23(2.26)	9.40(2.00)	8.72(2.23)	11.66(1.92)	12.72(1.61)	12.23(1.82)	Site, Group	1,3,4,5,6
BDI	M(SD)	11.39(8.84)	6.72(4.90)	9.44(7.77)	12.89(9.25)	4.55(5.90)	9.41(8.99)	Group	1,2,5,6
STAI-trait	M(SD)	39.80(10.39)	35.33(8.54)	37.93(9.87)	41.89(10.40)	33.73(7.79)	38.48(10.42)	Group	1,2,5
DSM-cross level 1	M(SD)	14.28(7.79)	10.67(4.45)	12.77(6.81)	18.11(10.40)	7.97(6.37)	13.87(10.21)	Site*Group	2,5,6
AUDIT	M(SD)	6.08(3.12)	7.25(4.10)	6.57(3.60)	6.38(3.67)	3.92(1.32)	5.67(3.35)	Site*Group	3
Daily smoker	%yes/no	48.44/51.56	23.91/76.09	38.18/61.82	6.52/93.48	0/100.00	3.80/96.20	-	1,4,5
Cigarettes per day	M(SD)	8.13(4.31)	7.00(3.00)	7.83(4.00)	7.00(6.00)	-	7.00(6.00)	-	1,4,5
Other drug use	M(SD)	2.89(2.39)	1.26(1.79)	2.21(2.30)	2.24(1.62)	.21(.42)	1.35(1.64)	Group	1,6
Cannabis use and related problems									
CUD symptoms	M(SD)	5.38(2.03)	-	-	5.98(2.18)	-	-	-	-
MPS	M(SD)	7.80(5.88)	-	-	4.61(4.19)	-	-	-	4
Gram/Week	M(SD)	6.42(4.58)	-	-	12.85(9.03)	-	-	-	4
CUDIT-R	M(SD)	15.88(5.41)	-	-	16.33(5.45)		-	-	-
Last month use days	M(SD)	26.89(7.45)	-	-	26.59(8.67)	-	-	-	-
Age of onset	M(SD)	15.58(1.48)	-	-	16.76(2.21)	-	-	-	4
Cultural attitudes									
Pos: Personal	M(SD)	22.89(4.69)	17.61(3.70)	20.68(5.02)	27.09(2.10)	17.97(4.34)	23.28(5.55)	Site*Group	1,2,4,5,6
Pos: Friends/Family	M(SD)	19.25(4.53))	17.07(3.57)	18.34(4.27)	22.28(5.90)	16.00(5.47)	19.66(5.99)	Site*Group	2,4,5,6
Pos: Country/State	M(SD)	17.11(3.55)	16.65(3.20)	16.92(3.40)	17.83(5.24)	15.15(4.50)	16.71(4.76)	Group	2
Neg: Personal	M(SD)	16.72(4.01)	19.63(4.55)	17.94(4.46)	12.00(3.75)	18.79(4.34)	14.84(5.21)	Site*Group	1,2,4,5
Neg: Friends/Family	M(SD)	19.89(4.56)	20.57(4.38)	20.17(4.48)	16.63(4.73)	20.49(5.55)	18.24(5.40)	Site*Group	2,4,5
Neg: Country/State	M(SD)	23.19(3.80)	21.96(4.07)	22.67(3.94)	21.67(5.00)	22.79(5.20)	22.14(5.06)	-	-

Note. All comparisons of continuous data represent significance levels of ANOVAs and Bonferroni corrected post hoc independent sample t-tests; All comparison of categorical data represent significance level of Chi-Square tests; [1] individuals identifying with a non-binary gender were omitted from the comparison tests; AUDIT: Alcohol Use Disorder Identification Test; BDI-II: Beck's Depression Inventory II; CUDIT-R: Cannabis Use Disorder Identification Test – Revised; M: Mean; MAD: Median Absolute Deviation; Med: median; MINI CUD: Mini International Neuropsychiatric Interview – Cannabis Use Disorder; MPS: Marijuana Problem Scale; Neg: negative; Pos: positive; SD: Standard deviation; STAI: State Trait Anxiety Inventory; 1 = NL-CON vs. NL-CAN; 2 = TX-CON vs. TX-CAN; 3 = NL-CON vs. TX-CON; 4 = NL-CAN vs. TX-CAN; 5 = NL-CON vs. TX-CAN; 6 = NL-CAN vs. TX-CON; * $p < .05$, ** $p < .01$, *** $p < .001$

Table S3. The effect of group, and cannabis culture questionnaire level on positive and negative attitudes towards cannabis

Model	**Model coefficients**					
	Fixed effects					**Random effects**
Positive attitudes	***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***
Intercept	17.409	16.607:18.211	.410	42.447	**<.001**	2.347
Group: CUD-CON	-1.384	-2.629:-0.139	.634	-2.181	**.030**	-
Perspective: CS-FF	3.109	2.161:4.058	.485	6.411	**<.001**	3.330
Perspective: CS-P	7.236	6.288:8.185	.485	14.921	**<.001**	
Group: CUD-CON * Perspective: CS-FF	-2.502	-3.981:-1.047	.750	-3.352	**<.001**	-
Group: CUD-CON * Perspective: CS-P	-5.502	-6.969:-4.035	.750	-7.335	**<.001**	-
Negative attitudes	***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***
Intercept	22.555	21.695:23.415	.440	51.293	**<.001**	2.801
Group: CUD-CON	-.251	-1.585:1.084	.680	-.369	.713	-
Perspective: CS-FF	-4.027	-4.991:-3.064	.492	-8.177	**<.001**	3.363
Perspective: CS-P	-7.809	-8.772:-6.846	.492	-15.856	**<.001**	
Group: CUD-CON * Perspective: CS-FF	2.255	.765:3.745	.762	2.960	**.003**	-
Group: CUD-CON * Perspective: CS-P	4.784	3.294:6.274	.762	6.280	**<.001**	-

Linear mixed model results using random intercept and maximum likelihood estimation; AIC: Akaike information criterion, BM: baseline model, CI: Confidence Interval, CON: control group, CS: country-state, CUD: cannabis users with cannabis use disorder group, FF: friends-family, P: personal, NL: Netherlands, SE: Standard Error, SD: Standard deviation, TX: Texas; CAN, NL & CS were used as the reference categories. Final models as discussed in the manuscript are presented in italic and significant results are presented in bold. Model – Positive attitudes: AIC = 3229.263 (ΔAIC best fit simpler model = 46.921). Model – Negative attitudes: AIC = 3283.460 (ΔAIC best fit simpler model = 33.934)

Table S4. fMRI results within-network resting state functional connectivity

Network	Comparison/ Association	Direction	Cluster Size (voxels)	Brain regions	Hemisphere	MNI coordinates			p-value
						X	Y	Z	
Group differences									
dSN	CON vs. CUD	CON>CUD	7	Lateral Occipital Lobe, SPL, Precuneus	Right	12	-57	64	<.04
Associations with measures of cannabis use									
dSN	Gram/Week[1]	Negative	1	SMG	Right	58	-27	50	<.05
Moderating effects of cannabis attitudes									
CUD score									
vDMN	PosCS	-	22	Precuneus	Left/Right	-3	-67	52	<.04
aSN	NegCS	-	90	Frontal Pole	Right	32	48	24	<.01*
MPS score									
dDMN	PosP	-	70	Precuneus, PCC	Right	8	-61	22	<.02
dDMN	PosFF	-	169	Paracingulate, ACC	Left	-5	42	18	<.01*
dDMN	PosCS	-	38	Paracingulate, ACC	Right	6	48	12	<.03
dDMN	NegCS	-	255	Paracingulate, ACC	Left/Right	-5	44	18	<.02
Gram/Week									
dDMN	PosP**	-	762	ACC, paracingulate	Left/Right	-3	40	12	<.001*
			39	Precuneus	Left/Right	10	-63	24	<.02
dDMN	NegP**	-	45	Frontal Pole	Left/Right	-1	60	18	<.03
LECN	NegP	-	41	MFG	Left	-31	26	48	<.04

MNI = Montreal Neurological Institute; MNI coordinates for each cluster (Threshold-Free Cluster Enhancement with FWE-corrected p-values); ACC: anterior cingulate cortex; aSN: anterior salience network; CON = control group, CUD = cannabis users with cannabis use disorder group,; dDMN: dorsal default mode network; dSN: dorsal salience network; LECN: left executive control network; MFG: middle frontal gyrus; PCC: posterior cingulate gyrus; RECN: right executive control network; SMG: supramarginal gyrus; SPL: superior parietal lobe; vDMN: ventral default mode network.*association significant after Bonferroni multiple comparison correction **similar results when replacing cultural attitude measure by site.

Appendix G

Supplementary materials chapter 10

English version

For the following statements, you will be asked to indicate how much you agree, from strongly disagree to strongly agree. In addition, you will be asked to indicate how much you think your close friends and family and people from Texas/the Netherlands would agree. In other words, try to answer as you think the majority of your friends and family, and people in your country and state/country would.

1 Strongly Disagree 2 Disagree 3 Neutral 4 Agree 5 Strongly Agree

Response columns: I… My family and friends… People in Texas…

1. People who smoke cannabis are more relaxed in the way they interact with others. (P/G)
2. People who do not smoke cannabis stress over all sorts of meaningless things. (P/G)
3. People get lazy and lose initiative when they smoke cannabis. (N/N)
4. People can become more creative, expand their consciousness and gain greater insight in life by smoking cannabis. (P/G)
5. People who smoke cannabis regularly have somewhat dropped out of ‘‘normal society’’. (N/N)
6. When people start to smoke cannabis, their brains will function poorly. (N/N)
7. Cannabis has contributed positively to our culture (e.g. in relation to music or humor). (P/G)
8. The cannabis plant is doing more good than harm, among other things because it can be used as medicine. (P/G)
9. It is important to remember that cannabis is a natural product. (P/G)
10. People who smoke cannabis lose ambition and become less career minded. (N/N)
11. Cannabis can cause dependence. (N/N)
12. Smoking cannabis will often lead to ‘‘hard drugs’’. (N/N)

Dutch version

Geef aan in hoeverre jij het eens bent met de volgende stellingen op een schaal van sterkt mee oneens (1) tot sterk mee eens (5; kolom 1). Daarnaast word je gevraagd aan te geven in hoeverre je denkt dat je directe vrienden en familie (kolom 2) & mensen in Nederland (kolom 3) het met de stellingen eens zijn. Probeer dus aan te geven hoe jij denkt dat de meerderheid van jouw vrienden/familie en mensen in Nederland zouden antwoorden.

1 Sterk mee oneens 2 Mee oneens 3 Neutraal 4 Mee eens 5 Sterk mee eens

Reactie kolommen: Ik… Mijn familie en vrienden… Mensen in Nederland…

1. Mensen die cannabis gebruiken zijn relaxter in de omgang. (P/G)
2. Mensen die geen cannabis gebruiken stressen over allerlei nutteloze dingen. (P/G)
3. Mensen worden lui en verliezen initiatief als ze cannabis gebruiken. (N/N)
4. Mensen kunnen creatiever worden, hun bewustzijn vergroten en krijgen meer inzicht in het leven door cannabis te gebruiken. (P/G)
5. Mensen die regelmatig cannabis gebruiken staan deels buiten de ‘normale’ samenleving. (N/N)
6. Als mensen cannabis beginnen te gebruiken, gaan hun hersenen slechter werken. (N/N)
7. Cannabis heeft positief bijgedragen aan onze cultuur (bv. wat betreft muziek of humor). (P/G)
8. De cannabisplant doet meer goed dan kwaad, onder andere omdat het gebruikt kan worden als medicijn. (P/G)
9. Het is belangrijk om te onthouden dat cannabis een natuurlijk product is. (P/G)
10. Mensen die cannabis gebruiken worden minder ambitieus en zijn minder gericht op hun carrière. (N/N)
11. Cannabis is verslavend. (N/N)
12. Cannabisgebruik leidt vaak tot harddrugsgebruik. (N/N)

Figure S1. Overview of adapted cannabis culture questionnaire items in English and Dutch based on Holm et al. (2016). P/G: positive/glorification; N/N: Negative/neutralization

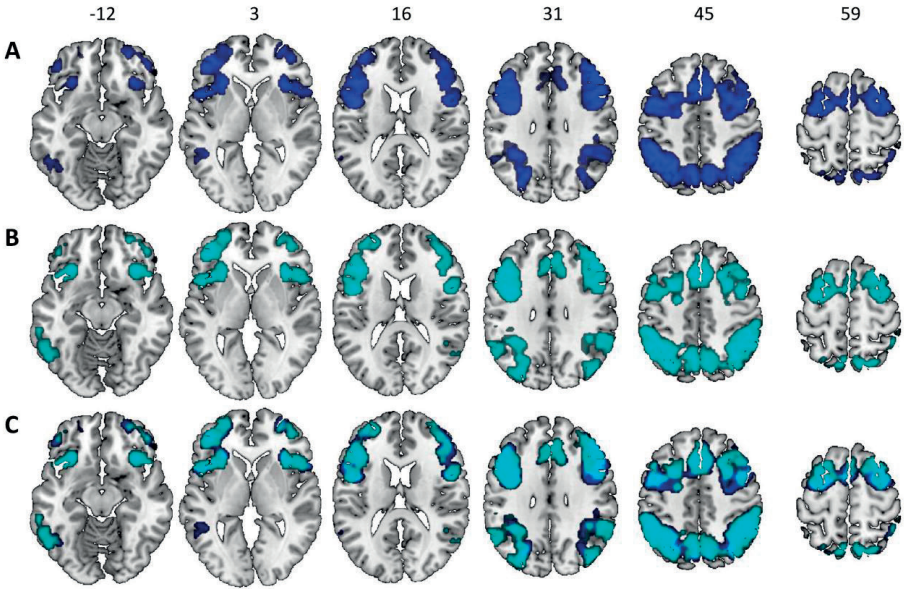


Figure S2. Main task effects of N-back task across participants. A) Overview of clusters showing WM-related task activity (2-back > 0-back). B) overview of clusters showing WM-load-related task activity (1-back > 0-back). C) Overlay of WM-related (dark colored) and WM-load-related (light colored) task activity. Note: cluster thresholding at Z > 2.3 for p < .05. Coordinates refer to MNI125 space.

Table S1. Overview of exclusions

Reason for exclusion	NL		TX		Total
	Cannabis	Control	Cannabis	Control	N
Incomplete data	3	3	6	4	16
Positive drug test	3	2	2	0	7
Excessive motion	11	1	7	1	20
Poor registration	0	1	0	0	1
				Initial sample	228
				Excluded sample	44
				Final sample	**184**

Table S2. Overview of model selection showing the effect of group, site, and cannabis culture questionnaire level on positive attitudes towards cannabis use

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Positive attitudes		*B*	95% *CI* (*B*)	*SE* (B)	*t*	*p*	*SD*	AIC	*χ2*	*p*
BM	(Intercept)	19.049	18.542 : 19.556	.258	73.758	**<.001**	2.433	3320.987	-	-
1	Intercept	18.119	17.331 : 18.908	.403	44.970	**<.001**	1.923	3129.807	125.288	**<.001**
	Group: CAN-CON	-3.842	-4.678 : -3.006	.426	9.023	**<.001**	-			
	Site: NL-TX	1.205	.351 : 2.058	.435	2.772	**.006**	-			
	Level: CS-FF	1.973	1.219 : 2.726	.385	5.125	**<.001**	3.445			
	Level: CS-P	4.553	3.910 : 5.417	.385	12.114	**<.001**				
2	Intercept	16.728	15.878 : 17.578	.435	38.447	**<.001**	2.110	3066.342	*67.465*	***<.001***
	Group: CAN-CON	-.794	-1.951 : .363	.590	1.346	.180	-			
	Site: NL-TX	1.205	.351 : 2.058	.435	2.767	**.006**	-			
	Level: CS-FF	3.390	2.457 : 4.323	.477	7.103	**<.001**	3.126			
	Level: CS-P	7.420	6.487 : 8.353	.477	15,546	**<.001**				
	Group: CAN-CON * Level: CS-FF	-3.104	-4.485 : -1.724	.706	4.395	**<.001**	-			
	Group: CAN-CON * Level: CS-P	-6.039	-7.419 : -4.659	.706	8.549	**<.001**	-			
3	Intercept	16.302	15.409 : 17.195	.457	35.642	**<.001**	2.031	3060.855	7.487	**.006**
	Group: CAN-CON	.123	-1.196 : 1.442	.673	.183	.855	-			
	Site: NL-TX	2.269	1.139 : 3.400	.577	3.934	**<.001**	-			
	Level: CS-FF	3.390	2.457 : 4.323	.478	7.096	**<.001**	3.129			
	Level: CS-P	7.420	6.487 : 8.353	.478	15.532	**<.001**				
	Group: CAN-CON * Level: CS-FF	-3.104	-4.485 : -1.734	.707	4.391	**<.001**	-			
	Group: CAN-CON * Level: CS-P	-6.039	-7.419 : -4.659	.707	8.541	**<.001**	-			
	Group: CAN-CON * Site: NL-TX	-2.354	-4.035 : -.674	.858	2.744	**.007**	-			
4	*Intercept*	*16.858*	*15.905 : 17.790*	*.484*	*34.830*	*<.001*	*2.065*	3050.897	13.957	**<.001**
	Group: CAN-CON	*.097*	*-1.213 : 1.407*	*.670*	*.145*	*.885*	-			
	Site: NL-TX	*.905*	*-.480 : 2.291*	*.708*	*1.278*	*.203*	-			
	Level: CS-FF	*2.812*	*1.743 : 3.882*	*.549*	*5.126*	***<.001***	*3.067*			
	Level: CS-P	*6.361*	*5.292 : 7.430*	*.549*	*11.592*	***<.001***				
	*Group: CAN-CON * Level: CS-FF*	*-3.077*	*-4.431 : -1.722*	*.695*	*4.426*	***<.001***	-			
	*Group: CAN-CON * Level: CS-P*	*-5.989*	*-7.343 : -4.634*	*.695*	*8.615*	***<.001***	-			
	*Group: CAN-CON * Site: NL-TX*	*-2.354*	*-4.035 : -.674*	*.860*	*2.739*	***.007***	-			
	*Site: NL-TX * Level: CS-FF*	*1.443*	*.061 : 2.826*	*.710*	*2.035*	***.043***	-			
	*Site: NL-TX * Level: CS-P*	*2.648*	*1.265 : 4.031*	*.710*	*3.732*	***<.001***	-			
5	Intercept	17.000	16.014 : 17.986	.507	33.553	**<.001**	2.067	3053.766	1.131	.568
	Group: CAN-CON	-.231	-1.682 : 1.220	.744	.310	.757	-			
	Site: NL-TX	.525	-1.039 : 2.089	.801	.655	.513	-			
	Level: CS-FF	2.617	1.437 : 3.796	.606	4.315	**<.001**	3.062			
	Level: CS-P	6.100	4.920 : 7.280	.606	10.058	**<.001**				
	Group: CAN-CON * Level: CS-FF	-2.655	-4.386 : -.924	.890	2.983	**.003**	-			
	Group: CAN-CON * Level: CS-P	-5.427	-7.158 : -3.696	.890	6.097	**<.001**	-			
	Group: CAN-CON * Site: NL-TX	-1.513	-3.838 : .812	1.191	1.270	.206	-			
	Site: NL-TX * Level: CS-FF	1.933	.068 : 3.798	.959	2.016	**.045**	-			
	Site: NL-TX * Level: CS-P	3.300	1.435 : 5.165	.959	3.441	**<.001**	-			
	Group: CAN-CON * Site: NL-TX * Level: CS-FF	-1.082	-3.856 : 1.691	1.426	.759	.448	-			
	Group: CAN-CON * Site: NL-TX * Level: CS-P	-1.442	-4.216 : 1.332	1.426	1.011	.313	-			

Linear mixed model results using random intercept and maximum likelihood estimation; AIC: Akaike information criterion, BM: baseline model, CAN: cannabis group, CI: Confidence Interval, CON: control group, CS: country-state, FF: friends-family, P: personal, NL: Netherlands, SE: Standard Error, SD: Standard deviation, TX: Texas; CAN, NL & CS were used as the reference categories. Note: final models as discussed in the manuscript are presented in italic and significant results are presented in bold.

Table S3. Overview of model selection showing the effect of group, site, and cannabis culture questionnaire level on negative attitudes towards cannabis use

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Negative attitudes		*B*	95% *CI* (*B*)	*SE* (B)	*t*	*p*	*SD*	AIC	*χ2*	*p*
BM	(Intercept)	19.527	19.010 : 20.044	.263	74.197	<.001	2.375	3369.232	-	-
1	Intercept	22.310	21.428 : 23.192	.451	49.515	**<.001**	2.590	3184.123	169.180	**<.001**
	Group: CAN-CON	1.726	.750 : 2.703	.497	3.473	**<.001**	-			
	Site: NL-TX	-1.805	-2.802 : -.809	.507	3.558	**<.001**	-			
	Level: CS-FF	-3.000	-3.751 : -2.249	.384	7.822	**<.001**	3.400			
	Level: CS-P	-5.592	-6.343 : -4. 842	.384	14.581	**<.001**				
2	Intercept	23.392	22.442 : 24.342	.486	48.130	**<.001**	2.673	3150.187	*37.937*	***<.001***
	Group: CAN-CON	-.645	-1.926 : .636	.653	.987	.325	-			
	Site: NL-TX	-1.805	-2.802 : -.809	.508	3.552	**<.001**	-			
	Level: CS-FF	-4.150	-5.117 : -3.183	.495	8.384	**<.001**	3.220			
	Level: CS-P	-7.690	-8.567 : -6.723	.496	15.535	**<.001**				
	Group: CAN-CON * Level: CS-FF	2.519	1.087 : 3.951	.733	3.438	**<.001**	-			
	Group: CAN-CON * Level: CS-P	4.595	3.163 : 6.026	.733	6.272	**<.001**	-			
3	Intercept	23.930	22.931 : 24.929	.512	46.749	**<.001**	2.573	3143.393	8.793	**.003**
	Group: CAN-CON	-1.803	-3.279 : -.328	.753	2.394	**.018**	-			
	Site: NL-TX	-3.150	-4.465 : -1.835	.671	4.693	**<.001**	-			
	Level: CS-FF	-4.150	-5.117 : -3.183	.495	8.376	**<.001**	3.224			
	Level: CS-P	-7.960	-8.657 : -6.723	.495	15.521	**<.001**				
	Group: CAN-CON * Level: CS-FF	2.519	1.087 : 3.951	.733	3.435	**<.001**	-			
	Group: CAN-CON * Level: CS-P	4.595	3.163 : 6.026	.733	6.266	**<.001**	-			
	Group: CAN-CON * Site: NL-TX	2.974	1.019 : 4.929	.998	2.979	**.003**	-			
4	*Intercept*	*23.370*	*22.322:24.417*	*.538*	*43.476*	*<.001*	*2.602*	3133.877	13.516	**.001**
	Group: CAN-CON	*-1.777*	*-3.244:-.309*	*.750*	*2.368*	***.019***	-			
	Site: NL-TX	*-1.749*	*-3.304:-.193*	*.796*	*2.198*	***.029***	-			
	Level: CS-FF	*-3.549*	*-4.659:-2.440*	*.569*	*6.233*	***<.001***	*3.262*			
	Level: CS-P	*-6.609*	*-7.719:-5.500*	*.569*	*11.607*	***<.001***				
	*Group: CAN-CON * Level: CS-FF*	*2.490*	*1.085:3.896*	*.721*	*3.452*	***<.001***	-			
	*Group: CAN-CON * Level: CS-P*	*4.543*	*3.137:5.949*	*.721*	*6.298*	***<.001***	-			
	*Group: CAN-CON * Site: NL-TX*	*2.973*	*1.019:4.929*	*1.000*	*2.974*	***.003***	-			
	*Site: NL-TX * Level: CS-FF*	*-1.502*	*-2.937:-.067*	*.736*	*2.040*	***.042***	-			
	*Site: NL-TX * Level: CS-P*	*-2.702*	*-4.136:-1.267*	*.736*	*3.669*	***<.001***	-			
5	Intercept	23.333	22.244 : 24.423	.560	41.645	**<.001**	2.602	3137.776	.101	.951
	Group: CAN-CON	-1.699	-3.304 : -.094	.822	2.066	**.040**	-			
	Site: NL-TX	-1.658	-3.387 : .071	.886	1.872	.063	-			
	Level: CS-FF	-3.467	-4.693 : -2.241	.630	5.501	**<.001**	3.162			
	Level: CS-P	-6.583	-7.809 : -5.257	.630	10.446	**<.001**				
	Group: CAN-CON * Level: CS-FF	2.313	.514 : 4.112	.925	2.500	**.013**	-			
	Group: CAN-CON * Level: CS-P	4.487	2.688 : 6.286	.925	4.851	**<.001**	-			
	Group: CAN-CON * Site: NL-TX	2.774	.203 : 5.345	1.317	2.105	**.037**	-			
	Site: NL-TX * Level: CS-FF	-1.708	-3.647 : .230	.997	1.714	.087	-			
	Site: NL-TX * Level: CS-P	-2.767	-4.705 : -.828	.997	2.776	**.006**	-			
	Group: CAN-CON * Site: NL-TX * Level: CS-FF	.456	-2.427 : 3.338	1.482	.308	.759	-			
	Group: CAN-CON * Site: NL-TX * Level: CS-P	.144	-2.738 : 3.027	1.482	.097	.923	-			

Linear mixed model results using random intercept and maximum likelihood estimation; AIC: Akaike information criterion, BM: baseline model, CAN: cannabis group, CI: Confidence Interval, CON: control group, CS: country-state, FF: friends-family, P: personal, NL: Netherlands, SE: Standard Error, SD: Standard deviation, TX: Texas; CAN, NL & CS were used as the reference categories. Note: final models as discussed in the manuscript are presented in italic and significant results are presented in bold.

Table S4. Overview of model selection to assess accuracy during the N-back task as a function of working memory (WM)-load, group, sex and their interaction

Model		Model coefficients						Model comparison		
		Fixed effects					Random effects			
Accuracy		B	95% CI (B)	SE (B)	*t*	*p*	*SD*	AIC	*χ2*	*P*
BM	(Intercept)	95.580	95.088 : 96.073	.251	381.078	**<.001**	2.046	3142.893	-	-
1	(Intercept)	97.996	97.060 : 98.932	.478	204.915	**<.001**	2.420	3020.073	1.851	.174
	WM-load: 0-back - 1-back	-1.596	-2.388 : -.804	.405	3.943	**<.001**	3.500			
	WM-load: 0-back - 2-back	-4.846	-5.638 : -4.054	.405	11.971	**<.001**				
	Group: CON-CAN	-1.008	-1.983 : -.032	.497	2.028	**.044**	-			
	Site: NL-TX	.685	-.306 : 1.677	.505	1.258	.176	-			
2	*(Intercept)*	*97.352*	*96.298:98.406*	*.540*	*180.433*	***<.001***	*2.443*	*3015.447*	*8.626*	***.013***
	WM-load: 0-back - 1-back	*-.936*	*-2.090:.218*	*.591*	*1.584*	*.114*	*3.454*			
	WM-load: 0-back - 2-back	*-3.571*	*-4.726:-2.417*	*.591*	*6.045*	***<.001***				
	Group: CON-CAN	*.186*	*-1.148:1.520*	*.681*	*.273*	*.785*	-			
	Site: NL-TX	*.685*	*-.306:1.677*	*.506*	*1.355*	*.177*	-			
	WM-load: 0-back - 1-back x Group: CON-CAN	*-1.222*	*-2.792:.349*	*.804*	*1.520*	*.130*	-			
	WM-load: 0-back - 2-back x Group: CON-CAN	*-2.259*	*-3.929:-.789*	*.804*	*2.935*	***.004***	-			
3	(Intercept)	97.526	96.412 : 98.641	.571	170.665	**<.001**	2.452	3016.179	3.268	.195
	WM-load: 0-back - 1-back	-.948	-2.261 : .365	.673	1.408	.160	3.437			
	WM-load: 0-back - 2-back	-4.084	-5.397 : -2.771	.673	6.066	**<.001**				
	Group: CON-CAN	.188	-1.143 : 1.519	.680	.276	.783	-			
	Site: NL-TX	.249	-1.105 : 1.602	.691	.359	.720	-			
	WM-load: 0-back - 1-back x Group: CON-CAN	-1.222	-2.785 : .341	.802	1.524	.128	-			
	WM-load: 0-back - 2-back x Group: CON-CAN	-2.365	-3.928 : -.801	.802	2.950	**.003**	-			
	WM-load: 0-back - 1-back x Site: NL-TX	.029	-1.560 : 1.618	.815	.036	.972	-			
	WM-load: 0-back - 2-back x Site: NL-TX	1.282	-.307 : 2.870	.815	1.573	.117	-			
4	(Intercept)	97.600	96.406 : 98.794	.613	159.254	**<.001**	2.451	3018.064	.115	.735
	WM-load: 0-back - 1-back	-.948	-2.261 : .365	.674	1.406	.161	3.437			
	WM-load: 0-back - 2-back	-4.084	-5.397 : -2.771	.674	6.060	**<.001**				
	Group: CON-CAN	.051	-1.502 : 1.604	.794	.064	.949	-			
	Site: NL-TX	.064	-1.665 : 1.793	.884	.072	.943	-			
	WM-load: 0-back - 1-back x Group: CON-CAN	-1.222	-2.785 : .341	.802	1.523	.129	-			
	WM-load: 0-back - 2-back x Group: CON-CAN	-2.282	-3.928 : -.801	.802	2.947	**.003**	-			
	WM-load: 0-back - 1-back x Site: NL-TX	.029	-1.560 : 1.618	.816	.036	.972	-			
	WM-load: 0-back - 2-back x Site: NL-TX	1.282	-.307 : 2.870	.816	1.572	.117	-			
	Group: CON-CAN x Site: NL-TX	.342	-1.648 : 2.331	1.018	.336	.738	-			
5	(Intercept)	97.487	96.229 : 98.745	.647	150.709	**<.001**	2.454	3020.930	1.134	.567
	WM-load: 0-back - 1-back	-.937	-2.418 : .544	.762	1.230	.220	3.431			
	WM-load: 0-back - 2-back	-3.756	-5.236 : -2.275	.762	4.931	**<.001**				
	Group: CON-CAN	.261	-1.459 : 1.981	.882	.296	.768	-			
	Site: NL-TX	.347	-1.649 : 2.342	1.023	.339	.735	-			
	WM-load: 0-back - 1-back x Group: CON-CAN	-1.242	-3.260 : .776	1.038	1.197	.232	-			
	WM-load: 0-back - 2-back x Group: CON-CAN	-2.975	-4.993 : -.957	1.038	2.866	**.004**	-			
	WM-load: 0-back - 1-back x Site: NL-TX	.002	-2.340 : 2.343	1.204	.001	.999	-			
	WM-load: 0-back - 2-back x Site: NL-TX	.450	-1.881 : 2.802	1.204	.382	.703	-			
	Group: CON-CAN x Site: NL-TX	-.181	-2.894 : 2.531	1.390	.131	.896	-			
	WM-load: 0-back - 1-back x Group: CON-CAN x Site: NL-TX	.051	-3.132 : 3.234	1.637	.031	.975	-			
	WM-load: 0-back - 2-back x Group: CON-CAN x Site: NL-TX	1.518	-1.665 : 4.701	1.637	.927	.354	-			

Note. Linear mixed model results using random intercept and maximum likelihood estimation; AIC: Akaike information criterion, BM: baseline model, CAN: cannabis group, CI: Confidence Interval, CON: control group, NL: Netherlands, SE: Standard Error, SD: Standard deviation, TX: Texas; 0-back, CON, and NL were used as the reference categories. Final models as discussed in the manuscript are presented in italic and significant results are presented in bold.

Appendix H

Supplementary materials chapter 11

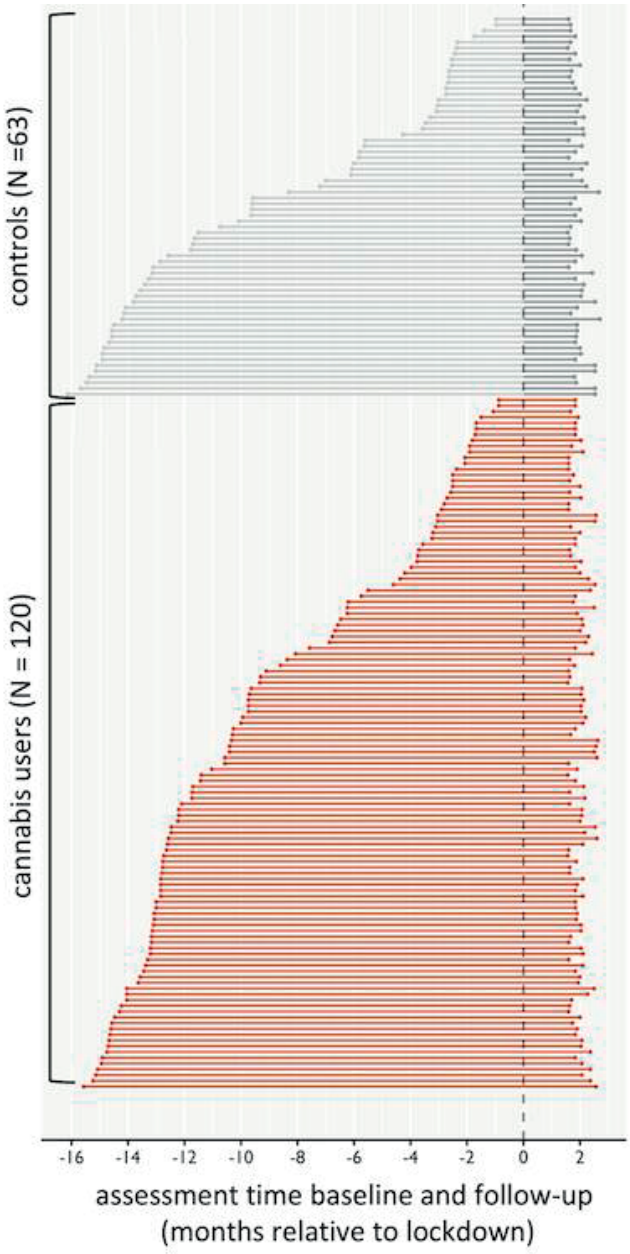


Figure S1. Baseline and follow-up assessment times for each cannabis user and control in months relative to lockdown onset (March 12).

Table S1. COVID-19-related worries about personal health, personal economic consequences, contamination, and societal functioning

Items	Dutch	English (translation)	Subscale
	Instruction: Hieronder staan verschillende coronavirusgerelateerde dingen waarover mensen zich in deze tijd zorgen kunnen maken. Geef op een schaal van 'helemaal geen zorgen' tot 'heel veel zorgen' aan in hoeverre jij je zorgen maakt over onderstaande dingen.	**Instruction:** Below you see several coronavirus-related things that people might worry about now. Indicate to what extent you worry about the following things on a scale from 'no worries at all' to 'a lot of worries'.	--
1.	Dat je zelf besmet raakt met het coronavirus	That you will get infected with the coronavirus	**contamination**
2.	Dat een familielid of goede vriend besmet raakt met het coronavirus	That a family member or close friend will get infected with the coronavirus	**contamination**
3.	Dat jij iemand anders besmet met het coronavirus	That you will infect someone else with the coronavirus	**contamination**
4.	Jouw financiële situatie ten gevolge van de uitbraak van het coronavirus	Your financial situation as a consequence of the coronavirus outbreak	**Personal economic consequences**
5.	De economische gevolgen van het coronavirus	The economic consequences of the coronavirus outbreak	**societal functioning**
6.	De bekwaamheid van de regering om de juiste maatregelen te nemen ten bestrijding van het coronavirus	The competence of the government to take the right precautions to fight the coronavirus outbreak	**societal functioning**
7.	De capaciteit van de intensive care afdelingen	The ICU capacity	**societal functioning**
8.	De mogelijkheid om niet-coronagerelateerde zorg te ontvangen	The opportunity to receive care unrelated to the coronavirus	**societal functioning**
9.	Jouw algemene fysieke gezondheid	Your general physical health	**Personal health**
10.	Jouw algemene mentale gezondheid	Your general mental health	**Personal health**
11.	Dat jij je baan verliest door de uitbraak van het coronavirus	Losing your job as a consequence of the coronavirus outbreak	**Personal economic consequences**

Table S2. Overview of model selection to assess change in cannabis use (days per month) and CUD symptom severity as a function of time and lockdown status

		Model coefficients										
Model		**Fixed effects**					**Random effects**		**Model comparison**			
DSM-5 CUD symptoms		***B***	**95% *CI* (*B*)**	***SE* (B)**	***t***	***p***	***SD***	***95%CI (SD)***	**AIC**	**BIC**	***χ2***	***p***
0	(intercept)	4.49	3.98 – 5.00	.26	17.41	<.001	2.49	2.13 – 2.90	1330.49	1341.55	-	-
1	(Intercept)	4.49	3.98 – 5.00	.26	17.24	<.001	2.48	2.13 – 2.90	1332.46	1347.20	.03	.857
	Time	-.00	-.00 – .00	.00	.17	.858	-	-				
2a	(Intercept)	4.62	4.07 – 5.17	.28	16.40	<.001	2.49	2.13 – 2.90	1332.88	1351.32	1.57	.210
	Time	.00	-.00 - .00	.00	.55	.583	-	-				
	Lockdown Status	-.29	-.74 - .16	.23	1.25	.213	-	-				
2b*	(Intercept)	4.61	4.06 – 5.16	.28	16.33	<.001	2.65	2.28 - 3.06	1313.91	1339.72	22.97	<.001
	Time	.00	-.00 - .00	.00	.12	.908	.01	.00 - .01				
	Lockdown Status	-.26	-.63 - .11	.19	1.39	.165	-	-				
3	*(Intercept)*	*4.61*	*4.06 – 5.17*	*.28*	*16.30*	*<.001*	*2.67*	*2.31 - 3.09*	*1311.06*	*1340.56*	*4.85*	*.028*
	Time	*.00*	*-.00 - .00*	*.00*	*.20*	*.839*	*.01*	*.00 - .01*				
	Lockdown Status	*2.30*	*0.04 – 4.55*	*1.15*	*2.00*	*.047*	-	-				
	Time x Lockdown Status	*-.04*	*-.08 - -.01*	*.02*	*2.26*	*.025*	-	-				
Model		**Fixed effects**					**Random effects**		**Model comparison**			
Cannabis use, days month		**B**	**95% CI (B)**	**SE (B)**	***t***	***p***	***SD***	***95%CI (SD)***	**AIC**	**BIC**	***χ2***	***P***
0	(intercept)	20.31	18.53 – 22.10	.91	22.38	<.001	9.16	7.89 – 10.64	2429.58	2441.03	-	-
1	(Intercept)	20.16	18.36 – 21.96	.92	21.98	<.001	9.16	7.89 – 10.64	2430.05	2445.32	1.54	.22
	Time	-.00	-.01 - .00	.00	1.24	0.22	-	-				
2a	*(Intercept)*	*19.26*	*17.30 – 21.22*	*1.00*	*19.25*	*<.001*	*9.16*	*7.91 – 10.65*	*2426.93*	*2446.02*	*5.11*	*.02*
	Time	*-.01*	*-.01 - -.00*	*.00*	*2.30*	*.022*	-	-				
	Lockdown Status	*1.96*	*.26 – 3.66*	*.87*	*2.26*	*.024*	-	-				
2b*	(Intercept)	19.26	17.30 – 21.22	1.00	19.30	<.001	9.25	7.96 – 10.76	2430.12	2456.84	.81	.67
	Time	-.01	-.01 - -.00	.00	2.19	.030	-.00	.00 – .03				
	Lockdown Status	1.96	.31 – 3.61	.84	2.33	.021	-	-				
3**	(Intercept)	19.29	17.32 – 21.26	1.00	19.20	<.001	9.24	7.96 – 10.71	2426.78	2449.68	2.16	.14
	Time	-.01	-.01 - -.00	.00	2.19	.029	-	-				
	Lockdown Status	8.77	-.45 – 18.00	4.71	1.86	.064	-	-				
	Time x Lockdown Status	-.12	-.27 - .04	.08	1.47	.143	-	-				

*Mixed model results using random intercept models and maximum likelihood estimation. DSM-5: Diagnostic and Statistical Manual of Mental Disorders; CUD: Cannabis Use Disorder; CI: Confidence Interval; SE: Standard Error; AIC: Akaike information criterion; *Allowing for individual differences in slopes (random slopes model);**Model comparison is a comparison with model 2a. Note: final models are presented in italic. Models assessing the effect of a continuous autocorrelation structure of order 1, quadratic effects of time and cubic effects of time did not improve model fit.*

Appendix I

Supplementary materials chapter 12

Table S1. Initial Dutch 26-item Social Attunement Questionnaire.

Participants were asked to answer using a 7-point likert scale (English: 1 = Completely disagree, 2 = disagree, 3 = more or less disagree, 4 = neutral, 5 = more or less agree, 6 = agree, 7 = Completely agree; Dutch: 1 = helemaal mee oneens, 2 = oneens, 3 = een beetje mee oneens, 4 = neutraal, 5 = een beetje mee eens, 6 = mee eens, 7 = helemaal mee eens) and all items followed by (R) are reverse coded items.

Items
1. Ik laat mijn kledingstijl niet beïnvloeden door de kledingstijl van mijn vrienden. (R)
2. Het valt me op als een vriend(in) meer of minder alcohol drinkt dan hij/zij normaal doet.
3. Ik gedraag mij weleens op een manier die niet echt bij mij past omdat dit beter aansluit op de situatie. (1)
4. Ik heb er geen probleem mee om anders te zijn dan de mensen in de groep waarin ik me bevind. (2; R)
5. Als iedereen tevreden is, ben ik ook tevreden.
6. Ik probeer te voorkomen dat anderen denken dat ik anders ben. (3)
7. Als iemand ongepast gedrag laat zien, valt dat mij op.
8. Als iedereen nog een drankje neemt, neem ik er ook nog één.
9. Ik neem vaak woorden van een ander over. (4)
10. Ik let op de kledingstijl van anderen.
11. Als ik met mijn vrienden uitga, pas ik mij meestal aan aan hun plannen.
12. Ik hecht veel waarde aan hoe mensen over mij denken. (5)
13. Als de meerderheid van een groep een bepaalde mening heeft, ga ik daar meestal in mee. (6)
14. In verschillende situaties met verschillende mensen gedraag ik mij anders. (7)
15. Als mijn vrienden interesse verliezen in dingen die we vaak doen, merk ik dat ik deze dingen ook minder leuk ga vinden.
16. Ik pas mijn kleding aan aan de kleding van mijn vrienden.
17. Het kan mij weinig schelen wat anderen van mij vinden. (8; R)
18. Ik pas mij vaak aan aan de wensen van anderen.
19. Als mijn vrienden een avond weinig alcohol drinken, houd ik me ook in.
20. Als ik niet goed weet hoe ik me moet gedragen, kijk ik naar wat anderen doen. (9)
21. Ik pas mijn taalgebruik aan aan mijn gezelschap. (10)
22. Ik probeer zo goed mogelijk aansluiting te vinden bij de groep waarin ik mij bevind. (11)
23. Als mijn vrienden ergens heen gaan, ga ik meestal mee, ook als het mij niet zo leuk lijkt.
24. Als mijn vrienden zich druk maken over bepaalde dingen, merk ik dat ik me hier na verloop van tijd ook meer mee bezig ga houden.
25. Ik ben afwachtend in een nieuwe groep mensen om te kijken hoe ik mij het beste kan gedragen.
26. Ik word er blij van wanneer mijn vrienden plezier maken, ongeacht wat we doen.

Note: final items of subscale 1 (cognition) are presented in bold-italic and final items of subscale 2 (behaviour) are presented in bold-underscore. Number between brackets indicate items number in the final scale. R: reverse coded item.

Table S2. Perceived peer drinking measure

Perceived peer drinking (PPD) items

1. Hoe vaak drinkt uw gemiddelde vriend (die alcohol drinkt) alcoholhoudende drank?
    a. Nooit
    b. Maandelijks of minder
    c. 2 tot 4 keer per maand
    d. 2 tot 3 keer per week
    e. 4 of meer keer per week
2. Hoeveel glazen alcohol drinkt uw gemiddelde vriend (die alcohol drinkt) op een typische dag waarop hij/zij drinkt?
    a. 1 of 2
    b. 3 of 4
    c. 5 of 6
    d. 7 tot 9
    e. 10 of meer
3. Hoe vaak drinkt uw gemiddelde vriend (die alcohol drinkt) 6 of meer glazen per gelegenheid?
    a. Nooit
    b. Minder dan maandelijks
    c. Maandelijks
    d. Wekelijks
    e. Dagelijks of bijna dagelijks

Comparable alcohol use disorder identification test (AUDIT) items

1. Hoe vaak drinkt u alcohol?
    a. Nooit
    b. Maandelijks of minder
    c. 2 tot 4 keer per maand
    d. 2 tot 3 keer per week
    e. 4 of meer keer per week
2. Op een dag waarop u alcohol drinkt, hoeveel glazen drinkt u dan gewoonlijk?
    a. 1 of 2
    b. 3 of 4
    c. 5 of 6
    d. 7 tot 9
    e. 10 of meer
3. Hoe vaak zijn er gelegenheden waarop u 6 of meer glazen alcohol drinkt?
    a. Nooit
    b. Minder dan maandelijks
    c. Maandelijks
    d. Wekelijks
    e. Dagelijks of bijna dagelijks

Table S3. Overview of EFA steps and factor structures							
Item # 26-item	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**	**KMO**	**Uniqueness**
Step 1 – initial							
1	.01	.05	.08	**.50**	-.04	.72	.71
3	.12	**.56**	.08	.03	-.06	.87	.57
4	**.55**	-.13	.08	.14	-.16	.83	.68
5	-.04	-.25	.27	-.24	**.49**	*.57*	.67
6	**.45**	-.08	.21	.12	-.03	.87	.69
7	.14	.04	-.28	-.17	.06	*.53*	.91
9	-.07	**.41**	.02	.06	-.05	.80	.84
10	.15	-.05	-.23	.29	.05	*.59*	.85
11	.01	.09	**.45**	-.08	-.04	.73	.77
12	**.68**	.16	-.19	-.06	.18	.76	.42
13	.26	-.14	**.44**	.12	.13	.84	.65
14	.01	**.75**	.02	-.09	-.15	.81	.49
15	.03	.16	.05	.09	.20	.75	.87
16	-.02	.04	.22	**.70**	.02	.78	.39
17	**.82**	-.04	-.10	-.08	.06	.75	.41
18	.10	.08	**.48**	-.01	.12	.87	.66
20	.16	**.37**	.09	-.05	-.06	.84	.77
21	-.18	**.48**	-.04	.04	.10	.77	.80
22	.08	**.34**	-.02	.01	.21	.85	.77
23	-.01	.12	.25	-.00	.17	.83	.85
24	.03	.12	-.00	.13	**.38**	.80	.76
25	.25	**.26**	.26	-.09	-.25	.85	.68
26	-.02	-.05	-.06	-.01	**.40**	*.54*	.85
Tot	-	-	-	-	-	.79	-
Step 2 – item reduction							
1	.20	.16	-	-	-	.69	.89
3	.12	**.55**	-	-	-	.84	.60
4	**.61**	-.16	-	-	-	.82	.73
6	**.59**	-.06	-	-	-	.85	.70
9	-.13	**.49**	-	-	-	.80	.83
11	.05	.27	-	-	-	.72	.91
12	**.63**	.05	-	-	-	.75	.57
13	**.43**	.06	-	-	-	.87	.78
14	-.05	**.65**	-	-	-	.80	.62
16	.28	.25	-	-	-	.77	.77
17	**.79**	-.16	-	-	-	.73	.51
18	.22	.29	-	-	-	.86	.79
20	.11	**.41**	-	-	-	.86	.77
21	-.21	**.54**	-	-	-	.77	.81
22	.10	**.35**	-	-	-	.87	.82
24	.15	.18	-	-	-	.80	.91
Tot	-	-	-	-	-	.80	-
Step 3 – final							
3	.15	**.56**	-	-	-	.79	.58
4	**.55**	-.10	-	-	-	.79	.74
6	**.53**	-.02	-	-	-	.82	.73
9	-.07	**.43**	-	-	-	.76	.84
12	**.63**	.13	-	-	-	.74	.51
13	**.39**	.03	-	-	-	.89	.83
14	-.00	**.68**	-	-	-	.77	.54
17	**.78**	-.07	-	-	-	.71	.44
20	.15	**.38**	-	-	-	.84	.77
21	-.14	**.47**	-	-	-	.76	.83
22	.14	**.35**	-	-	-	.87	.81
Tot	-	-	-	-	-	.78	-
Note: factor loadings >.30 are presented in bold. KMO <.60 are presented in italic.							

References

A

Adamson, S. J., Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., Thornton, L., Kelly, B. J., & Sellman, J. D. (2010). An improved brief measure of cannabis misuse: The Cannabis Use Disorders Identification Test-Revised (CUDIT-R). Drug and Alcohol Dependence, 110(1–2), 137–143. https://doi.org/10.1016/j.drugalcdep.2010.02.017

Agosti, V., Nunes, E., & Levin, F. (2002). Rates of psychiatric comorbidity among U.S. residents with lifetime cannabis dependence. American Journal of Drug and Alcohol Abuse, 28(4), 643–652. https://doi.org/10.1081/ADA-120015873

Agrawal, A., Lynskey, M. T., Bucholz, K. K., Madden, P. A. F., & Heath, A. C. (2007). Correlates of cannabis initiation in a longitudinal sample of young women: The importance of peer influences. Preventive Medicine, 45(1), 31–34. https://doi.org/10.1016/j.ypmed.2007.04.012

Agrawal, A., Lynskey, M. T., Bucholz, K. K., Martin, N. G., Madden, P. A. F., & Heath, A. C. (2007). Contrasting models of genetic co-morbidity for cannabis and other illicit drugs in adult Australian twins. Psychological Medicine, 37(1), 49–60. https://doi.org/10.1017/S0033291706009287

Agrawal, A., Silberg, J. L., Lynskey, M. T., Maes, H. H., & Eaves, L. J. (2010). Mechanisms underlying the lifetime co-occurrence of tobacco and cannabis use in adolescent and young adult twins. Drug and Alcohol Dependence, 108(1–2), 49–55. https://doi.org/10.1016/j.drugalcdep.2009.11.016

Agrawal, A., Verweij, K. J. H., Gillespie, N. A., Heath, A. C., Lessov-Schlaggar, C. N., Martin, N. G., Nelson, E. C., Slutske, W. S., Whitfield, J. B., & Lynskey, M. T. (2012). The genetics of addiction a translational perspective. Translational Psychiatry, 2 e140. https://doi.org/10.1038/tp.2012.54

Aharonovich, E. (2003). Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. Drug and Alcohol Dependence, 71(2), 207–211. https://doi.org/10.1016/S0376-8716(03)00092-9

Aharonovich, E., Brooks, A. C., Nunes, E. V., & Hasin, D. S. (2008). Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. Drug and Alcohol Dependence, 95(3), 279–283. https://doi.org/10.1016/j.drugalcdep.2008.01.009

Aharonovich, E., Hasin, D. S., Brooks, A. C., Liu, X., Bisaga, A., & Nunes, E. V. (2006). Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug and Alcohol Dependence, 81(3), 313–322. https://doi.org/10.1016/j.drugalcdep.2005.08.003

AIHW. (2017). National Drug Strategy Household Survey 2016: Detailed Findings. In Drug Statistics series no. 31. Cat. no. PHE 214. https://doi.org/Cat. no. PHE 214.

Alcorn, J.L., Marks, K.R., Stoops, W.W., Rush, C.R., & Lile, J.A. (2019). Attentional bias to cannabis cues in cannabis users but not cocaine users. Addictive Behaviors, 88, 129–136. https://doi.org/10.1016/j.addbeh.2018.08.023.

Alfulaij, N., Meiners, F., Michalek, J., Small-Howard, A. L., Turner, H. C., & Stokes, A. J. (2018). Cannabinoids, the Heart of the Matter. Journal of the American Heart Association, 7(14), 1–10. https://doi.org/10.1161/JAHA.118.009099

Aloi, J., Blair, K. S., Crum, K. I., Bashford-Largo, J., Zhang, R., Lukoff, J., ... & Blair, R. J. R. (2020). Alcohol use disorder, but not cannabis use disorder, symptomatology in adolescents is associated with reduced differential responsiveness to reward versus punishment feedback during instrumental learning. Biological psychiatry: cognitive neuroscience and neuroimaging, 5(6), 610-618. https://doi.org/10.1016/j.bpsc.2020.02.003.

American Psychiatric Association. (2012). Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV). In DSM. https://doi.org/10.1073/pnas.0703993104

American Psychiatric Association. (2013a). Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association. In DSM. https://doi.org/10.1176/appi.books.9780890425596.744053

American Psychiatric Association. (2013b). DSM-5 self-rated level 1 cross-cutting symptom measure–adult. American Psychiatric Publishing.

Ames, D. L., & Fiske, S. T. (2010). Cultural neuroscience. Asian Journal of Social Psychology, 13(2), 72–82. https://doi.org/10.1111/j.1467-839X.2010.01301.x

Apollonio, D., Philipps, R., & Bero, L. (2016). Recovery from substance use disorders. https://doi.org/10.1002/14651858.CD010274.pub2.www.cochranelibrary.com

Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ, 344, e536–e536. https://doi.org/10.1136/bmj.e536

Asmaro, D., Carolan, P. L., & Liotti, M. (2014). Electrophysiological evidence of early attentional bias to drug-related pictures in chronic cannabis users. Addictive Behaviors, 39(1), 114–121. https://doi.org/10.1016/j.addbeh.2013.09.012

Ataya, A. F., Adams, S., Mullings, E., Cooper, R. M., Attwood, A. S., & Munafò, M. R. (2012). Internal reliability of measures of substance-related cognitive bias. Drug and Alcohol Dependence, 121(1–2), 148–151. https://doi.org/10.1016/j.drugalcdep.2011.08.023

B

Babson, K. A., Sottile, J., & Morabito, D. (2017). Cannabis, Cannabinoids, and Sleep: a Review of the Literature. Current Psychiatry Reports, 19(4), 1-12. https://doi.org/10.1007/s11920-017-0775-9

Baker, A. L., Hides, L., & Lubman, D. I. (2010). Treatment of Cannabis Use Among People With Psychotic or Depressive Disorders. The Journal of Clinical Psychiatry, 71(03), 247–254. https://doi.org/10.4088/JCP.09r05119gry

Banich, M. T., Crowley, T. J., Thompson, L. L., Jacobson, B. L., Liu, X., Raymond, K. M., & Claus, E. D. (2007). Brain activation during the Stroop task in adolescents with severe substance and conduct problems: A pilot study. Drug and Alcohol Dependence, 90(2–3), 175–182. https://doi.org/10.1016/j.drugalcdep.2007.03.009

Barguil, Y., Chiaradia, L., Southwell, G., & Charlot, J. Y. (2022). Hair concentrations of Δ-9-tetrahydrocannabinol and cannabidiol in cannabis consumers psychiatric patients. Toxicologie Analytique et Clinique, 34(4), 247–254. https://doi.org/10.1016/J.TOXAC.2022.07.002

Bashford, J., Flett, R., & Copeland, J. (2010). The Cannabis Use Problems Identification Test (CUPIT): development, reliability, concurrent and predictive validity among adolescents and adults. Addiction, 105(4), 615–625. https://doi.org/10.1111/j.1360-0443.2009.02859.x

Bassir Nia, A., Mann, C., Kaur, H., & Ranganathan, M. (2018). Cannabis Use: Neurobiological, Behavioral, and Sex/Gender Considerations. Current Behavioral Neuroscience Reports, 5(4), 271–280. https://doi.org/10.1007/s40473-018-0167-4

Battisti, R. A., Roodenrys, S., Johnstone, S. J., Pesa, N., Hermens, D. F., & Solowij, N. (2010). Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. Psychopharmacology, 212(4), 613–624. https://doi.org/10.1007/s00213-010-1988-3

Bayrakçı, A., Sert, E., Zorlu, N., Erol, A., Sarıçiçek, A., & Mete, L. (2015). Facial emotion recognition deficits in abstinent cannabis dependent patients. Comprehensive Psychiatry, 58, 160–164. https://doi.org/10.1016/j.comppsych.2014.11.008

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. Archives of General Psychiatry, 4(6), 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004

Becker, B., Wagner, D., Gouzoulis-Mayfrank, E., Spuentrup, E., & Daumann, J. (2010). The impact of early-onset cannabis use on functional brain correlates of working memory. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34(6), 837–845. https://doi.org/10.1016/j.pnpbp.2010.03.032

Bender, K., Tripodi, S. J., Sarteschi, C., & Vaughn, M. G. (2011). A Meta-Analysis of Interventions to Reduce Adolescent Cannabis Use. Research on Social Work Practice, 21(2), 153–164. https://doi.org/10.1177/1049731510380226

Benschop, A., Liebregts, N., van der Pol, P., Schaap, R., Buisman, R., van Laar, M., van den Brink, W., de Graaf, R., & Korf, D. J. (2015). Reliability and validity of the Marijuana Motives Measure among young adult frequent cannabis users and associations with cannabis dependence. Addictive Behaviors, 40, 91–95. https://doi.org/10.1016/j.addbeh.2014.09.003

Berthet, A., De Cesare, M., Favrat, B., Sporkert, F., Augsburger, M., Thomas, A., & Giroud, C. (2016). A systematic review of passive exposure to cannabis. Forensic Science International, 269, 97-112. https://doi.org/10.1016/j.forsciint.2016.11.017

Bhattacharyya, S. (2012). Induction of Psychosis byΔ9-Tetrahydrocannabinol Reflects Modulation of Prefrontal and Striatal Function During Attentional Salience Processing. Archives of General Psychiatry, 69(1), 27. https://doi.org/10.1001/archgenpsychiatry.2011.161

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C. M., Seal, M., Allen, P., Mehta, M. A., Stone, J. M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R. M., Zuardi, A. W., Crippa, J. A., Atakan, Z., & McGuire, P. K. (2010). Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology, 35(3), 764–774. https://doi.org/10.1038/npp.2009.184

Bickel, W. K., Mellis, A. M., Snider, S. E., Athamneh, L. N., Stein, J. S., & Pope, D. A. (2018). 21st century neurobehavioral theories of decision making in addiction: Review and evaluation. Pharmacology Biochemistry and Behavior, 164, 4-21. https://doi.org/10.1016/j.pbb.2017.09.009

Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2020). A systematic review of human neuroimaging evidence of memory-related functional alterations associated with cannabis use complemented with preclinical and human evidence of memory performance alterations. Brain Sciences, 10(2), 102. https://doi.org/10.3390/brainsci10020102

Blest-Hopley, G., O'Neill, A., Wilson, R., Giampietro, V., & Bhattacharyya, S. (2021). Disrupted parahippocampal and midbrain function underlie slower verbal learning in adolescent-onset regular cannabis use. Psychopharmacology, 238, 1315-1331. https://doi.org/10.1007/s00213-019-05407-9.

Bloomfield, M. A. P., Morgan, C. J. A., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic Function in Cannabis Users and Its Relationship to Cannabis-Induced Psychotic Symptoms. Biological Psychiatry, 75(6), 470–478. https://doi.org/10.1016/j.biopsych.2013.05.027

Boehnke, K. F., Dean, O., Haffajee, R. L., & Hosanagar, A. (2022). U.S. Trends in Registration for Medical Cannabis and Reasons for Use From 2016 to 2020: An Observational Study. Annals of Internal Medicine, 175(7), 945–951. https://doi.org/10.7326/M22-0217

Boggs, D. L., Cortes-Briones, J. A., Surti, T., Luddy, C., Ranganathan, M., Cahill, J. D., ... & Skosnik, P. D. (2018). The dose-dependent psychomotor effects of intravenous delta-9-tetrahydrocannabinol (Δ9-THC) in humans. Journal of Psychopharmacology, 32(12), 1308-1318. https://doi.org/10.1177/0269881118799953.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J. L. (2002). Dose-related neurocognitive effects of marijuana use. Neurology, 59(9), 1337–1343.

Bollen, K. A. (1989). A New Incremental Fit Index for General Structural Equation Models. Sociological Methods & Research, 17(3), 303–316. https://doi.org/https://doi.org/10.1177/0049124189017003004

Boman, J. H., & Heck, C. (2017). Friendships and Cannabis Use. In Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment (pp. 188–197). Elsevier Inc. https://doi.org/10.1016/B978-0-12-800756-3.00022-3

Bonar, E. E., Goldstick, J. E., Collins, R. L., Cranford, J. A., Cunningham, R. M., Chermack, S. T., Blow, F. C., & Walton, M. A. (2017). Daily associations between cannabis motives and consumption in emerging adults. Drug and Alcohol Dependence, 178, 136–142. https://doi.org/10.1016/j.drugalcdep.2017.05.006

Bondallaz, P., Favrat, B., Chtioui, H., Fornari, E., Maeder, P., & Giroud, C. (2016). Cannabis and its effects on driving skills. Forensic Science International, 268, 92–102. https://doi.org/10.1016/j.forsciint.2016.09.007

Bonnet, U., & Preuss, U. (2017). The cannabis withdrawal syndrome: current insights. Substance Abuse and Rehabilitation, 8, 9–37. https://doi.org/10.2147/sar.s109576

Bonnet, U., Specka, M., Roser, P., & Scherbaum, N. (2023). Cannabis use, abuse and dependence during the COVID-19 pandemic: a scoping review. Journal of Neural Transmission, 130(1), 7–18. https://doi.org/10.1007/s00702-022-02564-8

Bonn-Miller, M. O., Babson, K. A., & Vandrey, R. (2014). Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. Drug and Alcohol Dependence, 136, 162–165. https://doi.org/10.1016/j.drugalcdep.2013.12.008

Borsboom, D. (2017). A network theory of mental disorders. World Psychiatry, 16(1), 5–13. https://doi.org/10.1002/wps.20375

Borsboom, D., & Cramer, A. O. J. (2013). Network analysis: An integrative approach to the structure of psychopathology. Annual Review of Clinical Psychology, 9, 91–121. https://doi.org/10.1146/annurev-clinpsy-050212-185608

Borsboom, D., Friend, E. I., Epskamp, S., Waldorp, L. J., van Borkulo, C. D., van der Maas, H. L. J., & Cramer, A. O. J. (2017). False Alarm? A Comprehensive Reanalysis of "Evidence That Psychopathology Symptom Networks Have Limited Replicability" by Forbes, Wright, Markon, and Krueger (2017). Journal of Abnormal Psychology. 126(7), 989-999. https://doi.org/10.1037/abn0000306.supp

Bosker, W. M., Karschner, E. L., Lee, D., Goodwin, R. S., Hirvonen, J., Innis, R. B., Theunissen, E. L., Kuypers, K. P. C., Huestis, M. A., & Ramaekers, J. G. (2013). Psychomotor Function in Chronic Daily Cannabis Smokers during Sustained Abstinence. PLoS ONE, 8(1), e53127. https://doi.org/10.1371/journal.pone.0053127

Bosker, W. M., Kuypers, K. P. C., Theunissen, E. L., Surinx, A., Blankespoor, R. J., Skopp, G., Jeffery, W. K., Walls, H. C., Leeuwen, C. J., & Ramaekers, J. G. (2012). Medicinal Δ9-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. Addiction, 107(10), 1837–1844. https://doi.org/10.1111/j.1360-0443.2012.03928.x

Bossong, M. G., Jansma, J. M., van Hell, H. H., Jager, G., Kahn, R. S., & Ramsey, N. F. (2013). Default Mode Network in the Effects of Δ9-Tetrahydrocannabinol (THC) on Human Executive Function. PLoS ONE, 8(7), 1–10. https://doi.org/10.1371/journal.pone.0070074

Bossong, M. G., van Berckel, B. N., Boellaard, R., Zuurman, L., Schuit, R. C., Windhorst, A. D., van Gerven, J. M. A., Ramsey, N. F., Lammertsma, A. A., & Kahn, R. S. (2009). Δ9-Tetrahydrocannabinol Induces Dopamine Release in the Human Striatum. Neuropsychopharmacology, 34(3), 759–766. https://doi.org/10.1038/npp.2008.138

Bossong, M., Jager, G., Bhattacharyya, S., & Allen, P. (2014). Acute and Non-acute Effects of Cannabis on Human Memory Function: A Critical Review of Neuroimaging Studies. Current Pharmaceutical Design, 20(13), 2114–2125. https://doi.org/10.2174/13816128113199990436

Bossong, M. G., van Hell, H. H., Jager, G., Kahn, R. S., Ramsey, N. F., & Jansma, J. M. (2013). The endocannabinoid system and emotional processing: a pharmacological fMRI study withΔ 9-tetrahydrocannabinol. European Neuropsychopharmacology, 23(12), 1687-1697. https://doi.org/10.1016/j.euroneuro.2013.06.009

Boyaji, S., Merkow, J., Elman, R. N. M., Kaye, A. D., Yong, R. J., & Urman, R. D. (2020). The Role of Cannabidiol (CBD) in Chronic Pain Management: An Assessment of Current Evidence. Current Pain and Headache Reports, 24(2). https://doi.org/10.1007/s11916-020-0835-4

Briand, L. A., & Blendy, J. A. (2010). Molecular and genetic substrates linking stress and addiction. Brain Research, 1314, 219–234. https://doi.org/10.1016/j.brainres.2009.11.002

Brooks-Russell, A., Simons-Morton, B., Haynie, D., Farhat, T., & Wang, J. (2014). Longitudinal Relationship Between Drinking with Peers, Descriptive Norms, and Adolescent Alcohol Use. Prevention Science, 15(4), 497–505. https://doi.org/10.1007/s11121-013-0391-9

Broyd, S. J., van Hell, H. H., Beale, C., Yücel, M., & Solowij, N. (2016). Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review. Biological Psychiatry, 79(7), 557–567. https://doi.org/10.1016/j.biopsych.2015.12.002

Buckner, J. D. (2013). College cannabis use: The unique roles of social norms, motives, and expectancies. Journal of Studies on Alcohol and Drugs, 74(5), 720–726. https://doi.org/10.15288/jsad.2013.74.720

Buckner, J. D., Zvolensky, M. J., & Schmidt, N. B. (2012). Cannabis-related impairment and social anxiety: The roles of gender and cannabis use motives. Addictive Behaviors, 37(11), 1294–1297. https://doi.org/10.1016/j.addbeh.2012.06.013

Budney, A. J., Novy, P. L., & Hughes, J. R. (1999). Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction, 94(9), 1311–1322. https://doi.org/10.1046/j.1360-0443.1999.94913114.x

Budney, A. J., Vandrey, R. G., Hughes, J. R., Thostenson, J. D., & Bursac, Z. (2008). Comparison of cannabis and tobacco withdrawal: Severity and contribution to relapse. Journal of Substance Abuse Treatment, 35(4), 362–368. https://doi.org/10.1016/j.jsat.2008.01.002

Burnham, K. P., & Anderson, D. R. (2002). Model selection and multimodel inference: A practical information-theoretic approach. (2nd ed.). Springer-Verlag.

C

Cacioppo, J. T., & Petty, R. E. (1982). The need for cognition. Journal of Personality and Social Psychology, 42(1), 116–131. https://doi.org/10.1037/0022-3514.42.1.116

Calabria, B., Degenhardt, L., Briegleb, C., Vos, T., Hall, W., Lynskey, M., Callaghan, B., Rana, U., & McLaren, J. (2010). Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence. Addictive Behaviors, 35(8), 741–749. https://doi.org/10.1016/j.addbeh.2010.03.019

Calakos, K. C., Bhatt, S., Foster, D. W., & Cosgrove, K. P. (2017). Mechanisms Underlying Sex Differences in Cannabis Use. Current Addiction Reports, 4(4), 439–453. https://doi.org/10.1007/s40429-017-0174-7

Cane, J. E., Sharma, D., & Albery, I. P. (2009). The addiction Stroop task: Examining the fast and slow effects of smoking and marijuana-related cues. Journal of Psychopharmacology, 23(5), 510–519. https://doi.org/10.1177/0269881108091253

Caouette, J. D., & Feldstein Ewing, S. W. (2017). Four Mechanistic Models of Peer Influence on Adolescent Cannabis Use. Current Addiction Reports, 4(2), 90-99. https://doi.org/10.1007/s40429-017-0144-0

Carpenter, K. M., Martinez, D., Vadhan, N. P., Barnes-Holmes, D., & Nunes, E. v. (2012). Measures of attentional bias and relational responding are associated with behavioral treatment outcome for cocaine dependence. American Journal of Drug and Alcohol Abuse, 38(2), 146–154. https://doi.org/10.3109/00952990.2011.643986

Carpenter, K. M., Schreiber, E., Church, S., & McDowell, D. (2006). Drug Stroop performance: Relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. Addictive Behaviors, 31(1), 174–181. https://doi.org/10.1016/j.addbeh.2005.04.012

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. Annals of the New York Academy of Sciences, 1124, 111–126. https://doi.org/10.1196/annals.1440.010

Caswell, A. J., Morgan, M. J., & Duka, T. (2013). Inhibitory Control Contributes to "Motor"- but not "Cognitive"-Impulsivity. Experimental Psychology, 60(5), 324–334. https://doi.org/10.1027/1618-3169/a000202

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. Brain, 129(3), 564-583. https://doi.org/10.1093/brain/awl004

Chabrol, H., Chauchard, E., Mabila, J. D., Mantoulan, R., Adèle, A., & Rousseau, A. (2006). Contributions of social influences and expectations of use to cannabis use in high-school students. Addictive Behaviors, 31(11), 2116–2119. https://doi.org/10.1016/j.addbeh.2006.01.005

Chan, G. C. K., Becker, D., Butterworth, P., Hines, L., Coffey, C., Hall, W., & Patton, G. (2021). Young-adult compared to adolescent onset of regular cannabis use: A 20-year prospective cohort study of later consequences. Drug and Alcohol Review, 40(4), 627–636. https://doi.org/10.1111/dar.13239

Chandra, S., Radwan, M. M., Majumdar, C. G., Church, J. C., Freeman, T. P., & ElSohly, M. A. (2019). New trends in cannabis potency in USA and Europe during the last decade (2008–2017). European Archives of Psychiatry and Clinical Neuroscience, 269(1), 5–15. https://doi.org/10.1007/s00406-019-00983-5

Chang, L., Yakupov, R., Cloak, C., & Ernst, T. (2006). Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain, 129(5), 1096–1112. https://doi.org/10.1093/brain/awl064

Charboneau, E. J., Dietrich, M. S., Park, S., Cao, A., Watkins, T. J., Blackford, J. U., Benningfield, M. M., Martin, P. R., Buchowski, M. S., & Cowan, R. L. (2013). Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: Preliminary results. Psychiatry Research: Neuroimaging, 214(2), 122–131. https://doi.org/10.1016/j.pscychresns.2013.06.005

Charles-Walsh, K., Upton, D. J., & Hester, R. (2016). Examining the interaction between cognitive control and reward sensitivity in substance use dependence. Drug and Alcohol Dependence, 166, 235–242. https://doi.org/10.1016/j.drugalcdep.2016.07.020

Chassin, L., Flora, D. B., & King, K. M. (2004). Trajectories of alcohol and drug use and dependence from adolescence to adulthood: The effects of familial alcoholism and personality. Journal of Abnormal Psychology, 113(4), 483–498. https://doi.org/10.1037/0021-843X.113.4.483

Chen, C.-Y., Wagner, F. A., & Anthony, J. C. (2002). Marijuana use and the risk of Major Depressive Episode. Social Psychiatry and Psychiatric Epidemiology, 37(5), 199–206. https://doi.org/10.1007/s00127-002-0541-z

Chiao, J. Y. (2015). Current Emotion Research in Cultural Neuroscience. Emotion Review, 7(3), 280–293. https://doi.org/10.1177/1754073914546389

Chiao, J. Y., Cheon, B. K., Pornpattananangkul, N., Mrazek, A. J., & Blizinsky, K. D. (2013). Cultural Neuroscience: Progress and Promise. Psychological Inquiry, 24(1), 1–19. https://doi.org/10.1080/1047840X.2013.752715

Christiansen, P., Schoenmakers, T. M., & Field, M. (2015). Less than meets the eye: Reappraising the clinical relevance of attentional bias in addiction. Addictive Behaviors, 44, 43–50. https://doi.org/10.1016/j.addbeh.2014.10.005

Chye, Y., Lorenzetti, V., Suo, C., Batalla, A., Cousijn, J., Goudriaan, A. E., Jenkinson, M., Martin-Santos, R., Whittle, S., Yücel, M., & Solowij, N. (2019). Alteration to hippocampal volume and shape confined to cannabis dependence: a multi-site study. Addiction Biology, 24(4), 822–834. https://doi.org/10.1111/adb.12652

Ciranka, S., & van den Bos, W. (2019). Social influence in adolescent decision-making: A formal framework. Frontiers in Psychology, 10, 1915. https://doi.org/10.3389/fpsyg.2019.01915

Clifton, L., & Clifton, D. A. (2019). The correlation between baseline score and post-intervention score, and its implications for statistical analysis. Trials, 20(1), 43. https://doi.org/10.1186/s13063-018-3108-3

Coalson, D. L., Raiford, S. E., Saklofske, D. H., & Weiss, L. G. (2010). WAIS-IV. In WAIS-IV Clinical Use and Interpretation. https://doi.org/10.1016/b978-0-12-375035-8.10001-1

Colell, E., Sánchez-Niubò, A., & Domingo-Salvany, A. (2013). Sex differences in the cumulative incidence of substance use by birth cohort. International Journal of Drug Policy, 24(4), 319–325. https://doi.org/10.1016/j.drugpo.2012.09.006

Colizzi, M., McGuire, P., Pertwee, R. G., & Bhattacharyya, S. (2016). Effect of cannabis on glutamate signalling in the brain: A systematic review of human and animal evidence. Neuroscience and Biobehavioral Reviews, 64, 359-381. https://doi.org/10.1016/j.neubiorev.2016.03.010

Connor, J. P., Gullo, M. J., Chan, G., Young, R. M. D., Hall, W. D., & Feeney, G. F. X. (2013). Polysubstance use in cannabis users referred for treatment: Drug use profiles, psychiatric comorbidity and cannabis-related beliefs. Frontiers in Psychiatry, 4, 1–7. https://doi.org/10.3389/fpsyt.2013.00079

Connor, J. P., Gullo, M. J., White, A., & Kelly, A. B. (2014). Polysubstance use: Diagnostic challenges, patterns of use and health. Current Opinion in Psychiatry, 27(4), 269–275. https://doi.org/10.1097/YCO.0000000000000069

Contreras, A., Nieto, I., Valiente, C., Espinosa, R., & Vazquez, C. (2019). The study of psychopathology from the network analysis perspective: A systematic review. Psychotherapy and Psychosomatics, 88(2), 71-83. https://doi.org/10.1159/000497425

Cooper, M. L. (1994). Motivations for alcohol use among adolescents: Development and validation of a four-factor model. Psychological Assessment, 6(2), 117–128. https://doi.org/10.1037/1040-3590.6.2.117

Copersino, M., Boyd, S., Tashkin, D., Huestis, M., Heishman, S., Dermand, J., Simmons, M., & Gorelick, D. (2006). Quitting among non-treatment-seeking marijuana users: Reasons and changes in other substance use. American Journal on Addictions, 15(4), 297–302. https://doi.org/10.1080/10550490600754341

Copersino, M. L., Fals-Stewart, W., Fitzmaurice, G., Schretlen, D. J., Sokoloff, J., & Weiss, R. D. (2009). Rapid cognitive screening of patients with substance use disorders. Experimental and Clinical Psychopharmacology, 17(5), 337–344. https://doi.org/10.1037/a0017260

Copersino, M. L., Schretlen, D. J., Fitzmaurice, G. M., Lukas, S. E., Faberman, J., Sokoloff, J., & Weiss, R. D. (2012). Effects of Cognitive Impairment on Substance Abuse Treatment Attendance: Predictive Validation of a Brief Cognitive Screening Measure. The American Journal of Drug and Alcohol Abuse, 38(3), 246–250. https://doi.org/10.3109/00952990.2012.670866

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2012). Approach-Bias Predicts Development of Cannabis Problem Severity in Heavy Cannabis Users: Results from a Prospective FMRI Study. PLoS ONE, 7(9), e42394. https://doi.org/10.1371/journal.pone.0042394

Cousijn, J., Goudriaan, A. E., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Wiers, R. W. (2013). Neural responses associated with cue-reactivity in frequent cannabis users. Addiction Biology, 18(3), 570–580. https://doi.org/10.1111/j.1369-1600.2011.00417.x

Cousijn, J., Goudriaan, A. E., & Wiers, R. W. (2011). Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. Addiction, 106(9), 1667–1674. https://doi.org/10.1111/j.1360-0443.2011.03475.x

Cousijn, J., Luijten, M., & Feldstein Ewing, S. W. (2018). Adolescent resilience to addiction: a social plasticity hypothesis. The Lancet Child and Adolescent Health, 2(1), 69–78. https://doi.org/10.1016/S2352-4642(17)30148-7

Cousijn, J., Núñez, A. E., & Filbey, F. M. (2018). Time to acknowledge the mixed effects of cannabis on health: a summary and critical review of the NASEM 2017 report on the health effects of cannabis and cannabinoids. Addiction, 113(5), 958-966. https://doi.org/10.1111/add.14084.

Cousijn, J., Ridderinkhof, K. R., & Kaag, A. M. (2021). Sex-dependent prefrontal cortex activation in regular cocaine users: A working memory functional magnetic resonance imaging study. Addiction Biology, 26(5), e13003. https://doi.org/10.1111/adb.13003

Cousijn, J., Snoek, R. W. M., & Wiers, R. W. (2013). Cannabis intoxication inhibits avoidance action tendencies: a field study in the Amsterdam coffee shops. Psychopharmacology, 229(1), 167–176. https://doi.org/10.1007/s00213-013-3097-6

Cousijn, J., van Benthem, P., van der Schee, E., & Spijkerman, R. (2015). Motivational and control mechanisms underlying adolescent cannabis use disorders: A prospective study. Developmental Cognitive Neuroscience, 16, 36–45. https://doi.org/10.1016/j.dcn.2015.04.001

Cousijn, J., & van Duijvenvoorde, A. C. K. (2018). Cognitive and Mental Health Predictors of Withdrawal Severity During an Active Attempt to Cut Down Cannabis Use. Frontiers in Psychiatry, 9, 1–10. https://doi.org/10.3389/fpsyt.2018.00301

Cousijn, J., Vingerhoets, W. A. M., Koenders, L., de Haan, L., van den Brink, W., Wiers, R. W., & Goudriaan, A. E. (2014). Relationship between working-memory network function and substance use: a 3-year longitudinal fMRI study in heavy cannabis users and controls. Addiction Biology, 19(2), 282–293. https://doi.org/10.1111/adb.12111

Cousijn, J., Watson, P., Koenders, L., Vingerhoets, W. A. M., Goudriaan, A. E., & Wiers, R. W. (2013). Cannabis dependence, cognitive control and attentional bias for cannabis words. Addictive Behaviors, 38(12), 2825–2832. https://doi.org/10.1016/j.addbeh.2013.08.011

Cousijn, J., Wiers, R. W., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., & Goudriaan, A. E. (2014). Effect of baseline cannabis use and working-memory network function on changes in cannabis use in heavy cannabis users: A prospective fMRI study. Human Brain Mapping, 35(5), 2470–2482. https://doi.org/10.1002/hbm.22342

Covey, D. P., Mateo, Y., Sulzer, D., Cheer, J. F., & Lovinger, D. M. (2017). Endocannabinoid modulation of dopamine neurotransmission. Neuropharmacology, 124, 52-61. https://doi.org/10.1016/j.neuropharm.2017.04.033.

Cox, W. M., Hogan, L. M., Kristian, M. R., & Race, J. H. (2002). Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. Drug and Alcohol Dependence, 68(3), 237–243. https://doi.org/10.1016/S0376-8716(02)00219-3

Crane, N. A., Schuster, R. M., Fusar-Poli, P., & Gonzalez, R. (2013). Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences. Neuropsychology Review, 23(2), 117–137. https://doi.org/10.1007/s11065-012-9222-1

Crane, N. A., Schuster, R. M., & Gonzalez, R. (2013). Preliminary Evidence for a Sex-Specific Relationship between Amount of Cannabis Use and Neurocognitive Performance in Young Adult Cannabis Users. Journal of the International Neuropsychological Society, 19(9), 1009–1015. https://doi.org/10.1017/S135561771300088X

Crean, R. D., Crane, N. A., & Mason, B. J. (2011). An Evidence-Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions. Journal of Addiction Medicine, 5(1), 1–8. https://doi.org/10.1097/ADM.0b013e31820c23fa

Crippa, J. A., Zuardi, A. W., Martín-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., & Fusar-Poli, P. (2009). Cannabis and anxiety: a critical review of the evidence. Human Psychopharmacology: Clinical and Experimental, 24(7), 515–523. https://doi.org/10.1002/hup.1048

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. Nature Reviews Neuroscience, 13(9), 636–650. https://doi.org/10.1038/nrn3313

Crutzen, R., Kuntsche, E., & Schelleman-offermans, K. (2013). Drinking Motives and Drinking Behavior Over Time : A Full Cross-Lagged Panel Study Among Adults. 27(1), 197–201. https://doi.org/10.1037/a0029824

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J. A., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. Nature Reviews Neuroscience, 17(5), 293–306. https://doi.org/10.1038/nrn.2016.28

Cuttler, C., Mischley, L. K., & Sexton, M. (2016). Sex Differences in Cannabis Use and Effects: A Cross-Sectional Survey of Cannabis Users. Cannabis and Cannabinoid Research, 1(1), 166–175. https://doi.org/10.1089/can.2016.0010

Cuttler, C., Spradlin, A., Nusbaum, A. T., Whitney, P., Hinson, J. M., & McLaughlin, R. J. (2019). Joint effects of stress and chronic cannabis use on prospective memory. Psychopharmacology, 236, 1973-1983. https://doi.org/10.1007/s00213-019-5184-9.

D

D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T. B., & Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. Biological Psychiatry, 57(6), 594–608. https://doi.org/10.1016/j.biopsych.2004.12.006

D'Souza D. C., Cortes-Briones J., Creatura G., Bluez G. Thurnauer H., Deaso E. et al. (2019). Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. Lancet Psychiatry, 6, 35–45. https://doi.org/10.1016/S2215-0366(18)30427-9

D'Souza, D. C., Cortes-Briones, J. A., Ranganathan, M., Thurnauer, H., Creatura, G., Surti, T., Planeta, B., Neumeister, A., Pittman, B., Normandin, M. D., Kapinos, M., Ropchan, J., Huang, Y., Carson, R. E., & Skosnik, P. D. (2016). Rapid Changes in Cannabinoid 1 Receptor Availability in Cannabis-Dependent Male Subjects after Abstinence from Cannabis. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1(1), 60–67. https://doi.org/10.1016/j.bpsc.2015.09.008

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y., Braley, G., Gueorguieva, R., & Krystal, J. H. (2004). The Psychotomimetic Effects of Intravenous Delta-9-Tetrahydrocannabinol in Healthy Individuals: Implications for Psychosis. Neuropsychopharmacology, 29(8), 1558–1572. https://doi.org/10.1038/sj.npp.1300496

D'Souza, D. C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., ... & Krystal, J. (2008). Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology, 33(10), 2505-2516. https://doi.org/10.1038/sj.npp.1301643.

Danckert, J., & Merrifield, C. (2018). Boredom, sustained attention and the default mode network. Experimental Brain Research, 236(9), 2507–2518. https://doi.org/10.1007/s00221-016-4617-5

Davis, M. L., Powers, M. B., Handelsman, P., Medina, J. L., Zvolensky, M., & Smits, J. A. J. (2015). Behavioral Therapies for Treatment-Seeking Cannabis Users. Evaluation & the Health Professions, 38(1), 94–114. https://doi.org/10.1177/0163278714529970

Dawson, D. A., Grant, B. F., Stinson, F. S., & Chou, P. S. (2006). Maturing out of alcohol dependence: The impact of transitional life events. Journal of Studies on Alcohol, 67(2), 195–203. https://doi.org/10.15288/jsa.2006.67.195

de Haan, L., Wiers, R. W., Vingerhoets, W. A. M., Cousijn, J., Koenders, L., Goudriaan, A. E., & van den Brink, W. (2013). Relationship between working-memory network function and substance use: a 3-year longitudinal fMRI study in heavy cannabis users and controls. Addiction Biology, 19(2), 282–293. https://doi.org/10.1111/adb.12111

de La Vega, A., Chang, L. J., Banich, M. T., Wager, T. D., & Yarkoni, T. (2016). Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. Journal of Neuroscience, 36(24), 6553–6562. https://doi.org/10.1523/JNEUROSCI.4402-15.2016

Degenhardt, L., Charlson, F., Ferrari, A., Santomauro, D., Erskine, H., Mantilla-Herrara, A., Whiteford, H., Leung, J., Naghavi, M., Griswold, M., Rehm, J., Hall, W., Sartorius, B., Scott, J., Vollset, S. E., Knudsen, A. K., Haro, J. M., Patton, G., Kopec, J., ... Vos, T. (2018). The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry, 5(12), 987–1012. https://doi.org/10.1016/S2215-0366(18)30337-7

Degenhardt, L., Dierker, L., Chiu, W. T., Medina-Mora, M. E., Neumark, Y., Sampson, N., Alonso, J., Angermeyer, M., Anthony, J. C., Bruffaerts, R., de Girolamo, G., de Graaf, R., Gureje, O., Karam, A. N., Kostyuchenko, S., Lee, S., Lépine, J.-P., Levinson, D., Nakamura, Y., ... Kessler, R. C. (2010). Evaluating the drug use "gateway" theory using cross-national data: Consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug and Alcohol Dependence, 108(1–2), 84–97. https://doi.org/10.1016/j.drugalcdep.2009.12.001

Degenhardt, L., Hall, W., & Lynskey, M. (2001). The relationship between cannabis use and other substance use in the general population. In Drug and Alcohol Dependence, 64, 319-327. https://doi.org/10.1016/s0376-8716(01)00130-2

Denis, C., Lavie, E., Fatseas, M., & Auriacombe, M. (2006). Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. Cochrane Database of Systematic Reviews, 3(3), CD005336.

DeWitt, S. J., Ketcherside, A., McQueeny, T. M., Dunlop, J. P., & Filbey, F. M. (2015). The hyper-sentient addict: An exteroception model of addiction. In American Journal of Drug and Alcohol Abuse, 41(5), 374-381. https://doi.org/10.3109/00952990.2015.1049701

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H. E., Ferraro, L., la Cascia, C., la Barbera, D., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., Velthorst, E., Bernardo, M., Del-Ben, C. M., ... van der Ven, E. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. The Lancet Psychiatry, 6(5), 427–436. https://doi.org/10.1016/S2215-0366(19)30048-3

Diaz, M. T., & McCarthy, G. (2009). A comparison of brain activity evoked by single content and function words: An fMRI investigation of implicit word processing. Brain Research, 1282, 38–49. https://doi.org/10.1016/j.brainres.2009.05.043

Dodds, S., & Hess, A. C. (2020). Adapting research methodology during COVID-19: lessons for transformative service research. Journal of Service Management. https://doi.org/10.1108/JOSM-05-2020-0153

Dom, G., Samochowiec, J., Evans-Lacko, S., Wahlbeck, K., Van Hal, G., & McDaid, D. (2016). The impact of the 2008 economic crisis on substance use patterns in the countries of the European Union. International Journal of Environmental Research and Public Health, 13(1), 122. https://doi.org/10.3390/ijerph13010122

Downey, L. A., King, R., Papafotiou, K., Swann, P., Ogden, E., Boorman, M., & Stough, C. (2013). The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. Accident Analysis and Prevention, 50, 879–886. https://doi.org/10.1016/j.aap.2012.07.016

Dubey, M. J., Ghosh, R., Chatterjee, S., Biswas, P., Chatterjee, S., & Dubey, S. (2020). COVID-19 and addiction. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 14(5), 817–823. https://doi.org/10.1016/j.dsx.2020.06.008

Dugan, S., Bogema, S., & Lappas, N. T. (1994). Stability of drugs of abuse in urine samples stored at -20 degrees C. Journal of Analytical Toxicology, 18(7), 391–396. https://doi.org/10.1093/JAT/18.7.391

Dumas, T. M., Ellis, W., & Litt, D. M. (2020). What Does Adolescent Substance Use Look Like During the COVID-19 Pandemic? Examining Changes in Frequency, Social Contexts, and Pandemic-Related Predictors. Journal of Adolescent Health, 67(3), 354–361. https://doi.org/10.1016/j.jadohealth.2020.06.018

Duperrouzel, J. C., Hawes, S. W., Lopez-Quintero, C., Pacheco-Colón, I., Coxe, S., Hayes, T., & Gonzalez, R. (2019). Adolescent cannabis use and its associations with decision-making and episodic memory: Preliminary results from a longitudinal study. Neuropsychology, 33(5), 701-710. https://doi.org/10.1037/neu0000538.

E

Efird, J. T., Friedman, G. D., Sidney, S., Klatsky, A., Habel, L. A., Udaltsova, N. V., Van Den Eeden, S., & Nelson, L. M. (2004). The Risk for Malignant Primary Adult-Onset Glioma in a Large, Multiethnic, Managed-Care Cohort: Cigarette Smoking and Other Lifestyle Behaviors. Journal of Neuro-Oncology, 68(1), 57–69. https://doi.org/10.1023/B:NEON.0000024746.87666.ed

Eisenberg, M. E., Toumbourou, J. W., Catalano, R. F., & Hemphill, S. A. (2014). Social Norms in the Development of Adolescent Substance Use: A Longitudinal Analysis of the International Youth Development Study. Journal of Youth and Adolescence, 43(9), 1486–1497. https://doi.org/10.1007/s10964-014-0111-1

EMCDDA. (2015). Treatment of cannabis-related disorders in Europe. In Insights. https://doi.org/10.2810/621856

EMCDDA. (2019). European Drug Report 2019: Trends and Developments. https://doi.org/10.2810/191370

Epskamp, S., Borsboom, D., & Fried, E. I. (2018). Estimating psychological networks and their accuracy: A tutorial paper. Behavior Research Methods, 50(1), 195–212. https://doi.org/10.3758/s13428-017-0862-1

Epskamp, S., Cramer, A. O. J., Waldorp, L. J., Schmittmann, V. D., & Borsboom, D. (2012). Qgraph: Network visualizations of relationships in psychometric data. Journal of Statistical Software, 48(4). https://doi.org/10.18637/jss.v048.i04

Erk, S., Kleczar, A., & Walter, H. (2007). Valence-specific regulation effects in a working memory task with emotional context. NeuroImage, 37(2), 623–632. https://doi.org/10.1016/j.neuroimage.2007.05.006

Esse, K., Fossati-Bellani, M., Traylor, A., & Martin-Schild, S. (2011). Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. Brain and Behavior, 1(1), 44–54. https://doi.org/10.1002/brb3.7

Esteban, O., Blair, R., Markiewicz, C. J., Berleant, S. L., Moodie, C., Ma, F., Isik, A. I., Erramuzpe, A., Goncalves, M., Poldrack, R. A., & Gorgolewski, K. J. (2017). fmriprep (1.0.0-rc5). https://doi.org/https://doi.org/10.5281/zenodo.996169

Ewald, D. R., Strack, R. W., & Orsini, M. M. (2019). Rethinking Addiction. Global Pediatric Health, 6, 1-16. https://doi.org/10.1177/2333794X18821943

F

Farmer, R. F., Seeley, J. R., Kosty, D. B., Gau, J. M., Duncan, S. C., Lynskey, M. T., & Lewinsohn, P. M. (2015). Internalizing and externalizing psychopathology as predictors of cannabis use disorder onset during adolescence and early adulthood. Psychology of Addictive Behaviors, 29(3), 541–551. https://doi.org/10.1037/adb0000059

Fatima, H., Howlett, A. C., & Whitlow, C. T. (2019). Reward, control & decision-making in cannabis use disorder: insights from functional MRI. The British Journal of Radiology, 92(1101), 20190165. https://doi.org/10.1259/bjr.20190165.

Feingold, D., Fox, J., Rehm, J., & Lev-Ran, S. (2015). Natural outcome of cannabis use disorder: A 3-year longitudinal follow-up. Addiction, 110(12), 1963–1974. https://doi.org/10.1111/add.13071

Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2015). The association between cannabis use and mood disorders: A longitudinal study. Journal of Affective Disorders, 172, 211–218. https://doi.org/10.1016/j.jad.2014.10.006

Ferland, J. M. N., & Hurd, Y. L. (2020). Deconstructing the neurobiology of cannabis use disorder. Nature Neuroscience, 23(5), 600-610. https://doi.org/10.1038/s41593-020-0611-0

Field, M. (2005). Cannabis “dependence” and attentional bias for cannabis-related words. Behavioural Pharmacology, 16(5–6), 473–476. https://doi.org/https://doi.org/10.1097/00008877-200509000-00021

Field, M. (2009). A Meta-Analytic Investigation of the Relationship Between Attentional Bias and Subjective Craving in Substance Abuse. Psychological Bulletin, 135(4), 589–607. https://doi.org/10.1037/a0015843.A

Field, M., & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. Drug and Alcohol Dependence, 97(1–2), 1–20. https://doi.org/10.1016/j.drugalcdep.2008.03.030

Field, M., Christiansen, P., Cole, J., & Goudie, A. (2007). Delay discounting and the alcohol Stroop in heavy drinking adolescents. Addiction, 102(4), 579–586. https://doi.org/10.1111/j.1360-0443.2007.01743.x

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. Psychopharmacology, 183(3), 350–357. https://doi.org/10.1007/s00213-005-0202-5

Field, M., Marhe, R., & Franken, I. H. A. (2014). The clinical relevance of attentional bias in substance use disorders. CNS Spectrums, 19(3), 225–230. https://doi.org/10.1017/S1092852913000321

Field, M., Mogg, K., & Bradley, B. P. (2004). Cognitive bias and drug craving in recreational cannabis users. Drug and Alcohol Dependence, 74(1), 105–111. https://doi.org/10.1016/j.drugalcdep.2003.12.005

Figueiredo, P. R., Tolomeo, S., Steele, J. D., & Baldacchino, A. (2020). Neurocognitive consequences of chronic cannabis use: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 108, 358-369. https://doi.org/10.1016/j.neubiorev.2019.10.014.

Filbey, F. M., Gohel, S., Prashad, S., & Biswal, B. B. (2018). Differential associations of combined vs. isolated cannabis and nicotine on brain resting state networks. Brain Structure & Function, 223(7), 3317–3326. https://doi.org/10.1007/S00429-018-1690-5

Filbey, F. M., Schacht, J. P., Myers, U. S., Chavez, R. S., & Hutchison, K. E. (2009). Marijuana craving in the brain. Proceedings of the National Academy of Sciences, 106(31), 13016–13021. https://doi.org/10.1073/pnas.0903863106

First, M. B. (2015). Structured Clinical Interview for the DSM (SCID) . In The Encyclopedia of Clinical Psychology. https://doi.org/10.1002/9781118625392.wbecp351

Fogel, J. S., Kelly, T. H., Westgate, P. M., & Lile, J. A. (2017). Sex differences in the subjective effects of oral Δ9-THC in cannabis users. Pharmacology Biochemistry and Behavior, 152, 44–51. https://doi.org/10.1016/j.pbb.2016.01.007

Forbes, M. K., Wright, A. G. C., Markon, K. E., & Krueger, R. F. (2017). Evidence that psychopathology symptom networks have limited replicability. Journal of Abnormal Psychology, 126(7), 969–988. https://doi.org/10.1037/abn0000276

Ford, T. C., Hayley, A. C., Downey, L. A., & Parrott, A. C. (2018). Cannabis: An Overview of its Adverse Acute and Chronic Effects and its Implications. Current Drug Abuse Reviews, 10(1), 6–18. https://doi.org/10.2174/1874473710666170712113042

Foulkes, L., Viding, E., McCrory, E., & Neumann, C. S. (2014). Social Reward Questionnaire (SRQ): Development and validation. Frontiers in Psychology, 5, 1–8. https://doi.org/10.3389/fpsyg.2014.00201

Fraga, S. G., Díaz-Flores Estévez, J. F., & Romero, C. D. (1998). Stability of cannabinoids in urine in three storage temperatures. Annals of Clinical and Laboratory Science, 28(3), 160–162.

Freeman, T. P., & Lorenzetti, V. (2020). ‘Standard THC units’: a proposal to standardize dose across all cannabis products and methods of administration. Addiction, 115(7), 1207-1216. https://doi.org/10.1111/add.14842.

Freeman, T. P., & Winstock, A. R. (2015). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. Psychological Medicine, 45(15), 3181–3189. https://doi.org/10.1017/S0033291715001178

Fridberg, D. J., Queller, S., Ahn, W. Y., Kim, W., Bishara, A. J., Busemeyer, J. R., Porrino, L., & Stout, J. C. (2010). Cognitive mechanisms underlying risky decision-making in chronic cannabis users. Journal of Mathematical Psychology, 54(1), 28–38. https://doi.org/10.1016/j.jmp.2009.10.002

Fried, E. I., van Borkulo, C. D., Cramer, A. O. J., Boschloo, L., Schoevers, R. A., & Borsboom, D. (2017). Mental disorders as networks of problems: a review of recent insights. Social Psychiatry and Psychiatric Epidemiology, 52(1), 1-10. https://doi.org/10.1007/s00127-016-1319-z

Fried, P., Watkinson, B., James, D., & Gray, R. (2002). Current and former marijuana use: Preliminary findings of a longitudinal study of effects on IQ in young adults. Cmaj, 166(7), 887–891.

Fusar-Poli, P., Crippa, J. A., Bhattacharyya, S., Borgwardt, S. J., Allen, P., Martin-Santos, R., Seal, M., Surguladze, S. A., O'Carrol, C., Atakan, Z., Zuardi, A. W., & McGuire, P. K. (2009). Distinct Effects of Δ9-Tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing. Archives of General Psychiatry, 66(1), 95. https://doi.org/10.1001/archgenpsychiatry.2008.519

G

Ganis, G., Thompson, W. L., & Kosslyn, S. M. (2004). Brain areas underlying visual mental imagery and visual perception: An fMRI study. Cognitive Brain Research, 20(2), 226–241. https://doi.org/10.1016/j.cogbrainres.2004.02.012

Ganzer, F., Bröning, S., Kraft, S., Sack, P. M., & Thomasius, R. (2016). Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. Neuropsychology Review, 26(2), 186–222. https://doi.org/10.1007/s11065-016-9316-2

Garavan, H. (2010). Insula and drug cravings. Brain Structure & Function, 214(5–6), 593–601. https://doi.org/10.1007/s00429-010-0259-8

García-García, I., Horstmann, A., Jurado, M. A., Garolera, M., Chaudhry, S. J., Margulies, D. S., Villringer, A., & Neumann, J. (2014). Reward processing in obesity, substance addiction and non-substance addiction. Obesity Reviews, 15(11), 853–869. https://doi.org/10.1111/obr.12221

Gardner, M., & Steinberg, L. (2005). Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: An experimental study. Developmental Psychology, 41(4), 625–635. https://doi.org/10.1037/0012-1649.41.4.625

Gates, P. J., Sabioni, P., Copeland, J., Le Foll, B., & Gowing, L. (2016). Psychosocial interventions for cannabis use disorder. Cochrane Database of Systematic Reviews, 2016(5). https://doi.org/10.1002/14651858.CD005336.pub4

Gilman, J. M., Calderon, V., Curran, M. T., & Evins, A. E. (2015). Young adult cannabis users report greater propensity for risk-taking only in non-monetary domains. Drug and alcohol dependence, 147, 26-31. https://doi.org/10.1016/j.drugalcdep.2014.12.020.

Gladwin, T. E., Figner, B., Crone, E. A., & Wiers, R. W. (2011). Addiction, adolescence, and the integration of control and motivation. Developmental Cognitive Neuroscience, 1(4), 364–376. https://doi.org/10.1016/j.dcn.2011.06.008

Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., & Mayo, N. (2019). Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood. JAMA Psychiatry, 76(4), 426. https://doi.org/10.1001/jamapsychiatry.2018.4500

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. Nature Reviews Neuroscience, 12(11), 652–669. https://doi.org/10.1038/nrn3119

Gonzalez, R., Schuster, R. M., Mermelstein, R. J., Vassileva, J., Martin, E. M., & Diviak, K. R. (2012). Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. Journal of Clinical and Experimental Neuropsychology, 34(9), 962–976. https://doi.org/10.1080/13803395.2012.703642

Gonzalez, S., Cebeira, M., & Fernández-Ruiz, J. (2005). Cannabinoid tolerance and dependence: A review of studies in laboratory animals. Pharmacology Biochemistry and Behavior, 81(2), 300–318. https://doi.org/10.1016/j.pbb.2005.01.028

Grant, J. E., Chamberlain, S. R., Schreiber, L., & Odlaug, B. L. (2012). Neuropsychological deficits associated with cannabis use in young adults. Drug and Alcohol Dependence, 121(1–2), 159–162. https://doi.org/10.1016/j.drugalcdep.2011.08.015

Griffith-Lendering, M. F. H., Huijbregts, S. C. J., Vollebergh, W. A. M., & Swaab, H. (2012). Motivational and cognitive inhibitory control in recreational cannabis users. Journal of Clinical and Experimental Neuropsychology, 34(7), 688–697. https://doi.org/10.1080/13803395.2012.668874

Grimm, S., Weigand, A., Kazzer, P., Jacobs, A. M., & Bajbouj, M. (2012). Neural mechanisms underlying the integration of emotion and working memory. NeuroImage, 61(4), 1188–1194. https://doi.org/10.1016/j.neuroimage.2012.04.004

Groshkova, T., Stoian, T., Cunningham, A., Griffiths, P., Singleton, N., & Sedefov, R. (2020). Will the Current COVID-19 Pandemic Impact on Long-Term Cannabis Buying Practices? Journal of Addiction Medicine, 6–8. https://doi.org/10.1097/ADM.0000000000000698

Gruber, S. A., Rogowska, J., & Yurgelun-Todd, D. A. (2009). Altered affective response in marijuana smokers: An FMRI study. Drug and Alcohol Dependence, 105(1–2), 139–153. https://doi.org/10.1016/j.drugalcdep.2009.06.019

Guidali, G., Pisoni, A., Bolognini, N., & Papagno, C. (2019). Keeping order in the brain: The supramarginal gyrus and serial order in short-term memory. Cortex, 119, 89–99. https://doi.org/10.1016/j.cortex.2019.04.009

H

Hackam, D. G. (2015). Cannabis and Stroke. Stroke, 46(3), 852–856. https://doi.org/10.1161/STROKEAHA.115.008680

Hall, W., & Lynskey, M. (2020). Assessing the public health impacts of legalizing recreational cannabis use: the US experience. World Psychiatry, 19(2), 179–186. https://doi.org/10.1002/WPS.20735

Hallgren, K., & McCrady, B. (2013). Interference in the alcohol Stroop task with college student binge drinkers. Journal of Behavioral Health, 2(2), 112. https://doi.org/10.5455/jbh.20130224082728

Hammes, J. G. W. (1971). De Stroop Kleur-Woord Test. Handleiding. Swets and Zeitlinger.

Harrison, L. D. (1995). The Validity of Self-Reported Data on Drug Use. Journal of Drug Issues, 25(1), 91–111. https://doi.org/10.1177/002204269502500107

Hartman, R. L., & Huestis, M. A. (2013). Cannabis effects on driving skills. Clinical Chemistry, 59(3), 478–492. https://doi.org/10.1373/clinchem.2012.194381

Harvey, M., Sellman, J., Porter, R., & Frampton, C. (2007). The relationship between non-acute adolescent cannabis use and cognition. Drug and Alcohol Review, 26(3), 309–319. https://doi.org/10.1080/09595230701247772

Hatchard, T., Byron-Alhassan, A., Mioduszewski, O., Holshausen, K., Correia, S., Leeming, A., Ayson, G., Chiasson, C., Fried, P., Cameron, I., & Smith, A. (2020). Working Overtime: Altered Functional Connectivity in Working Memory Following Regular Cannabis Use in Young Adults. International Journal of Mental Health and Addiction, 19, 1314-1329. https://doi.org/10.1007/s11469-020-00226-y

Hayes, A. F., & Coutts, J. J. (2020). Use Omega Rather than Cronbach's Alpha for Estimating Reliability. But.... Communication Methods and Measures, 14(1), 1–24. https://doi.org/10.1080/19312458.2020.1718629

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K.-O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Addiction, 86(9), 1119–1127. https://doi.org/10.1111/j.1360-0443.1991.tb01879.x

Hedden, T., Ketay, S., Aron, A., Markus, H. R., & Gabrieli, J. D. E. (2008). Cultural influences on neural substrates of attentional control. Psychological Science, 19(1), 12–17. https://doi.org/10.1111/j.1467-9280.2008.02038.x

Heidari, S., Babor, T. F., De Castro, P., Tort, S., & Curno, M. (2016). Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review, 1(1), 1–9. https://doi.org/10.1186/s41073-016-0007-6

Heishman, S. J., Evans, R. J., Singleton, E. G., Levin, K. H., Copersino, M. L., & Gorelick, D. A. (2009). Reliability and validity of a short form of the Marijuana Craving Questionnaire. Drug and Alcohol Dependence, 102(1–3), 35–40. https://doi.org/10.1016/j.drugalcdep.2008.12.010

Heishman, S. J., Singleton, E. G., & Liguori, A. (2001). Marijuana Craving Questionnaire: Development and initial validation of a self-report instrument. Addiction, 96(7), 1023–1034. https://doi.org/10.1046/j.1360-0443.2001.967102312.x

Helwig, C. C. (2006). The development of personal autonomy throughout cultures. Cognitive Development, 21(4), 458–473. https://doi.org/10.1016/j.cogdev.2006.06.009

Henkel, D. (2011). Unemployment and substance use: A review of the Literature (1990-2010). Current Drug Abuse Reviews, 4(1), 4–27. https://doi.org/10.2174/1874473711104010004

Henry, E. A., Kaye, J. T., Bryan, A. D., Hutchison, K. E., & Ito, T. A. (2014). Cannabis cue reactivity and craving among never, infrequent and heavy cannabis users. Neuropsychopharmacology, 39(5), 1214–1221. https://doi.org/10.1038/npp.2013.324

Herlin, B., Navarro, V., & Dupont, S. (2021). The temporal pole: From anatomy to function—A literature appraisal. Journal of Chemical Neuroanatomy, 13, 101925. https://doi.org/10.1016/j.jchemneu.2021.101925

Hester, R., & Garavan, H. (2004). Executive dysfunction in cocaine addiction: Evidence for discordant frontal, cingulate, and cerebellar activity. Journal of Neuroscience, 24(49), 11017–11022. https://doi.org/10.1523/JNEUROSCI.3321-04.2004

Hester, R., Dixon, V., & Garavan, H. (2006). A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. Drug and Alcohol Dependence, 81(3), 251–257. https://doi.org/10.1016/j.drugalcdep.2005.07.002

Hester, R., Lubman, D. I., & Yücel, M. (2010). The Role of Executive Control in Human Drug Addiction. In Brain Imaging in Behavioral Neuroscience, 301–318. https://doi.org/10.1007/7854_2009_28

Hester, R., & Luijten, M. (2014). Neural correlates of attentional bias in addiction. CNS Spectrums, 19(3), 231–238. https://doi.org/10.1017/S1092852913000473

Heyman, G. M. (2009). Addiction: a disorder of choice. Harvard University Press.

Hill, A. C., Laird, A. R., & Robinson, J. L. (2014). Gender differences in working memory networks: A BrainMap meta-analysis. Biological Psychology, 102, 18–29. https://doi.org/10.1016/j.biopsycho.2014.06.008

Hindocha, C., Brose, L. S., Walsh, H., & Cheeseman, H. (2021). Cannabis use and co-use in tobacco smokers and non-smokers: prevalence and associations with mental health in a cross-sectional, nationally representative sample of adults in Great Britain, 2020. Addiction, 116(8), 2209–2219. https://doi.org/10.1111/add.15381

Hindocha, C., Freeman, T. P., Ferris, J. A., Lynskey, M. T., & Winstock, A. R. (2016). No smoke without tobacco: A global overview of cannabis and tobacco routes of administration and their association with intention to quit. Frontiers in Psychiatry, 7. https://doi.org/10.3389/fpsyt.2016.00104

Hindocha, C., Freeman, T. P., Schafer, G., Gardener, C., Das, R. K., Morgan, C. J. A., & Curran, H. V. (2015). Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. European Neuropsychopharmacology, 25(3), 325–334. https://doi.org/10.1016/j.euroneuro.2014.11.014

Hines, L. A., Freeman, T. P., Gage, S. H., Zammit, S., Hickman, M., Cannon, M., Munafo, M., MacLeod, J., & Heron, J. (2020). Association of High-Potency Cannabis Use with Mental Health and Substance Use in Adolescence. JAMA Psychiatry, 77(10), 1044–1051. https://doi.org/10.1001/jamapsychiatry.2020.1035

Hirvonen, J., Goodwin, R. S., Li, C.-T., Terry, G. E., Zoghbi, S. S., Morse, C., Pike, V. W., Volkow, N. D., Huestis, M. A., & Innis, R. B. (2012). Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Molecular Psychiatry, 17(6), 642–649. https://doi.org/10.1038/mp.2011.82

Hjorthøj, C. R., Fohlmann, A., Larsen, A. M., Arendt, M., & Nordentoft, M. (2012). Correlations and agreement between delta-9-tetrahydrocannabinol (THC) in blood plasma and timeline follow-back (TLFB)-assisted self-reported use of cannabis of patients with cannabis use disorder and psychotic illness attending the CapOpus randomized clinical trial. Addiction, 107(6), 1123–1131. https://doi.org/10.1111/J.1360-0443.2011.03757.X

Hjorthøj, C. R., Hjorthøj, A. R., & Nordentoft, M. (2012). Validity of Timeline Follow-Back for self-reported use of cannabis and other illicit substances - Systematic review and meta-analysis. Addictive Behaviors, 37(3), 225–233. https://doi.org/10.1016/j.addbeh.2011.11.025

Hoch, E., Bühringer, G., Pixa, A., Dittmer, K., Henker, J., Seifert, A., & Wittchen, H. U. (2014). CANDIS treatment program for cannabis use disorders: Findings from a randomized multi-site translational trial. Drug and Alcohol Dependence, 134(1), 185–193. https://doi.org/10.1016/j.drugalcdep.2013.09.028

Hoch, E., Dittmer, K., Bühringer, G., Wittchen, H. U., Seifert, A., Pixa, A., & Henker, J. (2013). CANDIS treatment program for cannabis use disorders: Findings from a randomized multi-site translational trial. Drug and Alcohol Dependence, 134, 185–193. https://doi.org/10.1016/j.drugalcdep.2013.09.028

Hoch, E., Niemann, D., von Keller, R., Schneider, M., Friemel, C. M., Preuss, U. W., Hasan, A., & Pogarell, O. (2019). How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. European Archives of Psychiatry and Clinical Neuroscience, 269(1), 87–105. https://doi.org/10.1007/s00406-019-00984-4

Hoch, E., Preuss, U. W., Ferri, M., & Simon, R. (2016). Digital Interventions for Problematic Cannabis Users in Non-Clinical Settings: Findings from a Systematic Review and Meta-Analysis. European Addiction Research, 22(5), 233–242. https://doi.org/10.1159/000445716

Hoch, E., Zimmermann, P., Henker, J., Rohrbacher, H., Noack, R., & Bühringer, G. A Marijuana Treatment Program for Youth and Adults. CANDIS Cur. Racho-Mariage. CA: Hazelden Betty Ford: 2017.

Hodgins, D. C., & Stea, J. N. (2018). Psychometric evaluation of a lifetime version of the marijuana problems scale. Addictive Behaviors Reports, 8, 21–24. https://doi.org/10.1016/j.abrep.2018.05.001

Holm, S., Sandberg, S., Kolind, T., & Hesse, M. (2014). The importance of cannabis culture in young adult cannabis use. Journal of Substance Use, 19(3), 251–256. https://doi.org/10.3109/14659891.2013.790493

Holm, S., Tolstrup, J., Thylstrup, B., & Hesse, M. (2016). Neutralization and glorification: Cannabis culture-related beliefs predict cannabis use initiation. Drugs: Education, Prevention and Policy, 23(1), 48–53. https://doi.org/10.3109/09687637.2015.1087967

Holmes, A. J., Hollinshead, M. O., Roffman, J. L., Smoller, J. W., & Buckner, R. L. (2016). Individual differences in cognitive control circuit anatomy link sensation seeking, impulsivity, and substance use. Journal of Neuroscience, 36(14), 4038–4049. https://doi.org/10.1523/JNEUROSCI.3206-15.2016

Hooker, W. D., & Jones, R. T. (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. Psychopharmacology, 91(1), 20–24. https://doi.org/10.1007/BF00690920

Hooper, S. R., Woolley, D., & De Bellis, M. D. (2014). Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder. Psychopharmacology, 231(8), 1467–1477. https://doi.org/10.1007/s00213-014-3463-z

Hoorelbeke, K., Marchetti, I., de Schryver, M., & Koster, E. H. W. (2016). The interplay between cognitive risk and resilience factors in remitted depression: A network analysis. Journal of Affective Disorders, 195, 96–104. https://doi.org/10.1016/j.jad.2016.02.001

Hosseini, S., & Oremus, M. (2019). The Effect of Age of Initiation of Cannabis Use on Psychosis, Depression, and Anxiety among Youth under 25 Years. The Canadian Journal of Psychiatry, 64(5), 304–312. https://doi.org/10.1177/0706743718809339

Howe, E., Bosley, H. G., & Fisher, A. J. (2020). Idiographic network analysis of discrete mood states prior to treatment. Counselling and Psychotherapy Research, 20(3), 470-478. https://doi.org/10.1002/capr.12295

Huang, A. S., Mitchell, J. A., Haber, S. N., Alia-Klein, N., & Goldstein, R. Z. (2018). The thalamus in drug addiction: From rodents to humans. Philosophical Transactions of the Royal Society B: Biological Sciences, 373(1742). https://doi.org/10.1098/rstb.2017.0028

Huang, Y.-H. J., Zhang, Z.-F., Tashkin, D. P., Feng, B., Straif, K., & Hashibe, M. (2015). An Epidemiologic Review of Marijuana and Cancer: An Update. Cancer Epidemiology Biomarkers & Prevention, 24(1), 15–31. https://doi.org/10.1158/1055-9965.EPI-14-1026

Hyman, S. M., & Sinha, R. (2009). Stress-related factors in cannabis use and misuse: Implications for prevention and treatment. Journal of Substance Abuse Treatment, 36(4), 400–413. https://doi.org/10.1016/j.jsat.2008.08.005

I

Imperatori, C., Massullo, C., Carbone, G. A., Panno, A., Giacchini, M., Capriotti, C., Lucarini, E., Zampa, B. R., Murillo-rodr, E., Machado, S., & Farina, B. (2020). brain sciences Connectivity in Undergraduate Problematic Cannabis Users: A Preliminary EEG Coherence Study. Brain Sciences, 10(3), 1–17.

Inzlicht, M., Bartholow, B. D., & Hirsh, J. B. (2015). Emotional foundations of cognitive control. Trends in Cognitive Sciences, 19(3), 126–132. https://doi.org/10.1016/j.tics.2015.01.004

Iordan, A. D., Dolcos, S., & Dolcos, F. (2013). Neural signatures of the response to emotional distraction: A review of evidence from brain imaging investigations. Frontiers in Human Neuroscience, 7, 1–21. https://doi.org/10.3389/fnhum.2013.00200

Isvoranu, A.-M., Ziermans, T., Schirmbeck, F., Borsboom, D., Geurts, H. M., de Haan, L., van Amelsvoort, T., Bartels-Velthuis, A. A., Simons, C. J. P., & van Os, J. (2021). Autistic Symptoms and Social Functioning in Psychosis: A Network Approach. Schizophrenia Bulletin, 48(1), 1–10. https://doi.org/10.1093/schbul/sbab084

J

Jackson, K. M., Sher, K. J., Gotham, H. J., & Wood, P. K. (2001). Transitioning into and out of large-effect drinking in young adulthood. Journal of Abnormal Psychology, 110(3), 378–391. https://doi.org/10.1037//0021-843x.110.3.378

Jacobus, J., Taylor, C. T., Gray, K. M., Meredith, L. R., Porter, A. M., Li, I., Castro, N., & Squeglia, L. M. (2018). A multi-site proof-of-concept investigation of computerized approach-avoidance training in adolescent cannabis users. Drug and Alcohol Dependence, 187(6), 195–204. https://doi.org/10.1016/j.drugalcdep.2018.03.007

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. Memory, 18(4), 394–412. https://doi.org/10.1080/09658211003702171

Jager, G., Kahn, R. S., Van Den Brink, W., Van Ree, J. M., & Ramsey, N. F. (2006). Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. Psychopharmacology, 185(3), 358–368. https://doi.org/10.1007/s00213-005-0298-7

James, M. H., McNally, G. P., & Li, X. (2021). Editorial: Role of the Thalamus in Motivated Behavior. Frontiers in Behavioral Neuroscience, 15. 720592. https://doi.org/10.3389/fnbeh.2021.720592

JASP Team. (2020). JASP (Version 0.14.1).
JASP Team. (2022). JASP (Version 0.16.4.0).
JASP Team. (2023). JASP (Version 0.17.1).
Jeffreys, H. (1961). Theory of Probability (3rd ed.). Clarendon Press.
Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. NeuroImage, 62, 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

K

Källmén, H., Elgán, T. H., Wennberg, P., & Berman, A. H. (2019). Concurrent validity of the Alcohol Use Disorders Identification Test (AUDIT) in relation to Alcohol Use Disorder (AUD) severity levels according to the brief DSM-5 AUD diagnostic assessment screener. Nordic Journal of Psychiatry, 73(7), 397–400. https://doi.org/10.1080/08039488.2019.1642382
Kanayama, G., Rogowska, J., Pope, H. G., Gruber, S. A., & Yurgelun-Todd, D. A. (2004). Spatial working memory in heavy cannabis users: A functional magnetic resonance imaging study. Psychopharmacology, 176(3–4), 239–247. https://doi.org/10.1007/s00213-004-1885-8
Kandel, D., & Kandel, E. (2015). The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatrica, 104(2), 130–137. https://doi.org/10.1111/apa.12851
Karschner, E. L., Schwilke, E. W., Lowe, R. H., Darwin, W. D., Herning, R. I., Cadet, J. L., & Huestis, M. A. (2009). Implications of Plasma 9-Tetrahydrocannabinol, 11-Hydroxy-THC, and 11-nor-9-Carboxy-THC Concentrations in Chronic Cannabis Smokers. Journal of Analytical Toxicology, 33(8), 469–477. https://doi.org/10.1093/jat/33.8.469
Kedzior, K. K., & Laeber, L. T. (2014). A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Psychiatry, 14(1), 136. https://doi.org/10.1186/1471-244X-14-136
Khan, R., Naveed, S., Mian, N., Fida, A., Raafey, M. A., & Aedma, K. K. (2020). The therapeutic role of Cannabidiol in mental health: A systematic review. Journal of Cannabis Research, 2(1), 2. https://doi.org/10.1186/s42238-019-0012-y
Khan, S. S., Secades-Villa, R., Okuda, M., Wang, S., Pérez-Fuentes, G., Kerridge, B. T., & Blanco, C. (2013). Gender differences in cannabis use disorders: Results from the National Epidemiologic Survey of Alcohol and Related Conditions. Drug and Alcohol Dependence, 130(1–3), 101–108. https://doi.org/10.1016/j.drugalcdep.2012.10.015
Kim, H. S., & Sasaki, J. Y. (2014). Cultural neuroscience: Biology of the mind in cultural contexts. Annual Review of Psychology, 65, 487–514. https://doi.org/10.1146/annurev-psych-010213-115040
Kitayama, S., & Park, J. (2010). Cultural neuroscience of the self: Understanding the social grounding of the brain. Social Cognitive and Affective Neuroscience, 5(2–3), 111–129. https://doi.org/10.1093/scan/nsq052
Kloft, L., Otgaar, H., Blokland, A., Monds, L. A., Toennes, S. W., Loftus, E. F., & Ramaekers, J. G. (2020). Cannabis increases susceptibility to false memory. Proceedings of the National Academy of Sciences, 117(9), 4585-4589. https://doi.org/10.1073/pnas.1920162117.
Kober, H., Devito, E. E., Deleone, C. M., Carroll, K. M., & Potenza, M. N. (2014). Cannabis abstinence during treatment and one-year follow-up: Relationship to neural activity in men. Neuropsychopharmacology, 39(10), 2288–2298. https://doi.org/10.1038/npp.2014.82
Koenigs, M., Barbey, A. K., Postle, B. R., & Grafman, J. (2009). Superior parietal cortex is critical for the manipulation of information in working memory. Journal of Neuroscience, 29(47), 14980–14986. https://doi.org/10.1523/JNEUROSCI.3706-09.2009
Kögel, C. C., Balcells-Olivero, M. M., López-Pelayo, H., Miquel, L., Teixidó, L., Colom, J., ... & Gual, A. (2017). The standard joint unit. Drug and Alcohol Dependence, 176, 109-116. https://doi.org/10.1016/j.drugalcdep.2017.03.010.
Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. Neuropsychopharmacology, 35(1), 217–238. https://doi.org/10.1038/npp.2009.110
Korem, A., Horenczyk, G., & Tatar, M. (2012). Inter-group and intra-group assertiveness: Adolescents' social skills following cultural transition. Journal of Adolescence, 35(4), 855–862. https://doi.org/10.1016/j.adolescence.2011.12.002
Krieger, H., Neighbors, C., Lewis, M. A., Labrie, J. W., Foster, D. W., & Larimer, M. E. (2016). Injunctive Norms and Alcohol Consumption: A Revised Conceptualization. Alcoholism: Clinical and Experimental Research, 40(5), 1083–1092. https://doi.org/10.1111/acer.13037

Kroon, E., Kuhns, L., Colyer-Patel, K., Filbey, F., & Cousijn, J. (2023). Working memory-related brain activity in cannabis use disorder: The role of cross-cultural differences in cannabis attitudes, 28(6), e13283. https://doi.org/10.1111/adb.13283

Kroon, E., Kuhns, L., & Cousijn, J. (2021). The short-term and long-term effects of cannabis on cognition: recent advances in the field. Current Opinion in Psychology, 38, 49–55. https://doi.org/10.1016/j.copsyc.2020.07.005

Kroon, E., Kuhns, L., Hoch, E., & Cousijn, J. (2020). Heavy cannabis use, dependence and the brain: a clinical perspective. Addiction, 115(3), 559–572. https://doi.org/10.1111/add.14776

Kroon, E., Kuhns, L. N., Kaag, A. M., Filbey, F., & Cousijn, J. (2022). The role of sex in the association between cannabis use and working memory-related brain activity. Journal of Neuroscience Research, 100(6), 1347-1358. https://doi.org/10.1002/jnr.25041

Kuchinke, L., Jacobs, A. M., Grubich, C., Võ, M. L. H., Conrad, M., & Herrmann, M. (2005). Incidental effects of emotional valence in single word processing: An fMRI study. NeuroImage, 28(4), 1022–1032. https://doi.org/10.1016/j.neuroimage.2005.06.050

Kuhns, L., Kroon, E., Filbey, F., & Cousijn, J. (2021). Unraveling the role of cigarette use in neural cannabis cue reactivity in heavy cannabis users. Addiction Biology, 26(3). https://doi.org/10.1111/adb.12941

Kuntsche, E., Knibbe, R., Gmel, G., & Engels, R. (2006). ' I drink spirits to get drunk and block out my problems ...' Beverage preference , drinking motives and alcohol use in adolescence. Alcohol and Alcoholism, 41(5), 566–573. https://doi.org/10.1093/alcalc/agl046

L

Lance, C. E., Butts, M. M., & Michels, L. C. (2006). What Did They Really Say ? Organizational Research Methods, 9(2), 202–220. https://doi.org/http://dx.doi.org/10.1177/1094428105284919

Laurikainen, H., Tuominen, L., Tikka, M., Merisaari, H., Armio, R. L., Sormunen, E., Borgan, F., Veronese, M., Howes, O., Haaparanta-Solin, M., Solin, O., & Hietala, J. (2019). Sex difference in brain CB1 receptor availability in man. NeuroImage, 184, 834–842. https://doi.org/10.1016/j.neuroimage.2018.10.013

Leadbeater, B., Ames, M. E., Contreras, A., Thompson, K., & Goulet-Stock, S. (2022). Parent and Peer Influences and Longitudinal Trajectories of Cannabis Use from Adolescence to Young Adulthood. Journal of Child and Family Studies, 31(11), 3181–3191. https://doi.org/10.1007/s10826-022-02353-7

Leary, M. R., Kelly, K. M., Cottrell, C. A., & Schreindorfer, L. S. (2013). Construct validity of the need to belong scale: Mapping the nomological network. Journal of Personality Assessment, 95(6), 610–624. https://doi.org/10.1080/00223891.2013.819511

Lee, M. R., Ellingson, J. M., & Sher, K. J. (2015). Integrating Social-Contextual and Intrapersonal Mechanisms of "Maturing Out": Joint Influences of Familial-Role Transitions and Personality Maturation on Problem-Drinking Reductions. Alcoholism: Clinical and Experimental Research, 39(9), 1775–1787. https://doi.org/10.1111/acer.12816

Lee, S. A. (2020). Coronavirus Anxiety Scale: A brief mental health screener for COVID-19 related anxiety. Death Studies, 44(7), 393–401. https://doi.org/10.1080/07481187.2020.1748481

Lee, S., Parthasarathi, T., & Kable, J. W. (2021). The ventral and dorsal default mode networks are dissociably modulated by the vividness and valence of imagined events. Journal of Neuroscience, 41(24), 5243–5250. https://doi.org/10.1523/JNEUROSCI.1273-20.2021

Lees, B., Garcia, A. M., Debenham, J., Kirkland, A. E., Bryant, B. E., Mewton, L., & Squeglia, L. M. (2021). Promising vulnerability markers of substance use and misuse: A review of human neurobehavioral studies. Neuropharmacology, 187. 10850. https://doi.org/10.1016/j.neuropharm.2021.108500

Lees, R., Hines, L. A., D'Souza, D. C., Stothart, G., DI Forti, M., Hoch, E., & Freeman, T. P. (2021). Psychosocial and pharmacological treatments for cannabis use disorder and mental health comorbidities: A narrative review. Psychological Medicine, 51(3), 353-364. https://doi.org/10.1017/S0033291720005449

Lemyre, A., Poliakova, N., & Bélanger, R. E. (2019). The Relationship Between Tobacco and Cannabis Use: A Review. Substance Use and Misuse, 54(1), 130–145. https://doi.org/10.1080/10826084.2018.1512623

Lennox, R. D., & Wolfe, R. N. (1984). Revision of the self-monitoring scale. Journal of Personality and Social Psychology, 46(6), 1349–1364. https://doi.org/https://doi.org/10.1037/0022-3514.46.6.1349

Leung, J., Chan, G. C. K., Hides, L., & Hall, W. D. (2020). What is the prevalence and risk of cannabis use disorders among people who use cannabis? a systematic review and meta-analysis. In Addictive Behaviors, 109, 106479. Elsevier Ltd. https://doi.org/10.1016/j.addbeh.2020.106479

Levin, K. H., Copersino, M. L., Heishman, S. J., Liu, F., Kelly, D. L., Boggs, D. L., & Gorelick, D. A. (2010). Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. Drug and Alcohol Dependence, 111(1–2), 120–127. https://doi.org/10.1016/j.drugalcdep.2010.04.010

Lev-Ran, S., Le Foll, B., McKenzie, K., George, T. P., & Rehm, J. (2013). Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. Psychiatry Research, 209(3), 459–465. https://doi.org/https://doi.org/10.1016/j.psychres.2012.12.014

Licata, S. C., & Renshaw, P. F. (2010). Neurochemistry of drug action. Annals of the New York Academy of Sciences, 1187(1), 148–171. https://doi.org/10.1111/j.1749-6632.2009.05143.x

Lin, Y. H., Dhanaraj, V., Mackenzie, A. E., Young, I. M., Tanglay, O., Briggs, R. G., Chakraborty, A. R., Hormovas, J., Fonseka, R. D., Kim, S. J., Yeung, J. T., Teo, C., & Sughrue, M. E. (2021). Anatomy and White Matter Connections of the Parahippocampal Gyrus. World Neurosurgery, 148, e218–e226. https://doi.org/10.1016/j.wneu.2020.12.136

Linden, D. E. J., Bittner, R. A., Muckli, L., Waltz, J. A., Kriegeskorte, N., Goebel, R., Singer, W., & Munk, M. H. J. (2003). Cortical capacity constraints for visual working memory: Dissociation of fMRI load effects in a fronto-parietal network. NeuroImage, 20(3), 1518–1530. https://doi.org/10.1016/j.neuroimage.2003.07.021

Lindquist, M. A., Meng Loh, J., Atlas, L. Y., & Wager, T. D. (2009). Modeling the hemodynamic response function in fMRI: Efficiency, bias and mis-modeling. NeuroImage, 45(1), S187–S198. https://doi.org/10.1016/j.neuroimage.2008.10.065

Littman, R., & Takács, Á. (2017). Do all inhibitions act alike? A study of go/no-go and stop-signal paradigms. PloS one, 12(10), e0186774. https://doi.org/10.1371/journal.pone.0186774.

López-Pelayo, H., Batalla, A., Balcells, M. M., Colom, J., & Gual, A. (2015). Assessment of cannabis use disorders: a systematic review of screening and diagnostic instruments. Psychological Medicine, 45(6), 1121–1133. https://doi.org/10.1017/S0033291714002463

Lorenzetti, V., Chye, Y., Silva, P., Solowij, N., & Roberts, C. A. (2019). Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. European Archives of Psychiatry and Clinical Neuroscience, 269(1), 59–71. https://doi.org/10.1007/s00406-019-00979-1

Lorenzetti, V., Hindocha, C., Petrilli, K., Griffiths, P., Brown, J., Castillo-Carniglia, Á., Caulkins, J. P., Englund, A., ElSohly, M. A., Gage, S. H., Groshkova, T., Gual, A., Hammond, D., Lawn, W., López-Pelayo, H., Manthey, J., Mokrysz, C., Pacula, R. L., van Laar, M., … Freeman, T. P. (2022). The International Cannabis Toolkit (iCannToolkit): a multidisciplinary expert consensus on minimum standards for measuring cannabis use. Addiction, 117(6), 1510–1517. https://doi.org/10.1111/add.15702

Lorenzetti, V., Hoch, E., & Hall, W. (2020). Adolescent cannabis use, cognition, brain health and educational outcomes: A review of the evidence. European Neuropsychopharmacology, 36, 169–180. https://doi.org/10.1016/j.euroneuro.2020.03.012

Lynskey, M. T., & Agrawal, A. (2018). Denise Kandel's classic work on the gateway sequence of drug acquisition. Addiction, 113(10), 1927–1932. https://doi.org/10.1111/add.14190

M

Ma, L., Steinberg, J. L., Bjork, J. M., Keyser-Marcus, L., Vassileva, J., Zhu, M., Ganapathy, V., Wang, Q., Boone, E. L., Ferré, S., Bickel, W. K., & Gerard Moeller, F. (2018). Fronto-striatal effective connectivity of working memory in adults with cannabis use disorder. Psychiatry Research - Neuroimaging, 278, 21–34. https://doi.org/10.1016/j.pscychresns.2018.05.010

Mackworth, J. F. (1959). Paced memorization in a continuous task. Journal of Experimental Psychology, 58(3), 206–211. https://doi.org/https://doi.org/10.1037/h0049090

MacPherson, L., Magidson, J. F., Reynolds, E. K., Kahler, C. W., & Lejuez, C. W. (2010). Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. Alcoholism: Clinical and Experimental Research, 34(8), 1400–1408. https://doi.org/10.1111/j.1530-0277.2010.01223.x

Mann, L. M., Chassin, L., & Sher, K. J. (1987). Alcohol Expectancies and the Risk for Alcoholism. Journal of Consulting and Clinical Psychology, 55(3), 411-417. https://doi.org/10.1037//0022-006x.55.3.411

Mansueto, A. C., Wiers, R. W., van Weert, J. C. M., Schouten, B. C., & Epskamp, S. (2022). Investigating the feasibility of idiographic network models. Psychological Methods. https://doi.org/10.1037/met0000466

Marconi, A., di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophrenia Bulletin, 42(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Marhe, R., Waters, A. J., Van De Wetering, B. J. M., & Franken, I. H. A. (2013). Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: An ecological momentary assessment study. Journal of Consulting and Clinical Psychology, 81(1), 1–12. https://doi.org/10.1037/a0030754

Marissen, M. A. E., Franken, I. H. A., Waters, A. J., Blanken, P., van den Brink, W., & Hendriks, V. M. (2006). Attentional bias predicts heroin relapse following treatment. Addiction, 101(9), 1306–1312. https://doi.org/10.1111/j.1360-0443.2006.01498.x

Marsden, J., Darke, S., Hall, W., Hickman, M., Holmes, J., Humphreys, K., Neale, J., Tucker, J., & West, R. (2020). Mitigating and learning from the impact of COVID-19 infection on addictive disorders. Addiction, 115(6), 1007-1010. https://doi.org/10.1111/add.15080

Marshal, M. P., & Chassin, L. (2000). Parental , Sibling , and Peer Influences on Adolescent Substance Use and Alcohol Problems Parental , Sibling , and Peer Influences on Adolescent Substance Use and Alcohol Problems. Applied Developmental Science, 4(2), 80–88. https://doi.org/10.1207/S1532480XADS0402

Martin, G., Copeland, J., Gates, P., & Gilmour, S. (2006). The Severity of Dependence Scale (SDS) in an adolescent population of cannabis users: Reliability, validity and diagnostic cut-off. Drug and Alcohol Dependence, 83(1), 90–93. https://doi.org/10.1016/j.drugalcdep.2005.10.014

Mason, M. J., Zaharakis, N. M., Rusby, J. C., Westling, E., Light, J. M., Mennis, J., & Flay, B. R. (2017). A longitudinal study predicting adolescent tobacco, alcohol, and cannabis use by behavioral characteristics of close friends. Psychology of Addictive Behaviors, 31(6), 712–720. https://doi.org/10.1037/adb0000299

Mason, N. L., Theunissen, E. L., Hutten, N. R., Tse, D. H., Toennes, S. W., Jansen, J. F., ... & Ramaekers, J. G. (2021). Reduced responsiveness of the reward system is associated with tolerance to cannabis impairment in chronic users. Addiction biology, 26(1), e12870. https://doi.org/10.1111/adb.12870.

Matheson, J., Sproule, B., di Ciano, P., Fares, A., le Foll, B., Mann, R. E., & Brands, B. (2020). Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. Psychopharmacology, 237(2), 305–316. https://doi.org/10.1007/s00213-019-05369-y

McDonald, J., Schleifer, L., Richards, J. B., & de Wit, H. (2003). Effects of THC on behavioral measures of impulsivity in humans. Neuropsychopharmacology, 28(7), 1356-1365. https://doi.org/10.1038/sj.npp.1300176.

Mclean, S. P., Garza, J. P., Wiebe, S. A., Dodd, M. D., Smith, K. B., Hibbing, J. R., & Espy, K. A. (2014). Applying the flanker task to political psychology: A research note. Political Psychology, 35(6), 831–840. https://doi.org/10.1111/pops.12056

Mehrabian, A., & Stefl, C. A. (1995). Basic Temperament Components of Loneliness, Shyness, and Conformity. Social Behavior and Personality: an international journal, 23(3), 253-264. https://doi.org/10.2224/sbp.1995.23.3.253

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., McDonald, K., Ward, A., Poulton, R., & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences, 109(40), E2657–E2664. https://doi.org/10.1073/pnas.1206820109

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. Brain structure & function, 124(5-6), 655-667. https://doi.org/10.1007/s00429-010-0262-0

Metrik, J., Kahler, C. W., Reynolds, B., McGeary, J. E., Monti, P. M., Haney, M., de Wit, H., & Rohsenow, D. J. (2012). Balanced placebo design with marijuana: pharmacological and expectancy effects on impulsivity and risk taking. Psychopharmacology, 223(4), 489–499. https://doi.org/10.1007/s00213-012-2740-y

Miles, J., & Shevlin, M. (2007). A time and a place for incremental fit indices. Personality and Individual Differences, 42(5), 869–874. https://doi.org/10.1016/j.paid.2006.09.022

Miranda Jr, R., Wemm, S. E., Treloar Padovano, H., Carpenter, R. W., Emery, N. N., Gray, J. C., & Mereish, E. H. (2019). Weaker memory performance exacerbates stress-induced cannabis craving in youths' daily lives. Clinical Psychological Science, 7(5), 1094-1108. https://doi.org/10.1177/2167702619841976.

Moeller, S. J., & Goldstein, R. Z. (2014). Impaired self-awareness in human addiction: Deficient attribution of personal relevance. Trends in Cognitive Sciences, 18(12), 635-641. https://doi.org/10.1016/j.tics.2014.09.003

Mokrysz, C., Freeman, T. P., Korkki, S., Griffiths, K., & Curran, H. V. (2016). Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. Translational Psychiatry, 6(11), e961–e961. https://doi.org/10.1038/tp.2016.225

Mokrysz, C., Landy, R., Gage, S., Munafò, M., Roiser, J., & Curran, H. (2016). Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. Journal of Psychopharmacology, 30(2), 159–168. https://doi.org/10.1177/0269881115622241

Montanari, L., Guarita, B., Mounteney, J., Zipfel, N., & Simon, R. (2017). Cannabis Use among People Entering Drug Treatment in Europe: A Growing Phenomenon? European Addiction Research, 23(3), 113–121. https://doi.org/10.1159/000475810

Moon, K.-W. (2021). processR: Implementation of the "PROCESS" Macro. (R package version 0.2.6).

Moosmann, B., Roth, N., & Auwärter, V. (2015). Finding cannabinoids in hair does not prove cannabis consumption. Scientific Reports, 5(1), 1–6. https://doi.org/10.1038/srep14906

Moreno-López, L., Stamatakis, E. A., Fernández-Serrano, M. J., Gómez-Río, M., Rodríguez-Fernández, A., Pérez-García, M., & Verdejo-García, A. (2012). Neural correlates of hot and cold executive functions in polysubstance addiction: Association between neuropsychological performance and resting brain metabolism as measured by positron emission tomography. Psychiatry Research - Neuroimaging, 203(2–3), 214–221. https://doi.org/10.1016/j.pscychresns.2012.01.006

Morgan, C. J. A., Freeman, T. P., Hindocha, C., Schafer, G., Gardner, C., & Curran, H. V. (2018). Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. Translational Psychiatry, 8(1), 181. https://doi.org/10.1038/s41398-018-0191-x

Morgan, C. J., Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol Attenuates the Appetitive Effects of Δ9-Tetrahydrocannabinol in Humans Smoking Their Chosen Cannabis. Neuropsychopharmacology, 35(9), 1879–1885. https://doi.org/10.1038/npp.2010.58

Mottola, Carol. A. (1993). Measurement Strategies: The Visual Analogue Scale. Decubitus, 6(5), 56–58.

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., Sherif, M., McGuire, P., & D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. Neuropharmacology, 124, 89–104. https://doi.org/10.1016/j.neuropharm.2017.06.018

Musshoff, F., & Madea, B. (2006). Review of Biologic Matrices (Urine, Blood, Hair) as Indicators of Recent or Ongoing Cannabis Use. Therapeutic Drug Monitoring, 28(2), 155-163. https://doi.org/10.1097/01.ftd.0000197091.07807.22

Myles, H., Myles, N., & Large, M. (2016). Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. Australian & New Zealand Journal of Psychiatry, 50(3), 208–219. https://doi.org/10.1177/0004867415599846

N

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. Journal of the American Geriatrics Society, 53(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nestor, L., Roberts, G., Garavan, H., & Hester, R. (2008). Deficits in learning and memory: Parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. NeuroImage, 40(3), 1328–1339. https://doi.org/10.1016/j.neuroimage.2007.12.059

Newcomb, M. D., & Harlow, L. L. (1986). Life Events and Substance Use Among Adolescents: Mediating Effects of Perceived Loss of Control and Meaninglessness in Life. Journal of personality and social psychology, 51(3), 564-577. https://doi.org/10.1037/0022-3514.51.3.564

Nielsen, S., Gowing, L., Sabioni, P., & Le Foll, B. (2019). Pharmacotherapies for cannabis dependence. Cochrane Database of Systematic Reviews, 12. https://doi.org/10.1002/14651858.CD008940.pub3

Niesink, R. J. M., & van Laar, M. W. (2013). Does Cannabidiol Protect Against Adverse Psychological Effects of THC? Frontiers in Psychiatry, 4, 1–8. https://doi.org/10.3389/fpsyt.2013.00130

O

O'Neill, A., Bachi, B., & Bhattacharyya, S. (2020). Attentional bias towards cannabis cues in cannabis users: A systematic review and meta-analysis. Drug and alcohol dependence, 206, 107719. https://doi.org/10.1016/j.drugalcdep.2019.107719.

Orford, J. (2001). Addiction as excessive appetite. Addiction, 96(1), 15–31. https://doi.org/10.1046/j.1360-0443.2001.961152.x

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Human Brain Mapping, 25(1), 46–59. https://doi.org/10.1002/hbm.20131

Owens, M. M., McNally, S., Petker, T., Amlung, M. T., Balodis, I. M., Sweet, L. H., & MacKillop, J. (2019). Urinary tetrahydrocannabinol is associated with poorer working memory performance and alterations in associated brain activity. Neuropsychopharmacology, 44(3), 613–619. https://doi.org/10.1038/s41386-018-0240-4

P

Padula, C. B., Schweinsburg, A. D., & Tapert, S. F. (2007). Spatial working memory performance and fMRI activation interaction in abstinent adolescent marijuana users. Psychology of Addictive Behaviors, 21(4), 478–487. https://doi.org/10.1037/0893-164X.21.4.478

Pennington, C. R., Shaw, D. J., Adams, J., Kavanagh, P., Reed, H., Robinson, M., Shave, E., & White, H. (2020). Where's the wine? Heavy social drinkers show attentional bias towards alcohol in a visual conjunction search task. Addiction, 115(9), 1650–1659. https://doi.org/10.1111/add.14997

Pertwee, R. G. (2008). The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: Δ 9 -tetrahydrocannabinol, cannabidiol and Δ 9 -tetrahydrocannabivarin. British Journal of Pharmacology, 153(2), 199–215. https://doi.org/10.1038/sj.bjp.0707442

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-striatal-thalamic loop circuits of the salience network: A central pathway in psychiatric disease and treatment. Frontiers in Systems Neuroscience, 10, 1–23. https://doi.org/10.3389/fnsys.2016.00104

Petker, T., Owens, M. M., Amlung, M. T., Oshri, A., Sweet, L. H., & MacKillop, J. (2019). Cannabis involvement and neuropsychological performance: findings from the Human Connectome Project. Journal of Psychiatry and Neuroscience, 44(6), 414-422. https://doi.org/10.1503/jpn.180115.

Pierce, M., McManus, S., Jessop, C., John, A., Hotopf, M., Ford, T., Hatch, S., Wessely, S., & Abel, K. M. (2020). Says who? The significance of sampling in mental health surveys during COVID-19. The Lancet Psychiatry, 7(7), 567-568. https://doi.org/10.1016/S2215-0366(20)30237-6

Piontek, D., Kraus, L., Bjarnason, T., Demetrovics, Z., & Ramstedt, M. (2013). Individual and country-level effects of cannabis-related perceptions on cannabis use. A multilevel study among adolescents in 32 European countries. Journal of Adolescent Health, 52(4), 473–479. https://doi.org/10.1016/j.jadohealth.2012.07.010

Poldrack, R. A., Baker, C. I., Durnez, J., Gorgolewski, K. J., Matthews, P. M., Munafò, M. R., Nichols, T. E., Poline, J. B., Vul, E., & Yarkoni, T. (2017). Scanning the horizon: Towards transparent and reproducible neuroimaging research. Nature Reviews Neuroscience, 18(2), 115–126. https://doi.org/10.1038/nrn.2016.167

Polit, D. F., & Beck, C. T. (2006). The content validity index: Are you sure you know what's being reported? critique and recommendations. Research in Nursing & Health, 29(5), 489–497. https://doi.org/10.1002/nur.20147

Poulton, R. G., Brooke, M., Moffitt, T. E., Stanton, W. R., & Silva, P. A. (1997). Prevalence and correlates of cannabis use and dependence in young New Zealanders. The New Zealand Medical Journal, 110(1039), 68–70.

Prashad, S., Dedrick, E. S., & Filbey, F. M. (2018). Cannabis users exhibit increased cortical activation during resting state compared to non-users. NeuroImage, 179, 176–186. https://doi.org/10.1016/j.neuroimage.2018.06.031

Prashad, S., Milligan, A. L., Cousijn, J., & Filbey, F. M. (2017). Cross-Cultural Effects of Cannabis Use Disorder: Evidence to Support a Cultural Neuroscience Approach. Current Addiction Reports, 4(2), 100–109. https://doi.org/10.1007/s40429-017-0145-z

Prini, P., Zamberletti, E., Manenti, C., Gabaglio, M., Parolaro, D., & Rubino, T. (2020). Neurobiological mechanisms underlying cannabis-induced memory impairment. European Neuropsychopharmacology, 36, 181-190. https://doi.org/10.1016/j.euroneuro.2020.02.002.

Pujol, J., Blanco-Hinojo, L., Batalla, A., López-Solà, M., Harrison, B. J., Soriano-Mas, C., Crippa, J. A., Fagundo, A. B., Deus, J., de la Torre, R., Nogué, S., Farré, M., Torrens, M., & Martín-Santos, R. (2014). Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. Journal of Psychiatric Research, 51(1), 68–78. https://doi.org/10.1016/j.jpsychires.2013.12.008

R

R Core Team. (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing.

R Core Team. (2020). R: A language and environment for statistical computing (4.0.2). R Foundation for Statistical Computing. https://www.r-project.org/

R Core Team. (2021). R: A language and environment for statistical computing (4.1.2). R Foundation for Statistical Computing. https://www.r-project.org/.

R Core Team. (2022). R: A language and environment for statistical computing (4.2.2.). R Foundation for Statistical Computing. https://www.R-project.org/

Raichle, M. E. (2015). The Brain's Default Mode Network. Annual Review of Neuroscience, 38, 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Rajkumar, R. P. (2020). COVID-19 and mental health: A review of the existing literature. Asian Journal of Psychiatry, 52, 102066. https://doi.org/10.1016/j.ajp.2020.102066

Ramaekers, J. G., Berghaus, G., van Laar, M., & Drummer, O. H. (2004). Dose related risk of motor vehicle crashes after cannabis use. Drug and Alcohol Dependence, 73(2), 109–119. https://doi.org/10.1016/j.drugalcdep.2003.10.008

Ramaekers, J. G., Kauert, G., Theunissen, E. L., Toennes, S. W., & Moeller, M. R. (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Journal of Psychopharmacology, 23(3), 266–277. https://doi.org/10.1177/0269881108092393

Ramaekers, J. G., Kauert, G., van Ruitenbeek, P., Theunissen, E. L., Schneider, E., & Moeller, M. R. (2006). High-Potency Marijuana Impairs Executive Function and Inhibitory Motor Control. Neuropsychopharmacology, 31(10), 2296–2303. https://doi.org/10.1038/sj.npp.1301068

Ramaekers, J. G., Moeller, M. R., van Ruitenbeek, P., Theunissen, E. L., Schneider, E., & Kauert, G. (2006). Cognition and motor control as a function of Δ9-THC concentration in serum and oral fluid: Limits of impairment. Drug and Alcohol Dependence, 85(2), 114–122. https://doi.org/10.1016/j.drugalcdep.2006.03.015

Ramaekers, J. G., Robbe, H. W. J., & O'Hanlon, J. F. (2000). Marijuana, alcohol and actual driving performance. Human Psychopharmacology: Clinical and Experimental, 15(7), 551–558. https://doi.org/10.1002/1099-1077(200010)15:7<551::AID-HUP236>3.0.CO;2-P

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2003). Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia, 41(3), 378–389. https://doi.org/10.1016/S0028-3932(02)00169-0

Ranganathan, M., & D'Souza, D. C. (2006). The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology, 188(4), 425–444. https://doi.org/10.1007/s00213-006-0508-y

Ravi, D., Ghasemiesfe, M., Korenstein, D., Cascino, T., & Keyhani, S. (2018). Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes. Annals of Internal Medicine, 168(3), 187. https://doi.org/10.7326/M17-1548

Reinarman, C., & Cohen, P. (2007). Lineaments of Cannabis Culture: Rules Regulating Use in Amsterdam and San Francisco. Contemporary Justice Review, 10(4), 393–410. https://doi.org/10.1080/10282580701677451

Resnicow, K., Soler, R., Braithwaite, R. L., Ahluwalia, J. S., & Butler, J. (2000). Cultural sensitivity in substance use prevention. Journal of Community Psychology, 28(3), 271–290. https://doi.org/10.1002/(SICI)1520-6629(200005)28:3<271::AID-JCOP4>3.0.CO;2-I

Rezkalla, S., & Kloner, R. A. (2018). Cardiovascular effects of marijuana. Trends in Cardiovascular Medicine, 21(5), 452-455. https://doi.org/10.1016/j.tcm.2018.11.004

Rhee, T. G., & Rosenheck, R. A. (2023). Increasing Use of Cannabis for Medical Purposes among US Residents, 2013-2020. American Journal of Preventive Medicine. https://doi.org/10.1016/j.amepre.2023.03.005

Rhemtulla, M., Fried, E. I., Aggen, S. H., Tuerlinckx, F., Kendler, K. S., & Borsboom, D. (2016). Network analysis of substance abuse and dependence symptoms. Drug and Alcohol Dependence, 161, 230–237. https://doi.org/10.1016/j.drugalcdep.2016.02.005

Richardson, T. (2010). Cannabis Use and Mental Health: A Review of Recent Epidemiological Research. International Journal of Pharmacology, 6(6), 796–807. https://doi.org/10.3923/ijp.2010.796.807

Ritchay, M. M., Huggins, A. A., Wallace, A. L., Larson, C. L., & Lisdahl, K. M. (2021). Resting state functional connectivity in the default mode network: Relationships between cannabis use, gender, and cognition in adolescents and young adults. NeuroImage: Clinical, 30, 102664. https://doi.org/10.1016/j.nicl.2021.102664

Robinson, S. M., Sobell, L. C., Sobell, M. B., & Leo, G. I. (2014). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. Psychology of Addictive Behaviors, 28(1), 154–162. https://doi.org/10.1037/a0030992

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Research Reviews, 18(3), 247–291. https://doi.org/10.1016/0165-0173(93)90013-P

Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: Some current issues. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1507), 3137–3146. https://doi.org/10.1098/rstb.2008.0093

Rogeberg, O. (2013). Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. Proceedings of the National Academy of Sciences, 110(11), 4251–4254. https://doi.org/10.1073/pnas.1215678110

Rogers, A. H., Shepherd, J. M., Garey, L., & Zvolensky, M. J. (2020). Psychological factors associated with substance use initiation during the COVID-19 pandemic. Psychiatry Research, 293, 113407. https://doi.org/10.1016/j.psychres.2020.113407

Rogers, R. D., Wakeley, J., Robson, P. J., Bhagwagar, Z., & Makela, P. (2007). The Effects of Low Doses of Δ-9 Tetrahydrocannabinol on Reinforcement Processing in the Risky Decision-Making of Young Healthy Adults. Neuropsychopharmacology, 32(2), 417–428. https://doi.org/10.1038/sj.npp.1301175

Rolland, B., Haesebaert, F., Zante, E., Benyamina, A., Haesebaert, J., & Franck, N. (2020). Global Changes and Factors of Increase in Caloric/Salty Food Intake, Screen Use, and Substance Use During the Early COVID-19 Containment Phase in the General Population in France: Survey Study. JMIR Public Health and Surveillance, 6(3), e19630. https://doi.org/10.2196/19630

Rosseel, Y. (2012). lavaan: an R package for Structural Equation Modeling. Journal of Statistical Software, 48(2), 1–36.

RStudio Team. (2022). RStudio: Integrated Development Environment for R (2022.12.0). RStudio, PBC.

RStudio Team. (2022). RStudio: Integrated Development Environment for R (2021.9.2.382). RStudio, PBC.

Ruglass, L. M., Shevorykin, A., Dambreville, N., & Melara, R. D. (2019). Neural and behavioral correlates of attentional bias to cannabis cues among adults with cannabis use disorders. Psychology of Addictive Behaviors, 33(1), 69-80. https://doi.org/10.1037/adb0000423.

Rup, J., Goodman, S., & Hammond, D. (2020). Cannabis advertising, promotion and branding: Differences in consumer exposure between 'legal' and 'illegal' markets in Canada and the US. Preventive Medicine, 133, 106013. https://doi.org/10.1016/j.ypmed.2020.106013

Russo, E. B. (2016). Beyond cannabis: Plants and the endocannabinoid system. Trends in pharmacological sciences, 37(7), 594-605. https://doi.org/10.1016/j.tips.2016.04.005.

Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. NeuroImage, 9(2), 216–226. https://doi.org/10.1006/nimg.1998.0404

S

Saadon-Grosman, N., Loewenstein, Y., & Arzy, S. (2020). The 'creatures' of the human cortical somatosensory system. Brain Communications, 2(1), 1–10. https://doi.org/10.1093/braincomms/fcaa003

Sagar, K. A., & Gruber, S. A. (2019). Interactions between recreational cannabis use and cognitive function: lessons from functional magnetic resonance imaging. Annals of the New York Academy of Sciences, 1451(1), 42–70. https://doi.org/10.1111/nyas.13990

Salling, M. C., & Martinez, D. (2016). Brain stimulation in addiction. Neuropsychopharmacology, 41(12), 2798–2809. https://doi.org/10.1038/npp.2016.80

SAMHSA. (2018). Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health. In HHS Publication No. SMA 18-5068, NSDUH Series H-53.

Sandra Kooij, J. J., Marije Boonstra, A., Swinkels, S. H. N., Bekker, E. M., De Noord, I., & Buitelaar, J. K. (2008). Reliability, validity, and utility of instruments for self-report and informant report concerning symptoms of ADHD in adult patients. Journal of Attention Disorders, 11(4), 445–458. https://doi.org/10.1177/1087054707299367

Santor, D. A., Messervey, D., & Kusumakar, V. (2000). Measuring peer pressure, popularity, and conformity in adolescent boys and girls: Predicting school performance, sexual attitudes, and substance abuse. Journal of Youth and Adolescence, 29(2), 163–182. https://doi.org/10.1023/A:1005152515264

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. Addiction, 88(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Savulich, G., Rychik, N., Lamberth, E., Hareli, M., Evins, A. E., Sahakian, B. J., & Schuster, R. M. (2021). Sex Differences in Neuropsychological Functioning are Domain-Specific in Adolescent and Young Adult Regular Cannabis Users. Journal of the International Neuropsychological Society, 27(6), 592–606. https://doi.org/10.1017/S1355617720001435

Scarpina, F., & Tagini, S. (2017). The stroop color and word test. Frontiers in Psychology, 8, 1–8. https://doi.org/10.3389/fpsyg.2017.00557

Schlienz, N. J., Budney, A. J., Lee, D. C., & Vandrey, R. (2017). Cannabis Withdrawal: a Review of Neurobiological Mechanisms and Sex Differences. Current Addiction Reports, 4(2), 75–81. https://doi.org/10.1007/s40429-017-0143-1

Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). De Nederlandse Leestest voor Volwassenen: een maat voor het premorbide intelligentieniveau [The Dutch Reading Test for Adults: A measure of premorbid intelligence level]. Tijdschrift Voor Gerontologie En Geriatrie, 22(1).

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). E-prime computer software and manual. Pittsburgh, PA: Psychology Software Tools.

Schoeler, T., & Bhattacharyya, S. (2013). The effect of cannabis use on memory function: an update. Substance Abuse and Rehabilitation, 4, 11–27. https://doi.org/10.2147/SAR.S25869

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., & Bhattacharyya, S. (2016). The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. Psychological Medicine, 46(1), 177–188. https://doi.org/10.1017/S0033291715001646

Schoeler, T., Theobald, D., Pingault, J.-B., Farrington, D. P., Coid, J. W., & Bhattacharyya, S. (2018). Developmental sensitivity to cannabis use patterns and risk for major depressive disorder in mid-life: findings from 40 years of follow-up. Psychological Medicine, 48(13), 2169–2176. https://doi.org/10.1017/S0033291717003658

Scholz, C., Madry, M. M., Kraemer, T., & Baumgartner, M. R. (2022). LC–MS-MS Analysis of Δ9-THC, CBN and CBD in Hair: Investigation of Artifacts. Journal of Analytical Toxicology, 46(5), 504–511. https://doi.org/10.1093/JAT/BKAB056

Schreiner, A. M., & Dunn, M. E. (2012). Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. Experimental and Clinical Psychopharmacology, 20(5), 420–429. https://doi.org/10.1037/a0029117

Schweinsburg, A. D., Nagel, B. J., Schweinsburg, B. C., Park, A., Theilmann, R. J., & Tapert, S. F. (2008). Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. Psychiatry Research - Neuroimaging, 163(1), 40–51. https://doi.org/10.1016/j.pscychresns.2007.04.018

Schweinsburg, A. D., Schweinsburg, B. C., Medina, K. L., McQueeny, T., Brown, S. A., & Tapert, S. F. (2010). The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana Users. Journal of Psychoactive Drugs, 42(3), 401–412. https://doi.org/10.1080/02791072.2010.10400703

Schwope, D. M., Bosker, W. M., Ramaekers, J. G., Gorelick, D. A., & Huestis, M. A. (2012). Psychomotor performance, subjective and physiological effects and whole blood Δ9-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. Journal of analytical toxicology, 36(6), 405-412. https://doi.org/10.1093/jat/bks044.

Scott, J. C., Slomiak, S. T., Jones, J. D., Rosen, A. F. G., Moore, T. M., & Gur, R. C. (2018). Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults A Systematic Review and Meta-analysis. JAMA Psychiatry, 75(6), 585–595. https://doi.org/10.1001/jamapsychiatry.2018.0335

Sebastian, C., Burnett, S., & Blakemore, S. J. (2008). Development of the self-concept during adolescence. Trends in Cognitive Sciences, 12(11), 441–446. https://doi.org/10.1016/j.tics.2008.07.008

Shah, I., Al-Dabbagh, B., Salem, A. E., Hamid, S. A. A., Muhammad, N., & Naughton, D. P. (2019). A review of bioanalytical techniques for evaluation of cannabis (Marijuana, weed, Hashish) in human hair. BMC Chemistry, 13(1), 1–20. https://doi.org/10.1186/S13065-019-0627-2

Shapiro, K., & Hillstrom, A. P. (2002). Control of visuotemporal attention by inferior parietal and superior temporal cortex. Current Biology, 12(15), 1320–1325. https://doi.org/10.1016/S0960-9822(02)01040-0

Sharma, P., Murthy, P., & Bharath, M. M. S. (2012). Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iranian Journal of Psychiatry, 7(4), 149–156.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry, 59, 22–33.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M. F., & Dunbar, G. C. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. European Psychiatry, 12(5). https://doi.org/10.1016/S0924-9338(97)83297-X

Sherman, D. K., Kim, H. S., & Taylor, S. E. (2009). Culture and social support: neural bases and biological impact. Progress in Brain Research, 178, 227–237. https://doi.org/10.1016/S0079-6123(09)17816-0

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cerebral Cortex, 22(1), 158–165. https://doi.org/10.1093/cercor/bhr099

Shollenbarger, S., Thomas, A. M., Wade, N. E., Gruber, S. A., Tapert, S. F., Filbey, F. M., & Lisdahl, K. M. (2019). Intrinsic Frontolimbic Connectivity and Mood Symptoms in Young Adult Cannabis Users. Frontiers in Public Health, 7, 311. https://doi.org/10.3389/fpubh.2019.00311

Sholler, D. J., Strickland, J. C., Spindle, T. R., Weerts, E. M., & Vandrey, R. (2020). Sex differences in the acute effects of oral and vaporized cannabis among healthy adults. Addiction Biology, 26(4), 1–12. https://doi.org/10.1111/adb.12968

Silins, E., Horwood, L. J., Patton, G. C., Fergusson, D. M., Olsson, C. A., Hutchinson, D. M., Spry, E., Toumbourou, J. W., Degenhardt, L., Swift, W., Coffey, C., Tait, R. J., Letcher, P., Copeland, J., & Mattick, R. P. (2014). Young adult sequelae of adolescent cannabis use: an integrative analysis. The Lancet Psychiatry, 1(4), 286–293. https://doi.org/10.1016/S2215-0366(14)70307-4

Simons, J., Correia, C. J., Carey, K. B., & Borsari, B. E. (1998). Validating a Five-Factor Marijuana Motives Measure: Relations with Use, Problems, and Alcohol Motives. Journal of Counseling Psychology, 45(3), 265–273. https://doi.org/10.1037/0022-0167.45.3.265

Sim-Selley, L. J. (2003). Regulation of Cannabinoid CB1 Receptors in the Central Nervous System by Chronic Cannabinoids. Critical Reviews in Neurobiology, 15(2), 91–119. https://doi.org/10.1615/CritRevNeurobiol.v15.i2.10

Sinha, R. (2007). The role of stress in addiction relapse. Current Psychiatry Reports, 9(5), 388–395. https://doi.org/10.1007/s11920-007-0050-6

Skopp, G., & Pötsch, L. (2002). Stability of 11-Nor-Δ9-carboxy-tetrahydrocannabinol Glucuronide in Plasma and Urine Assessed by Liquid Chromatography-Tandem Mass Spectrometry. Clinical Chemistry, 48(2), 301–306. https://doi.org/10.1093/CLINCHEM/48.2.301

Smith, A. M., Longo, C. A., Fried, P. A., Hogan, M. J., & Cameron, I. (2010). Effects of marijuana on visuospatial working memory: An fMRI Study in young adults. Psychopharmacology, 210(3), 429–438. https://doi.org/10.1007/s00213-010-1841-8

Smith, D. G., & Ersche, K. D. (2014). Using a drug-word Stroop task to differentiate recreational from dependent drug use. CNS Spectrums, 19(3), 247–255. https://doi.org/10.1017/S1092852914000133

Snyder, M., & Gangestad, S. (1986). On the Nature of Self-Monitoring: Matters of Assessement, Matters of Validity. Journal of Personality and Social Psychology, 51(1), 125–139. https://doi.org/10.1037/0022-3514.51.1.125

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-Back. In Measuring Alcohol Consumption. 41-72. https://doi.org/10.1007/978-1-4612-0357-5_3

Sofis, M. J., Budney, A. J., Stanger, C., Knapp, A. A., & Borodovsky, J. T. (2020). Greater delay discounting and cannabis coping motives are associated with more frequent cannabis use in a large sample of adult cannabis users. Drug and alcohol dependence, 207, 107820. https://doi.org/10.1016/j.drugalcdep.2019.107820.

Sofuoglu, M., Devito, E. E., Waters, A. J., & Carroll, K. M. (2013). Cognitive enhancement as a treatment for drug addictions. Neuropharmacology, 64, 452–463. https://doi.org/10.1016/j.neuropharm.2012.06.021

Solowij, N., & Battisti, R. (2008). The Chronic Effects of Cannabis on Memory in Humans: A Review. Current Drug Abuse Reviews, 1(1), 81–98. https://doi.org/10.2174/1874473710801010081

Solowij, N., Jones, K. A., Rozman, M. E., Davis, S. M., Ciarrochi, J., Heaven, P. C. L., Lubman, D. I., & Yücel, M. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. Psychopharmacology, 216(1), 131–144. https://doi.org/10.1007/s00213-011-2203-x

Somaini, L., Manfredini, M., Amore, M., Zaimovic, A., Raggi, M. A., Leonardi, C., Gerra, M. L., Donnini, C., & Gerra, G. (2012). Psychobiological responses to unpleasant emotions in cannabis users. European Archives of Psychiatry and Clinical Neuroscience, 262(1), 47–57. https://doi.org/10.1007/s00406-011-0223-5

Spiegelhalder, K., Jähne, A., Kyle, S. D., Beil, M., Doll, C., Feige, B., & Riemann, D. (2011). Is smoking-related attentional bias a useful marker for treatment effects? Behavioral Medicine, 37(1), 26–34. https://doi.org/10.1080/08964289.2010.543195

Spielberger, C. D., & Sydeman, S. J. (1994). State-trait anxiety inventory and state-trait anger expression inventory. The use of psychological testing for treatment planning and outcome assessment. 292-312.

Stanger, C., Elton, A., Ryan, S. R., James, G. A., Budney, A. J., & Kilts, C. D. (2013). Neuroeconomics and adolescent substance abuse: Individual differences in neural networks and delay discounting. Journal of the American Academy of Child and Adolescent Psychiatry, 52(7). https://doi.org/10.1016/j.jaac.2013.04.013

Statistics Netherlands (CBS). (2020). Economic impact of Covid-19. https://www.cbs.nl/en-gb/dossier/coronavirus-crisis-cbs-figures/economic-impact-of-covid-19

Steinberg, L. (2005). Cognitive and affective development in adolescence. Trends in Cognitive Sciences, 9(2), 69–74. https://doi.org/10.1016/j.tics.2004.12.005

Steinhoff, A., Shanahan, L., Bechtiger, L., Zimmermann, J., Ribeaud, D., Eisner, M. P., Baumgartner, M. R., & Quednow, B. B. (2023). When Substance Use Is Underreported: Comparing Self-Reports and Hair Toxicology in an Urban Cohort of Young Adults. Journal of the American Academy of Child and Adolescent Psychiatry. https://doi.org/10.1016/j.jaac.2022.11.011

Stephens, R. S., Roffman, R. A., & Curtin, L. (2000). Comparison of extended versus brief treatments for marijuana use. Journal of Consulting and Clinical Psychology, 68(5), 898–908. https://doi.org/10.1037/0022-006X.68.5.898

Stinson, F. S., Ruan, W. J., Pickering, R., & Grant, B. F. (2006). Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. Psychological Medicine, 36(10), 1447–1460. https://doi.org/10.1017/S0033291706008361

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. Cortex, 45(9), 1091–1096. https://doi.org/10.1016/j.cortex.2008.12.004

Stroop, R. J. (1935). Studies of Interference in Serial Verbal Reactions. Journal of Experimental Psychology, 121(1), 15–23.

Sun, J. (2005). Assessing goodness of fit in confirmatory factor analysis. Measurement and Evaluation in Counseling and Development, 37(4), 240–256. https://doi.org/10.1080/07481756.2005.11909764

Sweeney, M. M., Rass, O., DiClemente, C., Schacht, R. L., Vo, H. T., Fishman, M. J., Leoutsakos, J.-M. S., Mintzer, M. Z., & Johnson, M. W. (2018). Working Memory Training for Adolescents With Cannabis Use Disorders: A Randomized Controlled Trial. Journal of Child & Adolescent Substance Abuse, 27(4), 211–226. https://doi.org/10.1080/1067828X.2018.1451793

Swick, D., Ashley, V., & Turken, U. (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. NeuroImage, 56(3), 1655–1665. https://doi.org/10.1016/j.neuroimage.2011.02.070

Sznitman, S. R., Shochat, T., & Greene, T. (2020). Is time elapsed between cannabis use and sleep start time associated with sleep continuity? An experience sampling method. Drug and Alcohol Dependence, 208, 107846. https://doi.org/10.1016/j.drugalcdep.2020.107846

T

Taber, K. S. (2018). The Use of Cronbach's Alpha When Developing and Reporting Research Instruments in Science Education. Research in Science Education, 48(6), 1273–1296. https://doi.org/10.1007/s11165-016-9602-2

Tait, R. J., & Christensen, H. (2010). Internet-based interventions for young people with problematic substance use: a systematic review. Medical Journal of Australia, 192(11), 15–21. https://doi.org/https://doi.org/10.5694/j.1326-5377.2010.tb03687.x

Takagi, M., Lubman, D. I., Cotton, S., Fornito, A., Baliz, Y., Tucker, A., & Yücel, M. (2011). Executive control among adolescent inhalant and cannabis users. Drug and Alcohol Review, 30(6), 629–637. https://doi.org/10.1111/j.1465-3362.2010.00256.x

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. International Journal of Medical Education, 2, 53–55. https://doi.org/10.5116/ijme.4dfb.8dfd

Taylor, M., Cousijn, J., & Filbey, F. (2019). Determining Risks for Cannabis Use Disorder in the Face of Changing Legal Policies. Current Addiction Reports, 6(4), 466–477. https://doi.org/10.1007/s40429-019-00288-6

Taylor, M. B., Hammonds, R., & Filbey, F. M. (2021). Relationship between behavioral inhibition and approach motivation systems (BIS/BAS) and intrinsic brain network connectivity in adult cannabis users. Social Cognitive and Affective Neuroscience, 16(9), 985–994. https://doi.org/10.1093/scan/nsab054

Taylor, M., Lees, R., Henderson, G., Lingford-Hughes, A., Macleod, J., Sullivan, J., & Hickman, M. (2017). Comparison of cannabinoids in hair with self-reported cannabis consumption in heavy, light and non-cannabis users. Drug and Alcohol Review, 36(2), 220–226. https://doi.org/10.1111/DAR.12412

Templeton, L., Velleman, R., & Russell, C. (2010). Psychological interventions with families of alcohol misusers: A systematic review. Addiction Research & Theory, 18(6), 616–648. https://doi.org/10.3109/16066350903499839

Terry-McElrath, Y. M., O'Malley, P. M., & Johnston, L. D. (2008). Saying no to marijuana: Why American youth report quitting or abstaining. Journal of Studies on Alcohol and Drugs, 69(6), 796–805. https://doi.org/10.15288/jsad.2008.69.796

Teunissen, H. A., Spijkerman, R., Prinstein, M. J., Cohen, G. L., Engels, R. C. M. E., & Scholte, R. H. J. (2012). Adolescents' Conformity to Their Peers' Pro-Alcohol and Anti-Alcohol Norms: The Power of Popularity. Alcoholism: Clinical and Experimental Research, 36(7), 1257–1267. https://doi.org/10.1111/j.1530-0277.2011.01728.x

Thames, A. D., Arbid, N., & Sayegh, P. (2014). Cannabis use and neurocognitive functioning in a non-clinical sample of users. Addictive Behaviors, 39(5), 994–999. https://doi.org/10.1016/j.addbeh.2014.01.019

Thayer, R. E., Feldstein Ewing, S. W., Dodd, A. B., Hansen, N. S., Mayer, A. R., Ling, J. M., & Bryan, A. D. (2015). Functional activation during the Stroop is associated with recent alcohol but not marijuana use among high-risk youth. Psychiatry Research - Neuroimaging, 234(1), 130–136. https://doi.org/10.1016/j.pscychresns.2015.09.009

Theunissen, E. L., Kauert, G. F., Toennes, S. W., Moeller, M. R., Sambeth, A., Blanchard, M. M., & Ramaekers, J. G. (2012). Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. Psychopharmacology, 220(2), 341–350. https://doi.org/10.1007/s00213-011-2479-x

Thomson, H., Labuschagne, I., Greenwood, L. M., Robinson, E., Sehl, H., Suo, C., & Lorenzetti, V. (2021). Is resting-state functional connectivity altered in regular cannabis users? A systematic review of the literature. Psychopharmacology, 239(5), 1191-1209. https://doi.org/10.1007/s00213-021-05938-0

Treloar Padovano, H., & Miranda, R. (2018). Subjective cannabis effects as part of a developing disorder in adolescents and emerging adults. Journal of Abnormal Psychology, 127(3), 282–293. https://doi.org/10.1037/abn0000342

Trimbos-instituut, & WODC. (2021). Nationale Drug Monitor Kerncijfers en Ontwikkelingen 2021. https://www.nationaledrugmonitor.nl/over-ndm-

Troup, L. J., Andrzejewski, J. A., & Torrence, R. D. (2019). The effects of sex and residual cannabis use on emotion processing: An event-related potential study. Experimental and Clinical Psychopharmacology, 27(4), 318. https://doi.org/10.1037/pha0000265.

Trucco, E. M. (2020). A review of psychosocial factors linked to adolescent substance use. Pharmacology Biochemistry and Behavior, 196, 172969. https://doi.org/10.1016/j.pbb.2020.172969

Trujillo, N., Gómez, D., Trujillo, S., López, J. D., Ibáñez, A., & Parra, M. A. (2021). Attentional bias during emotional processing: Behavioral and electrophysiological evidence from an emotional flanker task. PLoS ONE, 16, 1–20. https://doi.org/10.1371/journal.pone.0249407

Tucker, L. R., & Lewis, C. (1973). A reliability coefficient for maximum likelihood factor analysis. Psychometrika, 38(1), 1–10. https://doi.org/https://doi.org/10.1007/BF02291170

U

Uhl, G. R., Koob, G. F., & Cable, J. (2019). The neurobiology of addiction. Annals of the New York Academy of Sciences, 62(1), 118–127. https://doi.org/10.1111/nyas.13989

UNODC. (2015). World Drug Report 2015. In United Nations publication, Sales No. E.15.XI.6.

UNODC. (2016). World Drug Report 2016. In United Nations publication, Sales No. E.16.XI.7.

UNODC. (2018a). Global overview of drug demand and supply. In World Drug Report 2018.

UNODC. (2018b). Analysis of drug markets. In World Drug Report 2018.

UNODC. (2019). Cannabis and Hallucinogens. In World Drug Report 2019.

UNODC. (2020). World Drug Report 2020. In United Nations publication, Sales No. E.20.XI.6.

UNODC. (2021). Drug Market Trends: Cannabis Opioids. In World Drug Report 2021.

UNODC. (2022). Drug market trends: Cannabis Opioids. In World Drug Report 2022.

Unsworth, N., & Engle, R. W. (2007). The nature of individual differences in working memory capacity: Active maintenance in primary memory and controlled search from secondary memory. Psychological Review, 114(1), 104–132. https://doi.org/10.1037/0033-295X.114.1.104

Utevsky, A. v., Smith, D. v., & Huettel, S. A. (2014). Precuneus is a functional core of the default-mode network. Journal of Neuroscience, 34(3), 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014

V

Vadhan, N. P., Hart, C. L., van Gorp, W. G., Gunderson, E. W., Haney, M., & Foltin, R. W. (2007). Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. Journal of Clinical and Experimental Neuropsychology, 29(4), 357–364. https://doi.org/10.1080/13803390600693615

Van Borkulo, C. D., Boschloo, L., Kossakowski, J. J., Tio, P., Schoevers, R. A., Borsboom, D., & Waldorp, L. J. (2017). Comparing network structures on three aspects: A permutation test. Psychological Methods. https://doi.org/10.1037/met0000476

Van der Pol, P., Liebregts, N., de Graaf, R., Korf, D. J., Van den Brink, W., & Van Laar, M. (2013). Predicting the transition from frequent cannabis use to cannabis dependence: A three-year prospective study. Drug and Alcohol Dependence, 133(2), 352–359. https://doi.org/10.1016/j.drugalcdep.2013.06.009

Van der Pol, P., Liebregts, N., De Graaf, R., Ten Have, M., Korf, D. J., Van den Brink, W., & Van Laar, M. (2013). Mental health differences between frequent cannabis users with and without dependence and the general population. Addiction, 108(8), 1459–1469. https://doi.org/10.1111/add.12196

Van Kampen, A. D., Cousijn, J., Engel, C., Rinck, M., & Dijkstra, B. A. G. (2020). Attentional bias, craving and cannabis use in an inpatient sample of adolescents and young adults diagnosed with cannabis use disorder: The moderating role of cognitive control. Addictive Behaviors, 100, 106126. 106126. https://doi.org/10.1016/j.addbeh.2019.106126.

Van Laar, M. W., Oomen, P. E., van Miltenburg, C. J. A., Vercoulen, E., Freeman, T. P., & Hall, W. D. (2020). Cannabis and COVID-19: Reasons for Concern. Frontiers in Psychiatry, 11, 601653. https://doi.org/10.3389/fpsyt.2020.601653

Van Ours, J. C., & Williams, J. (2011). Cannabis use and mental health problems. Journal of Applied Econometrics, 26(7), 1137–1156. https://doi.org/10.1002/jae.1182

Van Rooijen, G., Isvoranu, A. M., Meijer, C. J., van Borkulo, C. D., Ruhé, H. G., & de Haan, L. (2017). A symptom network structure of the psychosis spectrum. Schizophrenia Research, 189, 75–83. https://doi.org/10.1016/j.schres.2017.02.018

Vandenberghe, R., Molenberghs, P., & Gillebert, C. R. (2012). Spatial attention deficits in humans: The critical role of superior compared to inferior parietal lesions. Neuropsychologia, 50(6), 1092–1103. https://doi.org/10.1016/j.neuropsychologia.2011.12.016

Vanderbruggen, N., Matthys, F., Van Laere, S., Zeeuws, D., Santermans, L., Van den Ameele, S., & Crunelle, C. L. (2020). Self-Reported Alcohol, Tobacco, and Cannabis Use during COVID-19 Lockdown Measures: Results from a Web-Based Survey. European Addiction Research, 26(6), 309-315. https://doi.org/10.1159/000510822

Vandrey, R. G., Budney, A. J., Hughes, J. R., & Liguori, A. (2008). A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. Drug and Alcohol Dependence, 92(1–3), 48–54. https://doi.org/10.1016/j.drugalcdep.2007.06.010

Vaske, J. J., Beaman, J., & Sponarski, C. C. (2017). Rethinking Internal Consistency in Cronbach's Alpha. Leisure Sciences, 39(2), 163–173. https://doi.org/10.1080/01490400.2015.1127189

Vatansever, D., Menon, D. K., & Stamatakis, E. A. (2017). Default mode contributions to automated information processing. Proceedings of the National Academy of Sciences of the United States of America, 114(48), 12821–12826. https://doi.org/10.1073/pnas.1710521114

Vergés, A., Haeny, A. M., Jackson, K. M., Bucholz, K. K., Grant, J. D., Trull, T. J., Wood, P. K., & Sher, K. J. (2013). Refining the notion of maturing out: Results from the national epidemiologic survey on alcohol and related conditions. American Journal of Public Health, 103(12), 67–73. https://doi.org/10.2105/AJPH.2013.301358

Verplanken, B., Hazenberg, P. T., & Palenéwen, G. R. (1992). Need for cognition and external information search effort. Journal of Research in Personality, 26(2), 128–136. https://doi.org/10.1016/0092-6566(92)90049-A

Vidot, D. C., Islam, J. Y., Camacho-Rivera, M., Harrell, M. B., Rao, D. R., Chavez, J. V., Ochoa, L. G., Hlaing, W. W. M., Weiner, M., & Messiah, S. E. (2020). The COVID-19 cannabis health study: Results from an epidemiologic assessment of adults who use cannabis for medicinal reasons in the United States. Journal of Addictive Diseases, 39(1), 26-36. https://doi.org/10.1080/10550887.2020.1811455

Vingerhoets, W., Koenders, L., van den Brink, W., Wiers, R., Goudriaan, A., van Amelsvoort, T., de Haan, L., & Cousijn, J. (2016). Cue-induced striatal activity in frequent cannabis users independently predicts cannabis problem severity three years later. Journal of Psychopharmacology, 30(2), 152–158. https://doi.org/10.1177/0269881115620436

Viveros, M. P., Marco, E. M., & File, S. E. (2006). Nicotine and cannabinoids: Parallels, contrasts and interactions. Neuroscience and Biobehavioral Reviews, 30(8) 1161-1181. https://doi.org/10.1016/j.neubiorev.2006.08.002

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic Advances from the Brain Disease Model of Addiction. New England Journal of Medicine, 374(4), 363–371. https://doi.org/10.1056/NEJMra1511480

Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Alexoff, D., Logan, J., Jayne, M., Wong, C., & Tomasi, D. (2014). Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proceedings of the National Academy of Sciences of the United States of America, 111(30), E3149-E3156. https://doi.org/10.1073/pnas.1411228111

Von Sydow, K., Lieb, R., Pfister, H., Höfler, M., & Wittchen, H.-U. (2002). What predicts incident use of cannabis and progression to abuse and dependence? Drug and Alcohol Dependence, 68(1), 49–64. https://doi.org/10.1016/S0376-8716(02)00102-3

Voogt, C. V., Larsen, H., Poelen, E. A. P., Kleinjan, M., & Engels, R. C. M. E. (2013). Longitudinal associations between descriptive and injunctive norms of youngsters and heavy drinking and problem drinking in late adolescence. Journal of Substance Use, 18(4), 275–287. https://doi.org/10.3109/14659891.2012.674623

W

Walker, D. M., Bell, M. R., Flores, C., Gulley, J. M., Willing, J., & Paul, M. J. (2017). Adolescence and reward: Making sense of neural and behavioral changes amid the chaos. Journal of Neuroscience, 37(45), 10855–10866. https://doi.org/10.1523/JNEUROSCI.1834-17.2017

Wallace, A. L., Maple, K. E., Barr, A. T., & Lisdahl, K. M. (2020). BOLD responses to inhibition in cannabis-using adolescents and emerging adults after 2 weeks of monitored cannabis abstinence. Psychopharmacology, 237(11), 3259–3268. https://doi.org/10.1007/s00213-020-05608-7

Waller, L., Erk, S., Pozzi, E., Toenders, Y. J., Haswell, C. C., Büttner, M., Thompson, P. M., Schmaal, L., Morey, R. A., Walter, H., & Veer, I. M. (2022). ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data. Human Brain Mapping, 43(9), 2727-2742. https://doi.org/10.1002/hbm.25829

Walsh, Z., Gonzalez, R., Crosby, K., S. Thiessen, M., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. Clinical Psychology Review, 51, 15–29. https://doi.org/10.1016/j.cpr.2016.10.002

Waters, A. J., Marhe, R., & Franken, I. H. A. (2015). Temptations To Use Heroin and Cocaine. 219(3), 909–921. https://doi.org/10.1007/s00213-011-2424-z.Attentional

Wechsler, D. (2012). WAIS-IV-NL: Wechsler adult intelligence scale -Nederlandstalige bewerking. Pearson.

Weinstein, A., Brickner, O., Lerman, H., Greemland, M., Bloch, M., Lester, H., Chisin, R., Sarne, Y., Mechoulam, R., Bar-Hamburger, R., Freedman, N., & Even-Sapir, E. (2008). A study investigating the acute dose-response effects of 13 mg and 17 mg 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. Journal of Psychopharmacology, 22(4), 441–451. https://doi.org/10.1177/0269881108088194

Wesley, M. J., Hanlon, C. A., & Porrino, L. J. (2011). Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. Psychiatry Research: Neuroimaging, 191(1), 51-59. https://doi.org/10.1016/j.pscychresns.2010.10.002

Wolpert, D. M., Goodbody, S. J., & Husain, M. (1998). Maintaining internal representations: The role of the human superior parietal lobe. Nature Neuroscience, 1(6), 529–533. https://doi.org/10.1038/2245

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. NeuroImage, 21(4), 1732–1747. https://doi.org/10.1016/j.neuroimage.2003.12.023

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage, 14(6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931

World Health Organization. (1993). The ICD-10 Classification of Mental and Behavioural Disorders.

World Health Organization. (2016). The health and Social Effects of Nonmedical Cannabis Use.

Z

Zhang, M. W. B., Ying, J., Wing, T., Song, G., Fung, D. S. S., & Smith, H. E. (2018). Cognitive Biases in Cannabis, Opioid, and Stimulant Disorders: A Systematic Review. Frontiers in Psychiatry, 9, 376. https://doi.org/10.3389/fpsyt.2018.00376

Zhang, R., & Volkow, N. D. (2019). Brain default-mode network dysfunction in addiction. NeuroImage, 200, 313–331. https://doi.org/10.1016/j.neuroimage.2019.06.036

Zhang, S., & Li, C-S. R. (2012). Functional connectivity mapping of the human precuneus by resting state fMRI. NeuroImage, 59(4), 3548–3562. https://doi.org/10.1016/j.neuroimage.2011.11.023

Zhao, Y., Sallie, S. N., Cui, H., Zeng, N., Du, J., Yuan, T., Li, D., De Ridder, D., & Zhang, C. (2021). Anterior Cingulate Cortex in Addiction: New Insights for Neuromodulation. Neuromodulation, 24(2), 187–196. https://doi.org/10.1111/ner.13291

Zhou, X., Zimmermann, K., Xin, F., Zhao, W., Derckx, R. T., Sassmannshausen, A., Scheele, D., Hurlemann, R., Weber, B., Kendrick, K. M., & Becker, B. (2019). Cue Reactivity in the Ventral Striatum Characterizes Heavy Cannabis Use, Whereas Reactivity in the Dorsal Striatum Mediates Dependent Use. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4(8), 751–762. https://doi.org/10.1016/j.bpsc.2019.04.006

Zilverstand, A., Huang, A. S., Alia-Klein, N., & Goldstein, R. Z. (2018). Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. Neuron, 98(5), 886–903. https://doi.org/10.1016/j.neuron.2018.03.048

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Summary

Looking for interactions: towards a more complete neurocognitive model of cannabis use and cannabis use disorder

This thesis explores the complex nature of cannabis use, including factors that influence initiation, escalation towards heavy use, and the potential development of a cannabis use disorder (CUD). The changing legal landscape and increasing availability of cannabis have contributed to a decrease in perceived harm and an upsurge in usage. The prevalence of cannabis use is high worldwide and the rise in the delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio, with increasing THC levels and decreasing CBD levels, may amplify the potential harms of cannabis use.

While cannabis initiation is common in all age groups, most individuals initiate cannabis use during adolescence (UNODC, 2019) and the prevalence of cannabis use peaks during young adulthood (e.g., 26.4% of the 20–24-year-old Dutch; Trimbos-instituut & WODC, 2021). Approximately 10% of cannabis initiators become daily users, but the factors driving escalation are not fully understood. Cultural attitudes, social environment, limited behavioral control, individual motivations for use, and sex or gender differences all contribute to the effects of cannabis use and the development of a cannabis use disorder (CUD).

CUD is one of the most prevalent substance use disorder characterized by problematic cannabis use that impairs functioning or causes distress. The direct effects of THC on the endocannabinoid system and the release of dopamine in the brain's reward pathway are thought contribute to CUD. Associative learning processes also heighten the significance of drug-related cues, leading to compulsive use and withdrawal symptoms upon cessation. Importantly, not all daily cannabis users develop CUD, highlighting the need to comprehend individual differences in usage patterns and potential negative consequences of heavy use. Heavy cannabis use and dependence can result in altered brain processes associated with cognitive control and motivation. Individuals with CUD may also exhibit altered activation patterns in various brain regions during tasks involving attention, interference control, and working memory. However, the causal relationships and long-term effects of these brain changes remain incompletely understood.

The thesis aims to investigate the complex interactions between internal and external factors influencing cannabis use trajectories and consequences of use. This includes examining brain functioning, cognition, motivation, sex/gender, mental health, drug cues and attentional bias, region, cultural attitudes, COVID-19, and social factors. By studying these factors, the goal of this thesis is to move towards a more complete neurocognitive model of cannabis use and dependence that can inform prevention, intervention, and policy.

Results summary

Chapter 2, aimed to summarize and evaluate knowledge of the relationship between heavy cannabis use, CUD, and the Brain, discussing epidemiology, clinical representations, potential causal mechanisms, assessment and treatment, as well of prognoses. Heavy use and CUD appeared to be consistently associated with learning and memory impairments – which might resolve after prolonged abstinence - and comorbid psychiatric disorders are common is heavy users and those with CUD. Evidence regarding other cognitive domains and neurological consequences is limited or inconsistent. Treatment results in abstinence in only a minority of patients, but treatments aiming for reduction of use appear more successful. The impact of heavy use and CUD on brain outcomes appears to depend on age of onset of use, heaviness and frequency of use, CUD severity, psychiatric comorbidity, as well as THC/CBD ratio. Specifically focusing on evaluating the recent evidence for short-term and long-term effects of cannabis use on cognition, **Chapter 3** found cannabis intoxication to be associated with impaired learning and memory, attentional control, and motor inhibition. Evidence regarding the long-term effects of heavy use is less consistent, with impairments most constantly observed for learning and memory, attentional control, and the presence of attentional bias towards cannabis cues. Studies of the effects of cannabis on cognition are hampered by difficulties measuring cannabis exposure, the lack of control over sub-acute effects, the incomparability of included cognitive measures, and the large variety of included samples.

Chapter 4 aimed to assess how hair-derived cannabinoid concentrations – offering insight into three-month cumulative exposure – were associated with common self-report measures of cannabis use and cannabis use-related problems (N = 74, near-daily cannabis users with CUD). THC was detectable in over 95% of the hair sample of individuals that tested positive for THC on a urine test, supporting the potential for of hair for detecting cannabinoids. However, THC, CBD, and THC/CBD concentrations were not associated with self-reported use and use-related problems, indicating limited utility for quantification of use. THC concentrations were associated with self-reported measures of potency, but additional research is needed to assess the utility of these self-reported potency measures as an indicator of THC concentrations in a wider sample of users. Importantly, research comparing hair-derived cannabinoid concentrations with other biological matrices of use (e.g., plasma) and self-report measures of use is crucial to evaluate and confirm the validity of hair analyses for quantification of cannabis use.

As cannabis use in women is increasing worldwide but research assessing gender differences in cannabis use and CUD is lacking, **Chapter 5** assessed gender differences in CUD symptoms using a network analysis approach (weekly cannabis users; N = 1257,

Men: N = 745, Women: N = 512). This approach allows for the assessment of interactions between different CUD symptoms which could well be crucial in the etiology of CUD. Looking at the prevalence of symptom endorsement, men more often reported 6 out of 11 symptoms than women, while total CUD scores were similar (mean difference < 1 symptom). However, the symptom network structure, strength, and centrality did not differ between men and women. When considering the presence of mood and anxiety disorders in the model, gender differences did appear. In men, mood disorder presence was only associated to the presence of anxiety disorders, which in turn was associated with the CUD symptom network through unsuccessful attempts to reduce or quit, which could increase anxiety but also be increased by anxiety (i.e., possible feedback loop). In women, the presence of anxiety disorders was only associated to the presence of mood disorder, which in turn was associated with the CUD symptom network through craving and withdrawal, indicating a potential women-specific self-medication loop. These results highlight the complexity of symptom interactions and the potential gender differences in how comorbid psychiatric disorders are associated with CUD.

Chapter 6 assessed sex differences in cognitive control related brain processes that might underly CUD, using an N-back working memory (WM) task performed inside an MRI scanner (N = 189, frequent cannabis users: N = 104 (63% men), controls: N = 85 (53% men). Task performance was lower in the cannabis group when the task got at its most difficult. MRI results indicated a relatively smaller reduction in WM-related activity in the precuneus and posterior cingulate cortex at higher WM load, indicating a relative over recruitment of default mode related regions in cannabis users when cognitive demand increased. Sex differences were only observed in exploratory analyses within the cannabis group: men showed higher WM-related activity in the superior frontal gyrus compared to women. Differences in brain activity were not directly associated with performance differences and further research is needed to assess whether altered brain activation might be associated with performance when cognitive load is increased further.

Chapter 7 aimed to increase this cognitive load by adding distracting cannabis-related and neutral flankers to the N-back working memory task (N = 69, near-daily cannabis users: N = 36, controls: N = 33). These cannabis-related flankers specifically were expected to cause interference in the cannabis users, reducing performance and affecting brain activity. The flanker presence did not affect performance, but in cannabis users compared to controls, the presence of cannabis flankers was associated with reduced WM-load related activity in the insula, thalamus, superior parietal lobe, and supramarginal gyrus. These results could indicate that the presence of cannabis cues can interfere with cognition related brain processes in cannabis users, especially when cognitive demand increases.

Heavy cannabis use has also been associated to attentional bias towards cannabis stimuli. Using the same words as presented as flankers in **chapter 7** as stimuli in a cannabis Stroop task, **chapter 8** assessed the presence of attentional bias in cannabis users with different levels of use and CUD severity (N = 560, 71% men). Only those is treatment for CUD showed an attentional bias towards cannabis stimuli and group differences were only observed when comparing those in treatment for CUD with those that never-sporadically used cannabis. Furthermore, the association between attentional bias and craving in their association with cannabis use and related problems was assessed in occasional and regular users (N = 358). Average craving during the test session mediated the association between attentional bias and cannabis use as well as cannabis-related problems. The expected moderating effects of interference control on these associations were not observed, but interference control was directly associated with heaviness of cannabis use, indicating potential sub-acute effects of use on control related processes.

Changes in cannabis legislation have been paralleled with reductions in the perceived harm of cannabis use, which has been associated with increased initiation and persistent use. Perceived harms and benefits exist on the personal level, friend and family level, as well as regional (state or country) level, affecting the experienced cannabis culture. Cultural neuroscience research has shown that culture can affect a variety of brain processes underlying our daily life behaviors, but this has not been explored regarding the brain processes underlying cannabis use. **Chapter 9** assessed the associations between cultural attitudes towards cannabis use and resting state functional connectivity (RSFC) in three brain networks regularly associated with substance use: the default mode network, executive control network and salience network (N = 189, near-daily cannabis users with CUD: N = 110, controls: N = 79). Cannabis users showed lower RSFC than controls within the dorsal salience network, with this lower RSFC being associated with higher cannabis use in the cannabis group. Furthermore, cultural attitudes – from all three perspectives – moderated several associations of cannabis use, CUD symptoms, and cannabis use related problems with RSFC within the default mode network, executive control network, and salience network. Looking at RSFC between these networks, no group differences were observed. However, personal perceived benefits and perceived harms on the country/state level moderated the association between CUD symptoms and RSFC of ventral and dorsal default mode network regions. While these complex interactions have unknown clinical utility at this stage, it highlights the importance of considering individual differences in cannabis culture in the association between measures of cannabis use, use related problems, and brain functioning.

Chapter 10 then explored how cultural attitudes as well as site differences – Texas, USA and The Netherlands – might moderate the association between cognitive control

related brain activity and cannabis use, CUD symptoms, and cannabis use related problems, using an N-back working memory task (NL participants: near-daily cannabis users with CUD: N = 60, controls: N = 52; US participants: near-daily cannabis users with CUD: N = 40, controls: N = 32). Looking at cannabis attitudes, cannabis users were more positive and less negative than controls from both the personal and perceived friend-family's perspective. US cannabis users were even more positive and less negative than the NL participants. Although legislation differences are large, there were no site differences in perceived country-state attitudes. MRI results showed that cannabis users from TX – compared to NL users – and those cannabis users that perceived more positive country-state attitudes, displayed stronger positive associations between grams/week and WM-related activity in the superior parietal lobe. On the other hand, cannabis users from NL – compared to TX users – and those cannabis users with less positive personal attitudes, showed stronger positive associations between gram/week and WM-load-related activity in the temporal pole. These results indicate that both site differences and individual differences in attitudes towards cannabis use moderate associations between heaviness of use – but not cannabis use related problems and CUD severity - and WM- and WM-load related brain activity. Interestingly, differences in legislation did not align with the perceived harms and benefits of cannabis use in individuals from Texas (USA) or The Netherlands, and site and individual perceptions appeared to be differentially associated with the association between cannabis use and control related brain activity.

Cultural factors are not the only external factors that can affect cannabis use: a variety of life changes can heavily impact cannabis use and the development of CUD. One of the biggest life changing events in the last decades has been the COVID-19 pandemic and the associated lockdown. In **chapter 11** we aimed to assess the influence of the first Dutch COVID-19 lockdown on cannabis use and CUD and to evaluate the role of changes in mental health and psychosocial stressors therein (N = 183, monthly-daily cannabis users: N = 120, non-using controls: N = 63). Results showed that the lockdown was associated with an increase in cannabis use, but not CUD severity. Furthermore, cannabis users showed increased loneliness, but improved contact with partners and family, which was similar to results in controls. On average, mental health was not affected. However, individual differences in severity of use before the lockdown, COVID-19 related worries, changes in anxiety, changes in use motives, and contact with family explained unique variance in changes in cannabis use or CUD during the lockdown.

Aside from changes in the social environment, social influence is also known to be associated with substance use. The social plasticity hypothesis suggests that social attunement - the adaptation to and harmonization with one's environment in the absence of group pressure and conformity motives - plays an important role in the

risk for developing alcohol use disorders (AUDs) during adolescence, whereas in adulthood it paradoxically may make individuals more sensitive to the social pull to reduce drinking. **Chapter 12** described the development and validation of the 11-item Dutch social attunement questionnaire, including two subscales of social attunement cognition and social attunement behavior (N = 576, exploratory factor analysis: N = 373, confirmatory factor analysis: N = 203), showing acceptable internal consistency and good measurement invariance to gender. Exploratory assessment of the role of social attunement in alcohol use behavior showed that social attunement explained additional variance in the association of age and perceived peer drinking with alcohol use. Further research is required to assess the utility of the social attunement questionnaire in a broader variety of social settings, including social cannabis use.

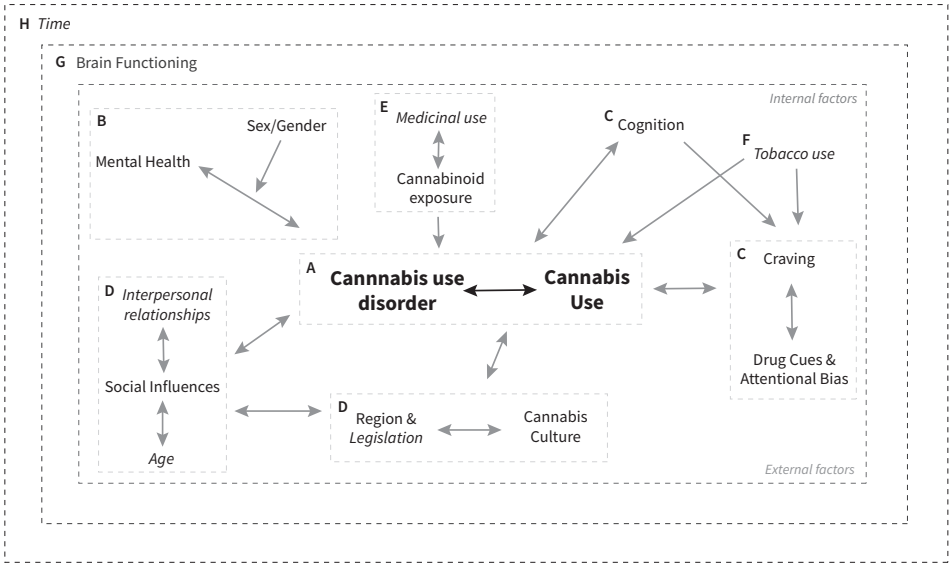


Figure 1. Initial neurocognitive model of cannabis use and CUD. Letters indicate different highlight themes and challenges for future research as discussed in this chapter. Grey lines represent the - often potentially bidirectional - associations that are crucial for future research to explore. The italic items represent novel factors that - although not directly assessed in my studies - appear to be important additions to this model. Additional layers have been added to indicate the overarching importance of brain functioning in the etiology of cannabis use and CUD and the importance of assessing those processes over time to assess developmental processes and causality.

Discussion & conclusion

The multimethod studies presented in this thesis can be a start to build towards a more complete neurocognitive model of cannabis use and CUD (Figure 1). First,

our studies highlight the importance of differentiating between heavy use and dependence – which most studies to date fail to do – as they differentially associate with cognition and brain functioning (Figure 1-A). Second, studies should embrace and assess the presence of comorbid mental health problems in those with CUD and consider potential interactions with gender therein (Figure 1-B). Third, studies should aim to include measures of motivation and control processes to test the theoretical importance of their interactions in cannabis use and CUD (Figure 1-C). Fourth, social and cultural factors are regularly ignored even though changes in the social environment, social use, and cultural attitudes towards use might be important drivers of initiation, continuation, and escalation of use (Figure 1-D). Studies should focus on developing and validating measures that assess these factors and include them in studies on cannabis use across the lifespan as the influence of these factors could be partially age dependent. Fifth, medical cannabis use is increasing, but evidence for its utility – especially as a treatment of mental health symptoms – is limited (Figure 1-E). It is crucial for studies to assess use motives – at least differentiating between primarily medical and recreational motives – to provide additional evidence for the risks and benefits of use. Furthermore, the measurement of cannabinoid exposure should be encouraged to start differentiating the effects of cannabinoid exposure, amount of use, and use related problems. Sixth, tobacco use remains one of the biggest challenges in cannabis research, particularly in Europe where combined use is very common (Figure 1-F). It is crucial to collect information on tobacco use with as much detail as is feasible (preferably using timeline follow-up measures) and to separate combined use from sequential use to help us understand the interactions between nicotine and cannabis.

The interactions described above are all fundamentally associated to brain functioning, but increasingly complex interactions make it difficult to assess the clinical implications of measures of brain functioning. It remains crucial to assess brain functioning as one of the fundamental factors underlying behavior (Figure 1-G) but assessing interactions between behavioral outcomes to inform prevention and treatment outcomes should be prioritized to reduce harm. Finally, we have limited understanding of causality and the development of these interactions over time. As the use of experimental designs is inherently limited by ethical constraints in the addiction field, it remains important to invest in studies assessing the effects of time on both the short (e.g., experience sampling methods) and longer time scale (e.g., multi-year cohort and longitudinal designs).

Together, these findings offer valuable but incremental contributions that can help to steer future research in the direction of developing a more comprehensive neurocognitive framework for understanding cannabis use and CUD. However, in order

to achieve this objective, it is crucial to prioritize measurement: we must strive towards a consensus on the essential assessments required in cannabis research. Drawing from my experience in conducting multimethod cross-cultural studies on cannabis use, I propose a starting point for the discussion in reaching this consensus. Figure 2 presents a cannabis research checklist that includes measurements I believe should be consistently incorporated in cannabis research, as well as additional measures that should be considered based on study goals, budgetary constraints, and time limitations. Extending these measurement standards beyond the mere measurement of cannabis use and cannabis use disorder can facilitate study comparison and prompt researchers to move beyond examining group differences, considering individual variations as well.

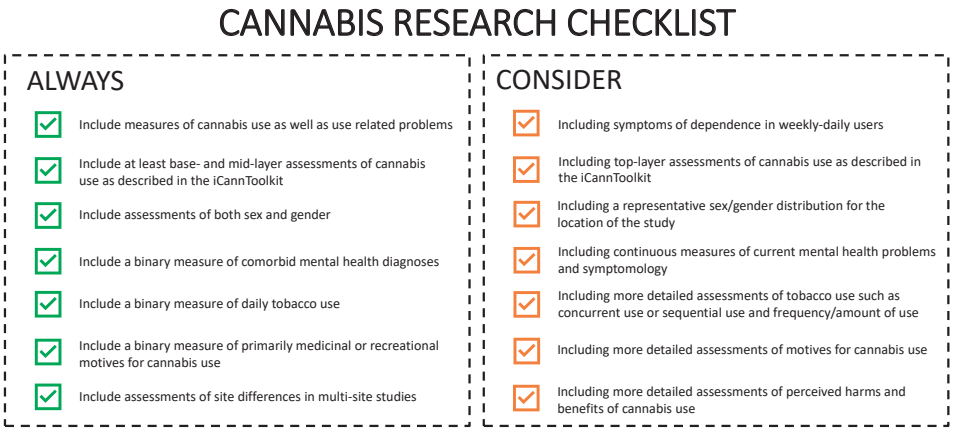


Figure 2. Cannabis research checklist. A proposal for a comprehensive field-wide cannabis research checklist, including measurements that should always be included to increase comparability of studies and measurements that should be considered based on the goals, budget, and time constraints of the study.

Samenvatting

Op zoek naar interacties: op weg naar een completer neurocognitief model van cannabisgebruik en cannabisverslaving

In dit proefschrift probeer ik meer inzicht te krijgen in de complexiteit van cannabisgebruik door te focussen op een breed scala aan factoren die invloed kunnen hebben op initiatie van gebruik, escalatie van gebruik en de ontwikkeling van een cannabisverslaving. De wereldwijd veranderende cannabis wetgeving en toenemende beschikbaarheid van cannabis hebben bijgedragen aan een afname van de waargenomen risico's van cannabisgebruik en een toename in cannabisgebruik. Cannabis is één van de meest gebruikte drugs wereldwijd en de toenemende delta-9-tetrahydrocannabinol (THC) ten opzichte van cannabidiol (CBD) concentraties in cannabis zijn zorgwekkend omdat dit de potentie heeft om de schadelijke effecten van cannabisgebruik te versterken.

Hoewel mensen van alle leeftijden cannabis gebruiken, beginnen de meeste gebruikers tijdens de adolescentie (UNODC, 2019) en bereikt de prevalentie van cannabisgebruik een hoogtepunt tijdens de jongvolwassen periode (bv. 26,4% van de 20-24-jarigen in Nederland; Trimbos-instituut & WODC, 2021). Ongeveer 10% van de mensen die cannabis gebruiken, wordt een dagelijkse gebruiker, maar hoe verschillende factoren - en de interacties tussen deze factoren - leiden tot deze escalatie van gebruik is onduidelijk. Culturele opvattingen, sociale omgeving, beperkte gedragscontrole, individuele motivaties voor gebruik en sekse- of genderverschillen zijn factoren die geassocieerd lijken te zijn aan de mate waarin gebruikers negatieve effecten van cannabis ervaren en aan de kans dat iemand een cannabisverslaving ontwikkelt.

Cannabisverslaving is een van de meest voorkomende verslavingen en wordt gekenmerkt door problematisch cannabisgebruik dat het functioneren belemmert of persoonlijk leed veroorzaakt. De directe effecten van THC op het endocannabinoïde systeem en het vrijkomen van dopamine in het beloningsnetwerk van de hersenen lijken bij te dragen aan de ontwikkeling van een cannabisverslaving. Daarnaast versterken associatieve leerprocessen de betekenis van druggerelateerde cues, wat kan leiden tot dwangmatig gebruik en ontwenningsverschijnselen bij het stoppen of minderen van gebruik. Niet alle dagelijkse cannabisgebruikers ontwikkelen een cannabisverslaving. Hierdoor blijft onderzoek naar de individuele verschillen tussen gebruikers die leiden tot de ontwikkeling van een verslaving in dagelijkse gebruikers cruciaal, maar is het ook van belang om te evalueren of - en in welke mate - dagelijkse gebruikers zonder een cannabisverslaving negatieve effecten ervaren. Frequent cannabisgebruik en verslaving kunnen leiden tot veranderingen in de hersenprocessen die verband houden met cognitieve controle en motivatie. Individuen met een cannabisverslaving kunnen

ook veranderde activatiepatronen vertonen in verschillende hersengebieden tijdens taken die aandacht, interferentiecontrole of werkgeheugen vereisen. Echter, causaliteit en de langetermijneffecten van deze veranderingen in de hersenen zijn onduidelijk.

Dit proefschrift heeft als doel de complexe interacties tussen de interne en externe factoren die bijdragen aan cannabisgebruik en de negatieve gevolgen van cannabisgebruik te evalueren. Dit omvat onderzoek naar hersenfunctie, cognitie, motivatie, sekse/gender, geestelijke gezondheid, drugscues en aandachtsbias, regio, culturele attitudes, COVID-19 en sociale factoren. Door deze factoren te combineren, beoogt dit proefschrift bij te dragen aan een completer neurocognitief model van cannabisgebruik en cannabisverslaving om preventie, interventie en beleidsvorming beter te informeren.

Samenvatting van de resultaten

Hoofdstuk 2 had als doel om de kennis over de relatie tussen frequent cannabisgebruik, cannabisverslaving en de hersenen samen te vatten en te evalueren. Hierbij werden epidemiologie, klinische symptomen, potentiële causale mechanismen, beoordeling en behandeling, evenals prognoses geëvalueerd. Frequent gebruik en verslaving bleken consistent geassocieerd te zijn met beperkingen in het leren en geheugen. Deze functies lijken zich wel (gedeeltelijk) te herstellen na langdurige onthouding. Comorbide psychiatrische stoornissen komen vaak voor bij frequente gebruikers en mensen met een cannabisverslaving. Het bewijs met betrekking tot andere cognitieve domeinen en neurologische gevolgen van cannabisgebruik is beperkt of inconsistent. Behandeling resulteert slechts bij een minderheid van de patiënten in onthouding, maar behandelingen gericht op het verminderen van gebruik lijken succesvoller te zijn. De impact van intensief gebruik en verslaving op de hersenen lijkt afhankelijk te zijn van de leeftijd waarop het gebruik begint, de frequentie en hoeveelheid gebruik, de ernst van de verslaving, psychiatrische comorbiditeit en de THC/CBD-verhouding. Het meest recente onderzoek naar de korte- en langetermijneffecten van cannabisgebruik op cognitie werd geëvalueerd in **Hoofdstuk 3.** Resultaten lieten zien dat cannabisintoxicatie gepaard gaat met beperkingen in het leren en geheugen, aandacht en motorinhibitie. Het bewijs met betrekking tot de langetermijneffecten van frequent gebruik is minder consistent, waarbij de meest constante beperkingen werden waargenomen in het leren en geheugen, aandacht en de aanwezigheid van een aandachtsbias voor cannabis gerelateerde stimuli. Studies naar de effecten van cannabis op cognitie worden bemoeilijkt door de complexiteit van het meten van cannabisgebruik, het gebrek aan controle over subacute effecten, de onvergelijkbaarheid van cognitieve taken en de grote variëteit aan proefpersonen.

Hoofdstuk 4 had als doel om te beoordelen hoe cannabinoïde concentraties

uit haarmonsters - die inzicht bieden in de cumulatieve blootstelling aan cannabis gedurende drie maanden - geassocieerd waren met veelvoorkomende zelfrapportagematen van cannabisgebruik en cannabis gerelateerde problemen (N = 74, bijna dagelijkse cannabisgebruikers met cannabisverslaving). THC werd gedetecteerd in meer dan 95% van de haarmonsters van individuen die positief testten op THC in een urinetest, wat wijst op het potentieel om haar te gebruiken voor het detecteren van cannabinoïden. Echter, THC-, CBD-, en THC/CBD-concentraties waren niet geassocieerd met zelf gerapporteerd gebruik en gebruik gerelateerde problemen, wat wijst op beperkte bruikbaarheid voor de kwantificering van gebruik. THC-concentraties waren wel geassocieerd met zelf gerapporteerde sterkte van de gebruikte cannabis, maar verder onderzoek is nodig om de bruikbaarheid van deze zelf gerapporteerde maten als indicatie van THC-concentraties in een breder scala van gebruikers te evalueren. Verder onderzoek dat cannabinoïde concentraties uit haar vergelijkt met andere biologische maten van gebruik (bijvoorbeeld cannabinoïden uit bloedplasma) en zelfrapportagematen van gebruik blijft cruciaal is om de validiteit en betrouwbaarheid van haaranalyses voor kwantificering van cannabisgebruik te evalueren en te bevestigen.

Aangezien cannabisgebruik onder vrouwen wereldwijd toeneemt, maar onderzoek naar genderverschillen in cannabisgebruik en cannabisverslaving ontbreekt, keek **Hoofdstuk 5** naar de genderverschillen in cannabisverslavingssymptomen met behulp van netwerkanalyse (wekelijkse cannabisgebruikers; N = 1257, Mannen: N = 745, Vrouwen: N = 512). Deze benadering maakt het mogelijk om de interacties tussen verschillende cannabisverslavingssymptomen te beoordelen, interacties die cruciaal kunnen zijn in de etiologie van cannabisverslaving. Bij het kijken naar de prevalentie van de verschillende symptomen rapporteerden mannen 6 van de 11 symptomen vaker dan vrouwen deden, terwijl het totaal aantal symptomen vergelijkbaar waren in mannen en vrouwen (gemiddeld verschil < 1 symptoom). De structuur, sterkte en centraliteit van het symptoomnetwerk verschilden echter niet tussen mannen en vrouwen. Bij het overwegen van de aanwezigheid van stemmings- en angststoornissen in het model, verschenen er wel genderverschillen. Bij mannen was de aanwezigheid van een stemmingsstoornis alleen geassocieerd met de aanwezigheid van angststoornissen, die op hun beurt geassocieerd waren met de cannabisverslavingssymptomen via onsuccesvolle pogingen om gebruik te minderen of te stoppen, wat angst zou kunnen verhogen maar ook versterkt zou kunnen worden door angst. Bij vrouwen was de aanwezigheid van angststoornissen alleen geassocieerd met de aanwezigheid van stemmingsstoornis, die op hun beurt geassocieerd waren met de verslavingssymptomen via craving (verlangen naar cannabis) en ontwenningsverschijnselen, wat wijst op een potentieel zelfmedicatiemechanisme dat specifiek is voor vrouwen. Deze

resultaten benadrukken de complexiteit van symptoominteracties en de mogelijke genderverschillen in de associatie tussen comorbide psychiatrische stoornissen en cannabisverslaving.

Hoofdstuk 6 keek naar potentiële sekseverschillen in cognitieve controle gerelateerde hersenprocessen die ten grondslag kunnen liggen aan cannabisverslaving, door gebruik te maken van een N-back-werkgeheugentaak in de MRI-scanner (N = 189, frequente cannabisgebruikers: N = 104 (63% mannen), controlegroep: N = 85 (53% mannen). De cannabisgroep gaf minder correcte antwoorden dan de controlegroep wanneer de taak het moeilijkst was. MRI-resultaten toonden een relatief kleinere vermindering van activiteit in de precuneus en de posterior cingulate cortex bij hogere werkgeheugenbelasting. Deze resultaten wijzen op een relatieve over rekrutering van hersengebieden die geassocieerd zijn met default-mode activiteit in cannabisgebruikers wanneer de cognitieve belasting hoger is. Sekseverschillen werden alleen waargenomen in een exploratieve analyse in de cannabisgroep: mannen vertoonden een hogere werkgeheugen-gerelateerde activiteit in de superior frontal gyrus dan vrouwen. Verschillen in hersenactiviteit waren niet direct geassocieerd met prestatieverschillen en verder onderzoek is nodig om te beoordelen of verschillen in hersenactivatie mogelijk geassocieerd zijn met prestaties wanneer de cognitieve belasting verder wordt verhoogd.

Hoofdstuk 7 had tot doel de cognitieve belasting te verhogen door cannabis gerelateerde en neutrale stimuli toe te voegen aan de N-back-werkgeheugentaak (N = 69, bijna dagelijkse cannabisgebruikers: N = 36, controlegroep: N = 33). Er werd verwacht dat deze cannabis gerelateerde stimuli specifiek zouden interfereren met de werkgeheugen presentaties en gerelateerde hersenactiviteit in de cannabisgebruikers. De aanwezigheid van de cannabisstimuli had geen invloed op de prestaties, maar bij cannabisgebruikers in vergelijking met controles was de aanwezigheid van cannabisstimuli geassocieerd met verminderde activiteit in de insula, thalamus, superior parietal lobe en supramarginal gyrus wanneer de werkgeheugenbelasting omhoogging. Deze resultaten kunnen erop wijzen dat cannabisstimuli kunnen interfereren met cognitie gerelateerde hersenprocessen in cannabisgebruikers, vooral wanneer de cognitieve belasting toeneemt.

Zeer frequent cannabisgebruik is ook geassocieerd met een aandachtsbias voor cannabisstimuli. Door het gebruik van dezelfde woorden die als cannabisstimuli werden gebruikt in **hoofdstuk 7** in een cannabis Stroop-taak, deed **hoofdstuk 8** onderzoek naar de aanwezigheid van aandachtsbias bij cannabisgebruikers met verschillende gebruiksfrequentie en verslavingsernst (N = 560, 71% mannen). Alleen degenen die in behandeling waren voor een cannabisverslaving vertoonden een aandachtsbias voor cannabisstimuli en groepsverschillen werden alleen waargenomen

bij het vergelijken van degenen die in behandeling waren voor cannabisverslaving met degenen die nooit of sporadisch cannabis hadden gebruikt. Daarnaast werd er gekeken naar de interactie tussen aandachtsbias en craving (verlangen naar cannabis) in hun associatie met cannabisgebruik en cannabis gerelateerde problemen in incidentele en frequente gebruikers (N = 358). De gemiddelde craving tijdens de testsessie medieerde de associatie tussen aandachtsbias en cannabisgebruik, evenals cannabis gerelateerde problemen. Het verwachte modererende effect van interferentiecontrole op deze associaties werd niet waargenomen, maar interferentiecontrole was direct geassocieerd met de mate van cannabisgebruik, wat wijst op mogelijke subacute effecten van gebruik op controle gerelateerde processen.

Het legaliseren en decriminaliseren van cannabis lijkt gepaard te gaan met een vermindering van de ervaren risico's van cannabisgebruik, terwijl een lager ingeschat risico verband lijkt te houden met een toename van initiatie en aanhoudend frequent gebruik. Ervaren risico's en voordelen bestaan op persoonlijk niveau, op het niveau van vrienden en familie, evenals op regionaal (staat of land) niveau en samen zijn zij van invloed op de ervaren cannabis-cultuur. Onderzoek naar culturele neurowetenschappen heeft aangetoond dat cultuur invloed kan hebben op verschillende hersenprocessen die ten grondslag liggen aan ons dagelijks gedrag, maar dit is nog niet onderzocht met betrekking tot de hersenprocessen die ten grondslag liggen aan cannabisgebruik. **Hoofdstuk 9** deed onderzoek naar de associaties tussen culturele percepties ten opzichte van cannabisgebruik en hersenconnectiviteit in rust in drie hersennetwerken die regelmatig geassocieerd worden met middelengebruik: het default-mode netwerk, het executieve controle netwerk en het salience netwerk (N = 189, bijna dagelijkse cannabisgebruikers met cannabisverslaving: N = 110, controlegroep: N = 79). Cannabisgebruikers vertoonden lagere hersenconnectiviteit in rust dan controles binnen het dorsale salience netwerk, waarbij deze lagere hersenconnectiviteit in rust geassocieerd werd met hoger cannabisgebruik in de cannabisgroep. Bovendien modereerde culturele percepties - vanuit alle drie de perspectieven - verschillende associaties tussen cannabisgebruik, verslavingssymptomen en cannabis gerelateerde problemen met hersenconnectiviteit in rust binnen het default-mode netwerk, het executieve controle netwerk en het salience netwerk. Hersen connectiviteit in rust tussen deze netwerken verschilde niet tussen cannabisgebruikers en controles. Echter, persoonlijk ervaren voordelen en ervaren risico's op het niveau van het land/de staat modereerde de associatie tussen verslavingssymptomen en hersenconnectiviteit in rust tussen de ventrale en dorsale regio's van het default-mode netwerk. Hoewel deze complexe interacties op dit moment van onbekende klinische waarde zijn, benadrukt het wel de potentiële rol van individuele verschillen in de cannabis-cultuur in de associatie tussen cannabisgebruik, verslaving en hersenfunctie.

Hoofdstuk 10 onderzocht vervolgens hoe culturele percepties en verschillen tussen locaties - Texas, VS en Nederland - de associatie tussen cognitieve controle gerelateerde hersenactiviteit en cannabisgebruik, verslavingssymptomen en cannabis gerelateerde problemen beïnvloeden, met behulp van een N-back-werkgeheugentaak (NL-deelnemers: bijna dagelijkse cannabisgebruikers met cannabisverslaving: N = 60, controlegroep: N = 52; US-deelnemers: bijna dagelijkse cannabisgebruikers met cannabisverslaving: N = 40, controlegroep: N = 32). Wat betreft de cannabis percepties waren cannabisgebruikers positiever en minder negatief dan controles vanuit zowel het persoonlijke als het waargenomen perspectief van vrienden en familie. Amerikaanse cannabisgebruikers waren zelfs positiever en minder negatief dan de Nederlandse cannabisgebruikers. Hoewel er grote verschillen zijn in wetgeving, waren er geen locatieverschillen in de waargenomen percepties in het land/de staat. MRI-resultaten toonden aan dat cannabisgebruikers uit Texas - in vergelijking met Nederlandse gebruikers - en degenen die positievere percepties in het land/de staat ervaarden, sterkere positieve associaties vertoonden tussen cannabisgebruik (gram/week) en werkgeheugen gerelateerde activiteit in de superior parietal lobe. Aan de andere kant vertoonden cannabisgebruikers uit Nederland - in vergelijking met gebruikers uit Texas - en degenen met minder positieve persoonlijke percepties, sterkere positieve associaties tussen cannabisgebruik (gram/week) en werkgeheugen gerelateerde activiteit in de temporal pole. Dit laat zien dat zowel locatieverschillen als individuele verschillen in percepties ten opzichte van cannabisgebruik de associaties tussen de mate van gebruik - maar niet cannabis gerelateerde problemen en de ernst van verslaving - en werkgeheugen gerelateerde hersenactiviteit kunnen modereren. Interessant is dat de verschillen in wetgeving niet overeenkwamen met de waargenomen risico's en voordelen van cannabisgebruik bij individuen uit Texas (VS) of Nederland, en locatie- en individuele percepties bleken verschillend gerelateerd te zijn aan de associatie tussen cannabisgebruik en cognitie gerelateerde hersenactiviteit.

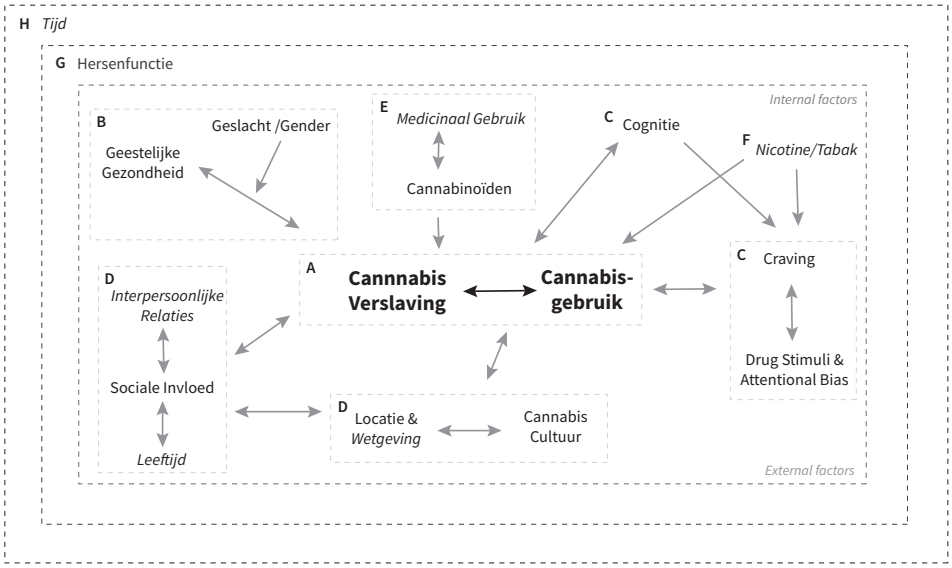
Cultuurfactoren zijn niet de enige externe factoren die van invloed kunnen zijn op cannabisgebruik: een heel scala van levensveranderingen en ervaringen kunnen een grote impact hebben op cannabisgebruik en de ontwikkeling van een cannabisverslaving. Eén van de grootste levensgebeurtenissen in de afgelopen decennia was de COVID-19-pandemie en de bijbehorende lockdown. In **hoofdstuk 11** hebben onderzoek gedaan naar de invloed van de eerste Nederlandse COVID-19-lockdown op cannabisgebruik en verslaving en de rol van veranderingen in de geestelijke gezondheid en psychosociale stressoren daarin (N = 183, maandelijks-dagelijkse cannabisgebruikers: N = 120, niet-gebruikende controlegroep: N = 63). De resultaten lieten zien dat de lockdown gepaard ging met een toename van cannabisgebruik, maar niet van de ernst van cannabisverslavingssymptomen. Verder vertoonden cannabisgebruikers een toename

van eenzaamheid, maar verbeterde contacten met partners en familie, wat vergelijkbaar was met de resultaten in de controlegroep. Gemiddeld genomen had de eerste lockdown geen invloed op de geestelijke gezondheid. Echter, individuele verschillen in de ernst van het gebruik vóór de lockdown, COVID-19-gerelateerde zorgen, veranderingen in angst, veranderingen in gebruiksmotieven en contact met familie verklaarden unieke variantie in veranderingen in cannabisgebruik of verslavingssymptomen tijdens de lockdown.

Naast veranderingen in de sociale omgeving kan sociale invloed van naasten ook effect hebben op middelengebruik. De sociale plasticiteitshypothese suggereert dat social attunement - de aanpassing aan en harmonisatie met de omgeving in afwezigheid van groepsdruk en conformiteitsmotieven - een belangrijke rol speelt bij het risico op het ontwikkelen van alcoholverslaving tijdens de adolescentie, terwijl het er paradoxaler wijs bij volwassenen toe kan leiden dat ze gevoeliger zijn voor de sociale invloed om alcoholgebruik te verminderen. **Hoofdstuk 12** beschrijft de ontwikkeling en validatie van de 11-item Nederlandse social attunement vragenlijst, die bestaat uit twee sub-schalen van social attunement gerelateerde cognitie en gedrag (N = 576, verkennende factoranalyse: N = 373, bevestigende factoranalyse: N = 203). De interne consistentie van de vragenlijst was acceptabel en de vragenlijst liet een goede meetinvariantie voor geslacht zien. Een exploratieve analyse die keek naar van de rol van social attunement in alcoholgebruik liet zien dat social attunement aanvullende variantie verklaarde in de associatie van de interactie tussen leeftijd en waargenomen alcoholgebruik van leeftijdsgenoten met alcoholgebruik. Verder onderzoek is nodig om de bruikbaarheid van de social attunement vragenlijst in een breder scala aan sociale omgevingen – inclusief cannabisgebruik voor sociale motieven - te beoordelen.

Discussie & conclusie

De studies in dit proefschrift leveren een eerste bijdrage aan het ontwikkelen van een completer neurocognitief model van cannabisgebruik en cannabisverslaving (Figuur 1). Ten eerste benadrukken deze studies het belang van het onderscheid tussen (zeer) frequent gebruik en verslaving - iets wat de meeste studies nalaten - omdat ze differentieel geassocieerd zijn met cognitie en hersenfunctie (Figuur 1-A). Ten tweede zouden studies de aanwezigheid van comorbide geestelijke gezondheidsproblemen bij mensen met een cannabisverslaving moeten omarmen en meten, rekening houdend met mogelijke interacties tussen comorbide geestelijke gezondheidsproblemen en gender in de associatie met cannabisgebruik en verslaving (Figuur 1-B). Ten derde zouden studies zowel taken die motivatie meten als taken die controleprocessen meten moeten opnemen in hun studieopzet om het theoretische belang van de interactie tussen motivatie en controle in cannabisgebruik te kunnen testen (Figuur 1-C). Ten vierde worden sociale en



Figuur 1. Initieel neurocognitief model van cannabisgebruik en cannabisverslaving. Letters corresponderen met verschillende highlights en uitdagingen voor verder onderzoek. Grijze lijnen zijn een indicatie van – potentieel bi-directionele - associaties die prioriteit hebben voor vervolgonderzoek. De schuingedrukte factoren zijn nieuwe factoren die – hoewel niet direct onderzocht in de gepresenteerde studies – belangrijk lijken te zijn voor een completer neurocognitief model van cannabisgebruik en cannabisverslaving. Extra lagen zijn toegevoegd om het overkoepelende belang van hersenfunctie voor de etiologie van cannabisgebruik en verslaving en het belang van onderzoek naar deze processen over tijd aan te geven.

culturele factoren regelmatig genegeerd in cannabisonderzoek terwijl veranderingen in de sociale omgeving, sociaal gebruik en culturele percepties ten opzichte van gebruik belangrijke drijfveren kunnen zijn voor het starten, voortzetten en escaleren van gebruik (Figuur 1-D). Studies zouden zich moeten richten op de ontwikkeling en validatie van meetinstrumenten voor deze factoren en ze opnemen in onderzoeken naar cannabisgebruik. Hierbij is het belangrijk om onderzoek te doen naar een breed scala aan leeftijden omdat de invloed van deze factoren gedeeltelijk leeftijdsafhankelijk zou kunnen zijn. Ten vijfde neemt het medicinale gebruik van cannabis toe, maar het bewijs voor positieve effecten hiervan - met name ter behandeling van geestelijke gezondheidssymptomen - is beperkt (Figuur 1-E). Het is cruciaal dat studies gebruiksmotieven beoordelen - ten minste onderscheid makend tussen hoofdzakelijk medische of hoofdzakelijk recreatieve motieven - om aanvullend bewijs te leveren voor de risico's en/of voordelen van gebruik. Bovendien moet het meten van blootstelling aan cannabinoïden worden aangemoedigd om dit te differentiëren van de hoeveelheid gebruik en gebruik gerelateerde problemen. Ten zesde blijft tabaksgebruik één van de grootste uitdagingen in cannabisonderzoek, met name in Europa waar gecombineerd

gebruik veel voorkomt (Figuur 1-F). Het is essentieel om informatie over tabaksgebruik zo gedetailleerd mogelijk te verzamelen (bij voorkeur met behulp van timeline follow-up-methoden) en gecombineerd gebruik te scheiden van opeenvolgend gebruik om kennis over de interacties tussen nicotine en cannabis te vergroten. De hierboven beschreven interacties zijn allemaal fundamenteel geassocieerd aan hersenfunctie, maar hoe complexer de interacties onderzocht, hoe moeilijker het is om de klinische implicaties de resultaten te beoordelen. Het blijft essentieel om hersenfunctie te onderzoeken als één van de fundamentele factoren geassocieerd aan cannabisgebruik en verslaving (Figuur 1-G). Echter, onderzoek naar interacties tussen gedragsuitkomsten moeten de prioriteit krijgen om preventiemaatregelen en de klinische praktijk te informeren. Ten slotte hebben we beperkte kennis over de causaliteit en de ontwikkeling van deze interacties over tijd. Aangezien het gebruik van experimentele studies naar de ontwikkeling van verslaving intrinsiek gelimiteerd wordt door ethische bezwaren, is het belangrijk om te investeren in studies die tijdseffecten op zowel korte termijn (bv. experience sampling methoden) als op langere termijn (bv. cohortstudies en meerjarige longitudinale studies) in kaart brengen.

Figuur 2. Checklist voor cannabis onderzoek. Een voorstel voor een uitgebreide checklist voor cannabisonderzoek, inclusief maten die altijd zouden moeten worden opgenomen in een cannabis studie om de vergelijkbaarheid van studies te vergroten en maten die moeten worden overwogen op basis van de doelstellingen, het budget en de tijdsbeperkingen van de studie.

Samen bieden de bevindingen in dit proefschrift een waardevolle maar incrementele bijdragen aan de ontwikkeling van een completer neurocognitief model van cannabisgebruik en cannabisverslaving dat verder onderzoek kan inspireren een bijdrage te leveren aan dit model. Om dit doel te bereiken is het cruciaal om prioriteit te geven aan methoden: we moeten streven naar een consensus over de

essentiële maten in cannabisonderzoek. Puttend uit mijn ervaring in het uitvoeren van interculturele cannabis studies die gebruik maken van een variatie aan methoden, doe ik een voorstel voor een startpunt voor de discussie om tot deze consensus te komen. Figuur 2 presenteert een checklist voor cannabisonderzoek die de maten bevat die naar mijn mening consequent moeten worden opgenomen in cannabisonderzoek, evenals aanvullende maten die moeten worden overwogen op basis van onderzoeksdoelen, budgettaire beperkingen en tijdsbeperkingen. Het uitbreiden van deze meetstandaarden – die verder gaan dan louter het meten van cannabisgebruik en verslaving – heeft de potentie om het vergelijken van studies te vergemakkelijken en onderzoekers te inspireren om verder te kijken dan groepsverschillen en ook onderzoek te doen naar individuele verschillen.

Publication list

Published international refereed articles

Kuhns, L., Mies, G., **Kroon, E.**, Willuhn, I., Lesscher, H., & Cousijn, J. (2023). Alcohol cue reactivity in the brain: Age-related differences in the role of social processes in addiction in male drinkers. *Journal of Neuroscience Research*. 1-17. https://doi.org/10.1002/jnr.25206

Kroon, E., Kuhns, L., Colyer-Patel, K., Filbey, F., & Cousijn, J. (2023). Working memory-related brain activity in cannabis use disorder: The role of cross-cultural differences in cannabis attitudes. *Addiction Biology. 28*(6), e13283. https://doi.org/10.1111/adb.13283 **[Chapter 10]**

Freichel, R., **Kroon, E.**, Kuhns, L., Filbey, F., Veer, I.M., Wiers, R., & Cousijn, J. (2023). Cannabis Use Disorder Symptoms in Weekly Cannabis Users: A Network Comparison Between Daily Tobacco Co-Users and Non-Co-Users. *Cannabis and Cannabinoid Research*. http://doi.org/10.1089/can.2022.0239

Gorey, C.*, **Kroon, E.***, Runia, N., Bornovalova, M., & Cousijn, J. (2023). Direct Effects of Cannabis Intoxication on Motivations for Softer and Harder Drug Use: An Experimental Approach to the Gateway Hypothesis. *Cannabis and Cannabinoid Research*. https://doi.org/10.1089/can.2022.0157

Kroon, E.*, Mansueto, A.C*., Kuhns, L.N., Wiers, R.W., Filbey, F., & Cousijn, J. (2022). Gender differences in cannabis use disorder symptoms: a network analysis. *Drug and Alcohol Dependence. 243,* 109733. https://doi.org/10.1016/j.drugalcdep.2022.109733. **[Chapter 5]**

Kroon, E., Kuhns, L, Dunkerbeck, A, & Cousijn, J. (2022). The who and how of attentional bias in cannabis users: associations with use severity, craving and interference control. *Addiction. 118*(2), 307-316. https://doi.org/10.1111/add.16059 **[Chapter 8]**

Kroon, E., Mies, G., Wiers, R. W., & Cousijn, J. (2022). Development and validation of the Dutch Social Attunement Questionnaire (SAQ). *Social Development. 32*(2), 546-565. https://doi.org/10.1111/sode.12652 **[Chapter 12]**

Kuhns, L., **Kroon, E.**, Lesscher, H., Mies, G., & Cousijn., J. (2022). Age-related differences in the effect of chronic alcohol on cognition and the brain: a systematic review. *Transl Psychiatry. 12*(1), 345. https://doi.org/10.1038/s41398-022-02100-y

Kroon, E., Kuhns, L. N., Kaag, A. M., Filbey, F., & Cousijn, J. (2022). The role of sex in the association between cannabis use and working memory related brain activity. *Journal of Neuroscience Research. 100*(6), 1347-1358. https://doi.org/10.1002/jnr.25041 **[Chapter 6]**

Kuhns, L.*, & **Kroon, E.*** (2021). The need to calibrate standardized cannabis measurements across cultures. *Addiction. 117*(6). 1518-1519. https://doi.org/10.1111/add.15744

Kroon, E., Kuhns, L.N., & Cousijn, J. (2021). Context Dependent Differences in Working Memory Related Brain Activity in Heavy Cannabis Users. *Psychopharmacology. 239*(5), 1373-1385. https://doi.org/10.1007/s00213-021-05956-y **[Chapter 7]**

Kuhns, L.N., **Kroon, E.**, Colyer-Patel, K., & Cousijn, J. (2021). Associations between Cannabis Use, Cannabis Use Disorder and Mood Disorders: Longitudinal, Genetic, and Neurocognitive Evidence. *Psychopharmacology. 239*(5), 1231-1249. https://doi.org/10.1007/s00213-021-06001-8

Cousijn, J., Kuhns, L., Larsen, H., & **Kroon, E.** (2021). For better or for worse? A pre–post exploration of the impact of the COVID-19 lockdown on cannabis users. *Addiction. 116*(8), 2104-2115. https://doi.org/10.1111/add.15387 **[Chapter 11]**

Kuhns, L. N., **Kroon, E.**, Filbey, F., & Cousijn, J. (2021). Unraveling the role of cigarette use in neural cannabis cue reactivity in heavy cannabis users. *Addiction Biology. 26*(3), e12941. https://doi.org/10.1111/adb.12941

Kroon, E., Kuhns, L. N., & Cousijn, J. (2021). The short-term and long-term effects of cannabis on cognition: recent advances in the field. *Current Opinion in Psychology. 38*, 49-55. https://doi.org/10.1016/j.copsyc.2020.07.005 **[Chapter 3]**

Kroon, E., Kuhns, L., Hoch, E., & Cousijn, J. (2020). Heavy Cannabis Use, Dependence and the Brain: A Clinical Perspective. *Addiction. 115*(3), 559-572. https://doi.org/10.1111/add.14776 [Chapter 2]

Gorey, C., Kuhns, L., Smaragdi, E., **Kroon, E.**, & Cousijn, J. (2019). Age-related differences in the impact of cannabis use on the brain and cognition: a systematic review. *European archives of psychiatry and clinical neuroscience. 269*(1), 37-58. https://doi.org/10.1007/s00406-019-00981-7

Derks, K., Burger, J., van Doorn, J., Kossakowski, J. J., Matzke, D., Atticciati, L., ... & Wagenmakers, E. J. (2018). Network Models to Organize a Dispersed Literature: The Case of Misunderstanding Analysis of Covariance. *Journal of European Psychology Students. 9*(1).48–57, https://doi.org/10.5334/jeps.458

Submitted manuscripts

Kroon, E., Toenders, Y.J., Kuhns, L., Filbey, F., & Cousijn, J. (n.d.). Resting state functional connectivity in dependent cannabis users: the moderating role of cannabis attitudes **[Chapter 9]**

Kroon, E., Cousijn, J., Filbey, F., Binz, T.M., & Kuhns, L. (n.d.). Associations between hair-derived cannabinoid levels, self-reported use, and cannabis-related problems. **[Chapter 4]**

Kroon, E., Zhang, R., Colyer-Patel, K., Ünsal, D., Larsen, H., & Cousijn, J. (n.d.). Implicit Social Attunement & Alcohol Use: The Effect of Peer Feedback on Changes in Willingness to Drink in Social Settings

Kuhns, L., **Kroon, E.**, Filbey, F., & Cousijn, J. (n.d.). A cross-cultural fMRI investigation of cannabis approach bias in individuals with cannabis use disorder

Back, S., **Kroon, E.**, Colyer-Patel, K., Cousijn J. (n.d.). Does nitrous oxide addiction exist? An evaluation of the evidence for the presence and prevalence of substance use disorder symptoms in Nitrous Oxide users

Kuhns, L., **Kroon, E.**, Filbey, F., Freeman, T., Cousijn, J. (n.d.). Cannabis research in context: the case for measuring and embracing cultural variation

Kuhns, L., **Kroon, E.**, Cousijn, J., Filbey, F. (n.d). Cannabis cue-reactivity in cannabis use disorder: Diverging evidence across distinct cannabis cultures

Colyer-Patel, K., Romein, C., Kuhns, L., Cousijn, J., **Kroon, E.** (n.d.). Recent evidence on the relation between cannabis use, brain structure and function: highlights and challenges

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