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REVIEW

Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences

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Abstract Decades of research have examined the effects of cannabis on neurocognition. Recent advances in this field provide us with a better understanding of how cannabis use influences neurocognition both acutely (during intoxication) and non-acutely (after acute effects subside). Evidence of problems with episodic memory is one of the most consistent findings reported; however, several other neurocognitive domains appear to be adversely affected by cannabis use under various conditions. There is significant variability in findings across studies, thus a discussion of potential moderators is increasingly relevant. The purpose of this review was to 1) provide an update on research of cannabis' acute and non-acute effects on neurocognition, with a focus on findings since 2007 and 2) suggest and discuss how neurodevelopmental issues and sex differences may influence cannabis effects on neurocognition. Finally we discuss how future investigations may lead to better understanding of the complex interplay among cannabis, stages of neurodevelopment, and sex on neurocognitive functioning.

Keywords Cannabis · Cognition · Marijuana · Neuropsychology · Sex differences · THC

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Introduction

In the last 5 years, significant advances have been made in understanding the endogenous cannabinoid system and how cannabis may affect its functioning, particularly as it pertains to the brain. The abundance of cannabinoid receptors in the hippocampus, amygdala, basal ganglia, and prefrontal cortex (Mackie 2005; Piomelli 2003) suggests that disruption of the cannabinergic system by administration of exogenous cannabinoids, like delta-9-tetrahydrocannabinol (THC; the main psychoactive compound in cannabis), may have important implications for various neurobehavioral processes, including mood and anxiety regulation (Crippa et al. 2011, 2009), learning, memory, motivation, motor control, reward processing, and executive functions (Crean et al. 2011; Gonzalez 2007; Solowij and Pesa 2010). Indeed, it seems frontal-limbic neurocircuitry is most prominently affected by cannabis use (for review see Martin-Santos et al. 2010), while other structures in the brain, including the brain stem, occipital lobe, and parietal lobe may be less affected. Not surprisingly, the neurobehavioral effects of cannabis use have been intensely studied over several decades and summarized in numerous published reviews (Crean et al. 2011; Ferraro 1980; Gonzalez et al. 2002; Gonzalez 2007; Grant et al. 2003; Iversen 2003; Jager and Ramsey 2008; Pope et al. 1995; Ranganathan and D'Souza 2006; Schweinsburg et al. 2008; Solowij and Battisti 2008; Solowij and Pesa 2010; Wert and Raulin 1986). However, many of these reviews conclude that the findings for several neurocognitive domains are equivocal, speaking to the importance of further research in this field.

Research on the neurocognitive effects of cannabis continues to grow rapidly. This is an especially pertinent area of research because cannabis continues to be the most widely used illicit substance worldwide (UNODC 2011). In the

U.S., cannabis use has recently risen and now surpasses that of cigarette use among adolescents (Johnston et al. 2012). These statistics are particularly concerning, given that cannabis use is associated with negative health outcomes (Kalant 2004), psychosocial and cognitive impairments (Kalant 2004; Solowij and Pesa 2010), and other neurobehavioral consequences such as an increased risk of an automobile crash when driving while intoxicated (Asbridge et al. 2012; Drummer et al. 2003; Li et al. 2012; Mura et al. 2003; Ramaekers et al. 2004). Furthermore, some have argued that the potency of cannabis, as indexed by THC content, has increased in recent years (Burgdorf et al. 2011) and may account for increases in cannabis use disorder diagnoses (Compton et al. 2004), as well as cannabis-related psychosis (Malone et al. 2010). On the other hand, societal acceptance of cannabis use for medicinal applications continues to increase (Cohen 2010; Fairfield et al. 1998; O'Connell and Bou-Matar 2007) and there is a growing body of literature suggesting medical benefits from cannabis use (Elikkottil et al. 2009; Ellis et al. 2009; Ware et al. 2005; Watson et al. 2000). All of these factors underscore the continued importance of investigating the acute and non-acute neurocognitive effects of cannabis use.

Given the outstanding reviews currently available on acute and non-acute effects of cannabis use on neurocognitive functioning and the rapid growth of new research in this area, we aimed to provide an update of research principally conducted during the past 5 years (since 2007) in the first half of this review. To orient the reader and provide a consistent organizational framework, we begin sections on acute and non-acute effects by first briefly summarizing the general findings from recent reviews of the field and then describing detailed findings from studies conducted since 2007. Studies that examine the impact of cannabis on measures generally thought to assess the same neurocognitive domain are discussed together when feasible. However, it is important to keep in mind that most neurocognitive measures are multidimensional in nature and some of these groupings, although not arbitrary, are not absolute. We also decided to present studies from samples with adolescents separately from those that employed adult samples in the non-acute section. In the second half of the review, we focus on two emerging influential factors, neurodevelopmental influences and sex differences, by reviewing critical animal and human studies and examining how these factors may interact with cannabis use to affect neurocognition.

Acute Effects of Cannabis on Neurocognitive Functioning

Studies on the acute effects of cannabis allow us to understand the immediate and direct effects that the psychoactive constituents of cannabis have on neurocognitive functioning during intoxication. These studies often rely on oral or intravenous administration of THC, but some have participants smoke actual cannabis joints under standardized conditions. Several review articles have been written on acute cannabis intoxication and neuropsychological functioning (Crean et al. 2011; Gonzalez 2007; Ferraro 1980; Ranganathan and D'Souza 2006; Solowij and Pesa 2010), with equivocal findings for most neurocognitive domains other than aspects of episodic memory—the autobiographical memory of specific events, situations, and experiences (Tulving 2001). For example, some of the first acute administration studies reported equivocal findings on several measures of executive functions, but found intoxicated individuals performed more poorly in the domain of episodic memory, especially recall of newly acquired information (Ferraro 1980). More recent studies also suggest that acute THC intoxication seems to impair retrieval-based memory of new material, but evidence regarding the effects of THC on other neuropsychological domains remained mixed (Gonzalez 2007; Ranganathan and D'Souza 2006). For instance, a recent review of cannabis' effects on executive functioning suggests that THC administration adversely affects inhibition, impulsivity, and working memory, but not verbal fluency, and findings are mixed for decision-making, risk-taking, and aspects of attention (Crean et al. 2011).

Acute Effects of Cannabis: Update from Research Published in the Last 5 Years

Learning and Memory

Recent research on acute effects of cannabis has benefited from using placebo-controlled designs and administration of different doses of THC in the laboratory. Data from the past 5 years is consistent with previous studies, generally showing acute administration of THC to impair episodic memory, including immediate (D'Souza et al. 2008a, b; Dumont et al. 2011; Morrison et al. 2009) and delayed recall (D'Souza et al. 2008a, b); procedural memory (Dumont et al. 2011); and associative learning and memory (Ballard et al. 2012) among occasional and regular cannabis users as well as non-users. Evidence indicates there may be a dose-dependent relationship between amount of intravenous THC and impairments in total free and delayed verbal recall, but not delayed cued or recognition recall (D'Souza et al. 2008b). D'Souza and colleagues (2008b) also found that, compared to non-using controls, frequent cannabis users showed blunted THC-related impairments in verbal episodic memory, suggesting potential tolerance effects to cannabis' negative influence on memory. In studies of visuospatial memory, THC impaired accuracy in regular cannabis users

(Weinstein et al. 2008a, b). On the other hand, others report no effect from THC on visuospatial memory (Anderson et al. 2010), associative memory (Bossong et al. 2012a), or verbal episodic memory (Sugarman et al. 2011). Hart and colleagues (2010) also found that THC administration did not affect overall performance on a task of verbal episodic memory in regular cannabis users, but participants performed more poorly on a recognition task suggesting a deleterious impact of cannabis on retrieval-based memory.

Attention, Concentration, and Working Memory

Most studies document impairments in attention and concentration following administration of small (i.e., 2.5 mg) and large (i.e., 0.5 mg/kg) doses of THC in cannabis users and non-users compared to placebo administration (Anderson et al. 2010; D'Souza et al. 2008a, b; Hunault et al. 2009; Ramaekers et al. 2009, 2011; Theunissen et al. 2011), with some evidence for a dose-dependent relationship between amount of THC smoked and degree of impairment (Hunault et al. 2009). However, two studies found no differences in performance on measures of auditory selective attention and concentration in regular cannabis users after smoking cannabis standardized to 20 mg THC (O'Leary et al. 2007) or on a measure of sustained attention in occasional cannabis users after ingesting 15 mg THC (Sugarman et al. 2011) compared to placebo. Impairments in working memory have been observed following acute administration of vaporized THC (Bossong et al. 2012b), oral THC (D'Souza et al. 2008a; Dumont et al. 2011), smoked cannabis containing different doses of THC (Hart et al. 2010), and intravenous THC (Morrison et al. 2009).

Abstract Reasoning, Decision-Making, and Risk-Taking

Research on the effects of cannabis on abstract reasoning and problem-solving have been conducted for many years; however, a recent trend in cannabis research has been the study of decision-making and risk-taking—often defined as processes of evaluating a variety of response options and choosing the option considered to be optimal in the present moment (Clark et al. 2004). THC has been found to impair healthy young adults' performance on a reasoning task (but not a verbal fluency task; Morrison et al. 2009) and significantly increased total errors and nonpreservative errors in regular cannabis users on a task of abstract reasoning (Weinstein et al. 2008a, b). Additionally, problems with cognitive flexibility have been reported after smoking cannabis standardized to different doses of THC compared to a placebo condition (Anderson et al. 2010). In contrast, most current evidence suggests that acute intoxication does not negatively impact decision-making or risk-taking in occasional, regular, or heavy cannabis users (D'Souza et al. 2008a; Ramaekers et al. 2009, 2011; Vadhan et al. 2007; Weinstein et al. 2008a, b), but it may slow decision-making (Vadhan et al. 2007). Some contradictory evidence does exist. Whereas a previous study demonstrated increasing levels of cannabis intoxication were associated with more risky responses in occasional cannabis users (Lane et al. 2005), a recent study found THC may actually reduce risk-taking behaviors in healthy young adults (Rogers et al. 2007).

Inhibitory Control, Motor Impulsivity, and Psychomotor Control

Similar to the findings for decision-making and risk taking, studies examining inhibition, motor impulsivity, and psychomotor control (these domains are invariably linked and generally defined as behavior involving rapid reactions to internal and external stimuli; Moeller et al. 2001) are mixed. THC was found to negatively influence inhibitory control, as evidenced by increased stop reaction time and decreased accuracy of responses in occasional and heavy cannabis users during a stop signal task in two studies (Ramaekers et al. 2009; Theunissen et al. 2011), but THC administration, 3 h after placebo alcohol administration, did not have an effect on inhibition or motor impulsivity in heavy cannabis users on the same task in another study (Ramaekers et al. 2011). Given the motor components inherent in the aforementioned tasks, it is worth considering that some studies find THC to impair psychomotor performance (D'Souza et al. 2008a; Hunault et al. 2009; Ramaekers et al. 2009), but several others do not (Dumont et al. 2011; O'Leary et al. 2007; Ramaekers et al. 2011). Interestingly, Ramaekers and colleagues (2009) found THC administration impaired psychomotor control in occasional cannabis users, but not in heavy cannabis users, suggesting a potential tolerance effect. Hunault and colleagues (2009) found THC to significantly decrease response time and increase errors in a dose-dependent manner in heavy cannabis users on a motor control task.

Recent Innovations in Acute Administration Studies: The Role of Cannabidiol

It is important to consider that the *Cannabis sativa* plant contains hundreds of known compounds and at least 70 cannabinoids (Elsohly and Slade 2005), but only THC has been extensively studied. Yet cannabidiol (CBD), another major cannabinoid found in cannabis, has opposing effects on CB1 and CB2 receptors compared to THC, mediates the effects of THC (Pertwee 2008), and has neuroprotective properties (Hampson et al. 1998; Lastres-Becker et al. 2005; Mechoulam et al. 2002, 2007). Ratios of THC to CBD in street cannabis can vary considerably (Burgdorf et

al. 2011), which may have implications for neurocognitive sequelae from use; however, only recently have the combined effects of THC and CBD administration been studied.

To better understand the potential differential impact of THC and CBD on neurocognition, Borgwardt and colleagues (2008) administered 10 mg THC, 600 mg CBD, or placebo capsules to 15 men with minimal cannabis exposure (<15 times in life) on three separate occasions in a double-blind, within-subject design. In this study, and across several other investigations using the same sample, participants' performance was unaffected by THC or CBD on measures of inhibition, verbal memory, accuracy of gender discrimination, and visual and auditory processing (Bhattacharyya et al. 2009, 2010; Borgwardt et al. 2008; Fusar-Poli et al. 2009; Winton-Brown et al. 2011). In contrast, Roser and colleagues (2009) found combined THC and CBD, but not THC alone, impaired psychomotor control in 24 occasional cannabis users who were administered a combination of 10 mg THC and 5.4 mg CBD, 10 mg THC alone, or a placebo pill on three separate visits in a double-blind, cross-over design. Recently, Morgan and colleagues (2010) found 22 cannabis users with low cumulative levels of CBD (as evidenced from hair analysis) demonstrated poorer performance on immediate and delayed episodic memory (but not verbal and category fluency) compared to 22 users with higher cumulative CBD exposure when both groups were intoxicated. The same group showed that daily cannabis users who had higher cumulative THC exposure demonstrated poorer performance on measures of immediate and delayed episodic memory, as well as source memory, compared to daily cannabis users with lower cumulative THC exposure when participants were intoxicated (Morgan et al. 2012). However, there were no differences in episodic memory and source memory performance between the 54 occasional cannabis users regardless of the cumulative THC exposure. On the other hand, both daily and occasional cannabis users with CBD present in hair analysis displayed better recognition memory than users without CBD present when all individuals were intoxicated (Morgan et al. 2012).

Recent neuroimaging studies suggest differential neurophysiological effects of THC and CBD. A number of functional neuroimaging studies demonstrated that THC and CBD can exert opposite actions on the neurofunctional correlates of cognitive and emotional processes in humans (Bhattacharyya et al. 2009, 2010, 2012; Borgwardt et al. 2008; Fusar-Poli et al. 2010a, 2009). Specifically, although no neurocognitive differences were found, THC and CBD had opposite effects of brain activation patterns in the striatum during verbal recall, in the hippocampus during inhibition, in the superior temporal cortex during auditory processing, in the occipital cortex during visual processing, and in the amygdala while subjects viewed fearful faces when compared to placebo (Bhattacharyya et al. 2010). These complex effects of cannabinoids on underlying neural networks may help to explain some of aforementioned mixed findings in the field and warrant further investigation.

Summary of Recent Advances on the Acute Effects of Cannabis

In summary, the recent literature suggests acute THC administration impairs specific aspects of learning and memory, in line with the previous literature, as well as attention, concentration, and working memory. A notable contribution to the literature during the past 5 years has been examining how acute cannabis intoxication affects neuropsychological measures of abstract reasoning, decision-making, risk-taking, inhibition, motor impulsivity, and psychomotor control. Studies indicate abstract reasoning may be impaired after acute THC administration, while decision-making and risk-taking largely remain intact, despite some evidence for THC potentially slowing decision-making. However, future research in this area may benefit from more detailed analyses on the various components of decision-making and risk-taking (Busemeyer and Stout 2002) and examining different types of risk (i.e., ambiguous versus explicit risk; Weller et al. 2010) in affecting performance. The mixed findings for measures of inhibition, motor impulsivity, and psychomotor control, suggest more work is needed to understand the role of motor slowing and dose–response effects. Moreover, findings of differential performance following THC administration in heavy cannabis users, occasional cannabis users, and healthy controls, as well as the potential role of different types of cannabinoids present in cannabis, highlight the importance considering these issues in future research. Finally, examining neurocognitive effects of other naturally-occurring cannabinoids in combination with THC is a promising line of research. The literature on acute administration (although nascent) suggests little behavioral differences from THC alone compared to THC/CBD combinations. Conversely, associations between higher cumulative CBD exposure and better neuropsychological functioning indicate CBD may buffer against the negative effect of THC, but these neurocognitive differences may only emerge after prolonged administration.

Non-Acute Effects of Cannabis on Neurocognitive Functioning

Studies on the non-acute effects of cannabis focus on the period after the intoxicating effects of cannabis have subsided. As such, they often examine participants from after about 8 h to a month since their last cannabis use. These studies are best apt to inform the chronicity of cannabis-

associated neuropsychological deficits that may linger after acute intoxication has ceased. As with acute-administration studies, various review articles have broached this topic over the years. Some suggest residual effects (i.e., after several hours to several days of abstinence) and long-term effects (i.e., after several weeks of abstinence and beyond), while others find no clear evidence for residual or long-term neuropsychological deficits among cannabis users across several domains (Crean et al. 2011; Gonzalez et al. 2002; Gonzalez 2007; Grant et al. 2003; Pope et al. 1995; Schweinsburg et al. 2008; Solowij and Battisti 2008; Solowij and Pesa 2010; Wert and Raulin 1986). As found in the acute intoxication studies, the evidence is mixed for most domains other than episodic memory, which remains adversely impacted for up to 28 days following abstinence (Gonzalez 2007; Grant et al. 2003; Solowij and Battisti 2008). Novel contributions from recent studies include increased attention to adolescent samples and assessing measures of decision-making, risk-taking, and other aspects of impulsive behavior.

Non-Acute Effects of Cannabis: Update from Research Published in the Past 5 Years

Learning and Memory

As found in previous reviews, aspects of memory are often impaired among recently abstinent cannabis users, particularly verbal episodic memory. Regular adolescent cannabis users who have been abstinent between 12 h and 21 days demonstrate poorer immediate (Hanson et al. 2010; Harvey et al. 2007; Solowij et al. 2011) and delayed recall (Harvey et al. 2007; Solowij et al. 2011), as well as impaired recognition (Solowij et al. 2011). However, one of these studies found no difference in recognition between regular and occasional cannabis users (Harvey et al. 2007). After longer periods of abstinence (28 days), Tapert and colleagues (2007) found adolescent cannabis users made more recall intrusions than controls, while other studies found no differences between groups on any measure of episodic memory (Jacobsen et al. 2007; Mahmood et al. 2010; Medina et al. 2007a). Recently abstinent adult cannabis users also demonstrate poorer immediate (Battisti et al. 2010b; Gonzalez et al. 2012b; Hadjiefthyvoulou et al. 2011; Korver et al. 2010; Nestor et al. 2008; Wagner et al. 2010; Yucel et al. 2008) and delayed recall (Gonzalez et al. 2012b; Wadsworth et al. 2006; Yucel et al. 2008), but have intact recognition (Gonzalez et al. 2012b; Nestor et al. 2008; Wadsworth et al. 2006). Although this is not invariably the case, as some studies report intact immediate (Chang et al. 2006; Gruber et al. 2012a; Wadsworth et al. 2006) and delayed recall (Chang et al. 2006; Gruber et al. 2012a) among cannabis users. Other evidence suggests that recall performance is negatively associated with amount of past year (Jager et al. 2007) and lifetime cannabis use (Indlekofer et al. 2009; Jager et al. 2007; Murphy et al. 2011; Solowij et al. 2011), duration of cannabis use (Solowij et al. 2011; Wadsworth et al. 2006), frequency of cannabis use, and age of first cannabis use (Solowij et al. 2011). In a longitudinal study of young adults, trajectories of performance on measures of episodic memory in non-users, former users, and current users were different, such that non-users and former users immediate and delayed recall improved over a period of 8 years, while performance on these measures worsened over time in light and heavy current users (Tait et al. 2011).

Deficits in other aspects of learning and memory among cannabis users not acutely intoxicated are less commonly reported than those for verbal episodic memory. Adolescent cannabis users who were abstinent between 12 to 24 h demonstrated intact associative learning (Harvey et al. 2007; Jager et al. 2010). After longer periods of abstinence (28 days), adolescent cannabis users exhibited deficits on a story memory task (Medina et al. 2007a), but had intact visuospatial memory (Mahmood et al. 2010; Medina et al. 2007a; Schweinsburg et al. 2010). In recently abstinent adult cannabis users, some studies report visuospatial memory deficits (Hermann et al. 2007; McHale and Hunt 2008), but others do not (Chang et al. 2006; Gruber et al. 2012a). Amount of lifetime cannabis use did not predict visuospatial memory in a community sample of recently abstinent polydrug users (Indlekofer et al. 2009). Recently abstinent adult cannabis users have demonstrated intact associative learning (Fisk and Montgomery 2008) and semantic memory (Wadsworth et al. 2006). Evidence for prospective memory deficits is split with one study reporting deficits (Montgomery et al. 2012) and another no deficits (Hadjiefthyvoulou et al. 2011).

Attention and Concentration

Attention and concentration continue to be well-studied among adolescent and adult samples. Several studies cite impairments in attention and concentration in recently abstinent adolescent cannabis users (Abdullaev et al. 2010; Hanson et al. 2010; Harvey et al. 2007; Lane et al. 2007). After at least 21 days of abstinence, complex attention continues to be impaired in adolescent cannabis users (Hanson et al. 2010; Jacobsen et al. 2004; Medina et al. 2007a; Tapert et al. 2007), with evidence of a dose-dependent relationship with amount of lifetime use (Medina et al. 2007a). Conversely, others reported that after 45 days of abstinence, selective and divided attention was intact in adolescent cannabis users (Jacobsen et al. 2004). Recently abstinent adult cannabis users also demonstrated impairments in attention and concentration in several studies (Hermann et al. 2007; Indlekofer et al. 2009; Scholes and

Martin-Iverson 2009; Scholes-Balog and Martin-Iverson 2011; Wadsworth et al. 2006), which persisted for several hours to 1 week of abstinence. However, a few studies report no impairments among adult cannabis users when the time of last cannabis use was either unknown (Grant et al. 2011; Korver et al. 2010) or after at least 4 h to approximately 38 months of abstinence (Chang et al. 2006).

Working Memory

In studies examining working memory, the evidence for cannabis-associated deficits is mixed. Adolescent regular cannabis users who are abstinent demonstrated poorer working memory compared to controls after 3 and 13 days, during a challenging task that required active manipulation of items (Hanson et al. 2010), but not after 8 days, during a more simple matching task (Jager et al. 2010). Thus, it is possible that impairments in working memory are only detected among adolescent cannabis users with more complex tasks that place a greater load on working memory systems, as seen in Jacobsen et al. (2007). On the other hand, working memory deficits may be related to amount of cannabis use, as Harvey and colleagues (2007) found regular adolescent cannabis users performed more poorly on spatial working memory than occasional cannabis users and amount of cannabis use was one of the strongest predictors of poorer spatial working memory. The evidence is also mixed regarding the persistence of working memory deficits among adolescents after abstinence, with some studies reporting deficits after 28 days (Jacobsen et al. 2004, 2007), whereas others do not (Hanson et al. 2010; Padula et al. 2007; Schweinsburg et al. 2008, 2010). In contrast to studies with adolescent samples, most studies report intact working memory among recently abstinent adult cannabis users (Becker et al. 2010; Chang et al. 2006; Fisk and Montgomery 2008; Grant et al. 2011; Gruber et al. 2012a; Jager et al. 2006; Looby and Earleywine 2010; Piechatzek et al. 2009; Scholes and Martin-Iverson 2010). Additionally, in a longitudinal study, working memory performance remained intact among recently abstinent current cannabis users, former cannabis users, and controls over a period of 8 years (Tait et al. 2011). On the other hand, frequency of cannabis use was negatively correlated with working memory performance among abstinent cannabis users (Wadsworth et al. 2006) and among polysubstance users (Fernandez-Serrano et al. 2010).

Verbal Fluency

Evidence for deficits in verbal fluency among abstinent cannabis users is also mixed. Only one recent study examined verbal fluency in a sample of adolescent cannabis users and found it to be impaired after 28 days of abstinence (Tapert et al. 2007). Studies of recently abstinent adult cannabis users report deficits in verbal fluency after 8–24 h since last use (Korver et al. 2010; Mason et al. 2012; McHale and Hunt 2008) and after 15 days of abstinence (Fernandez-Serrano et al. 2010). However, others report intact verbal fluency after a few hours to a week since last cannabis use (Chang et al. 2006; Fisk and Montgomery 2008; Gruber et al. 2012a; Piechatzek et al. 2009). Of note, recently abstinent adult cannabis users have also been reported to demonstrate deficits in text comprehension (Huestegge et al. 2010).

Abstract Reasoning

Poorer cognitive flexibility has been reported among adolescent cannabis users abstinent for approximately 8 h compared to controls (Lane et al. 2007), but not between recently abstinent occasional and regular adolescent cannabis users (Harvey et al. 2007). After at least 23 days of abstinence, adolescent cannabis users appear to evidence intact cognitive flexibility (Medina et al. 2007a). As with adolescent cannabis users, abstinent adult cannabis users also demonstrated impairments in cognitive flexibility (Fontes et al. 2011a, b; Grant et al. 2011; Mason et al. 2012). Similarly, planning and reasoning were poorer among adult cannabis users who were abstinent for at least 5 days compared to controls (Montgomery et al. 2012). Furthermore, amount of lifetime cannabis use predicted worse performance on a reasoning task for adult polysubstance users who were abstinent for at least 15 days (Fernandez-Serrano et al. 2010).

Decision-Making and Risk-Taking

Compared to findings from acute investigations, recently abstinent adult cannabis users show more consistent deficits in decision-making and risk-taking (Grant et al. 2011; Vaidya et al. 2012; Wesley et al. 2011), even after 15 days of abstinence (Fernandez-Serrano et al. 2010). Fridberg and colleagues (2010) also reported impairments in decision-making among cannabis users, and through using computational modeling they found these impairments were likely due to cannabis users' decreased sensitivity to losses and increased sensitivity to immediate gains. However, others have not observed such deficits (Boggio et al. 2010; Hermann et al. 2009; Martin-Soelch et al. 2009). In our own studies, cannabis users and non-users, who were matched on various potential comorbidities, performed equivalently on measures of decision-making and risk-taking (Gonzalez et al. 2012b). However, we found that decision-making performance (but not performance on measures of episodic memory or other measures associated with impulsive behavior) is related to more DSM-IV

cannabis use dependence symptoms among cannabis users (Gonzalez et al. 2012b). Similarly, we found that amount of cannabis use is related to more problems experienced from cannabis use among individuals with poor decision-making performance, but not among those with intact decision-making (Gonzalez et al. 2012a). Further, poorer decision-making and more risk-taking among cannabis users predicted more risky sexual behaviors in our sample (Schuster et al. 2012). Thus, despite a lack of differences between cannabis users and non-users on measures of decision-making and risk-taking in our sample, performance on some neurocognitive measures influenced important functional outcomes.

Inhibitory Control, Motor Impulsivity, and Psychomotor Control

The evidence seems to be mixed as to whether deficits in inhibition, motor impulsivity, or psychomotor control are evident in abstinent cannabis users. Among recently abstinent adolescent cannabis users, regular and non-regular users showed no difference in inhibition or psychomotor control (Harvey et al. 2007). After 28 days of abstinence, adolescent cannabis users demonstrated intact inhibition and motor impulsivity (Tapert et al. 2007). Yet, after at least 23 days of abstinence, adolescent cannabis users had impairments in psychomotor performance compared to controls, and there was a negative, dose-dependent association between performance and lifetime cannabis use episodes (Medina et al. 2007a). In recently abstinent adult cannabis users, some studies report impairments in inhibition and motor impulsivity (Battisti et al. 2010a; Clark et al. 2009; Cunha et al. 2010; Fontes et al. 2011a, b; Scholes and Martin-Iverson 2010), with some evidence for a dose-dependent relationship between amount of past 30 days use and performance (Cunha et al. 2010; Piechatzek et al. 2009). However, many other studies report no differences in performance between recently abstinent adult cannabis users and controls (Aharonovich et al. 2008; Becker et al. 2010; Cane et al. 2009; Chang et al. 2006; Fernandez-Serrano et al. 2010; Fontes et al. 2011b; Gonzalez et al. 2012b; Grant et al. 2011; Gruber et al. 2012a; Hermann et al. 2007; Hester et al. 2009; Roberts and Garavan 2010; Scholes and Martin-Iverson 2010). Interestingly, Mason and colleagues (2012) found recently abstinent adult cannabis users were able to successfully inhibit prepotent responses on a simple task of inhibition, but their performance became significantly more impaired compared to normative data as the task became more complex. Performance on measures of psychomotor control are also mixed, with one investigation finding deficits in psychomotor control across several measures among adult cannabis users abstinent for 12 h (King et al. 2011), but others suggesting intact psychomotor control in recently abstinent cannabis users (Chang et al. 2006; Korver et al. 2010; Wadsworth et al. 2006) and after 28 days of abstinence (Pillay et al. 2008). Relatedly, Gonzalez and colleagues (2011) found poorer complex psychomotor performance (but no procedural learning deficits) among polydrug-using individuals with a history of cannabis dependence compared to those without a history of cannabis dependence and this deficit was exacerbated in the context of HIV.

Summary of Recent Advances on Non-Acute Effects of Cannabis

In conclusion, recent studies of episodic memory continue to suggest non-acute impairments among cannabis users both with adult and adolescent samples. On the other hand, the results for deficits in other types of memory seem to be more nuanced when considering length of abstinence, age at which cannabis users discontinue their use, amount and duration of cannabis use, whether prospective study designs were used, and whether samples consisted of adolescents or adults, as emerging evidence suggests memory deficits among younger samples may be more pronounced than what has been previously observed in adults (Pope et al. 2003; Solowij et al. 2011). Attention and concentration seem to be consistently impaired among adolescent and adult cannabis users, while evidence is mixed regarding the enduring effects of cannabis use on working memory and verbal fluency. Abstract reasoning seems to be impaired after short periods of abstinence, but these deficits may resolve after longer periods of abstinence, at least in adolescent users. Similarly, findings suggest abstinent cannabis users often demonstrate poorer decision-making and risk-taking, which have been reported alongside functional brain alterations, especially in the orbitofrontal cortex, and may persist even after 28 days of abstinence in heavy cannabis users (Bolla et al. 2005). Further, although there are equivocal findings in working memory, inhibitory control, motor impulsivity, and psychomotor control, preliminary evidence suggests cognitive load may be an important factor to consider in understanding cannabis' effect on some of these domains. It is also important to consider that the same neurocognitive domain may be assessed with different tasks that may also vary in complexity and sensitivity. Less complex tasks may be less sensitive to more subtle brain abnormalities among cannabis users, but as the difficulty of the task increases, impairments in performance may emerge, as observed with some measures of inhibition (Mason et al. 2012) and working memory (Jacobsen et al. 2007). Moreover, as mentioned previously, some evidence suggests THC and CBD may exert opposing effects on neurocognition after prolonged exposure; however, to our knowledge this has not been examined in studies of non-acute use.

Thus, it is possible that regional and individual differences in the THC/CBD ratios of the cannabis consumed by cannabis users may also contribute to discrepant findings. There are many other factors that may contribute to the disparate findings and identifying these sources of variability is crucial in helping us to understand the non-acute effects of cannabis on cognition. One factor not discussed in this review, but that deserves mention, includes interactions of cannabis with other substances. Some evidence suggests differential neurocognitive effects of cannabis that depend on whether the individual also uses other substances. For example, there is some evidence indicating cannabis may exert neuroprotective effects among heavy alcohol using adolescents (Jacobus et al. 2009; Mahmood et al. 2010; Medina et al. 2007b; Schweinsburg et al. 2011), alcohol-dependent adults (Nixon et al. 1998), and methamphetamine-dependent adults (Gonzalez et al. 2004). On the other hand, nicotine may mask cannabis-related neurocognitive impairments, and these deficits may only be evident during abstinence from nicotine (Jacobsen et al. 2007). Given that cannabis users often use other substances as well, this is an important factor that needs further examination, especially considering the overlap in the neurocognitive domains affected by cannabis and other drugs of abuse. These domains include learning and memory, attention and concentration, working memory, abstract reasoning, decision-making and risk-taking, inhibitory control, and psychomotor control; however, the presence and magnitude of such deficits may vary by substance. For example, Gonzalez et al. (2007) reported deficits in decision-making both among abstinent individuals with recent history of alcohol dependence and among those with recent methamphetamine dependence; however, only those with methamphetamine dependence also demonstrated deficits in working memory. Comparisons of the neurocognitive impact of various substances of abuse have been reviewed by others (Bava and Tapert 2010; Fernandez-Serrano et al. 2011; Gonzalez et al. 2009).

Neurodevelopment and Sex Differences as Emerging Influential Factors

It is evident that disparate findings are common across studies examining acute and non-acute effects of cannabis on neurocognition. Heterogeneity in methods, participant samples, dosing, and cannabis use history are all likely contributors. However, in recent years there has been a more systematic search for potential neurobiological factors that may influence the impact of cannabis use on neurocognition. Two areas receiving substantial attention include neurodevelopmental factors and the potential for cannabis to affect males and females differently (i.e., sex differences). Although many of the issues discussed below have received more attention recently, unlike the previously cited studies, our review on these factors was not limited to the last 5 years.

Cannabis Use and Neurodevelopmental Processes

Initiation of cannabis use often occurs during adolescence, an important period for neurodevelopment; thus, it is important to consider this time when examining the impact of cannabis use on neurocognitive functioning. Although 90 % of the brain's total volume has developed by approximately age 6 (Giedd 2004), global cortical development follows an inverted U-shaped trajectory, peaking around 12 to 14 years of age then decreasing in volume and thickness over adolescence (Giedd et al. 1999; Gogtay et al. 2004). This synaptic pruning of gray-matter density occurs first in more primary sensorimotor areas and last in higher-order association areas like the prefrontal cortex (Giedd 2004; Gogtay et al. 2004). In contrast, white matter density increases during adolescence and into adulthood, reflecting significant increases in projectional, associational, and commissural myelination (Durston et al. 2001; Giedd 2004). Given the extensive and complex development going on at this time, it is conceivable that the brain may be more vulnerable to insults and disturbances from exogenous compounds that may alter normal brain functioning. Moreover, the endocannabinoid system plays an important role in neuromaturation and synaptic pruning (Viveros et al. 2012). Thus, it is possible that use of cannabis during this time period may be disruptive to normal neuromaturation (Bava and Tapert 2010). Further, cannabis use during this neurodevelopmental period may trigger a psychotic disorder in individuals vulnerable for psychosis (Fusar-Poli et al. 2012a, in press). The neural networks showing functional (Fusar-Poli et al. 2010b, 2011b, d), structural (Fusar-Poli et al. 2011a, c) and neurochemical alterations (Fusar-Poli and Meyer-Lindenberg 2012a, b) during the pre-psychotic phases are similar to those affected by cannabinoids, supporting the neurodevelopmental hypothesis of psychosis.

To better understand how cannabis use may interfere with neurodevelopmental processes, animal studies have compared how administration of botanical or synthetic cannabinoids during different developmental time periods affect neurocognitive processes in adolescent and adult rats. Many of these studies have focused on working memory. For example, rats exposed to synthetic cannabinoids or THC during adolescence experience impaired working memory during adulthood (O'Shea et al. 2004, 2006; Rubino et al. 2009a, b). These impairments have been correlated with less active synapses in the prefrontal cortex (Rubino et al. 2009a), as well as shorter dendrites and reduced spine densities in the hippocampus, suggesting enduring neurobiological consequences of early cannabis exposure (Rubino

et al. 2009b). The heightened vulnerability of younger brains is highlighted by the fact that the same amount of THC exposure that led to decreased working memory performance in adolescent rats had no effect in adult rats (Quinn et al. 2008). However, some have suggested that heavy THC administration during adolescence may be needed to produce significant and persistent impairments in working memory (Realini et al. 2009). With regards to learning, impairments with synthetic cannabinoid administration during late adolescence were reported, but these resolved after a prolonged period of abstinence (Abush and Akirav 2012). Conversely, rats exposed to chronic doses of THC during adolescence, but not during late adolescence, evidenced deficits in learning during adulthood (Harte and Dow-Edwards 2010). There may be a critical time during adolescence when cannabis use may have the most negative effects. When taken together, these studies suggest that cannabis use during adolescence may have a more significant and lasting impact on neurocognition than if cannabis use is initiated during adulthood.

In line with the animal literature, accumulating evidence from studies with human subjects suggests initiation of cannabis use during early adolescence may be more detrimental to some aspects of neurocognition compared to later initiated use. Indeed, earlier age of cannabis use onset is negatively associated with neurocognitive functioning in several studies (see Table 1). For example, those who initiate use before 15 to 17 years of age demonstrate more pronounced deficits in visual attention (Ehrenreich et al. 1999), verbal fluency (Gruber et al. 2012a; Pope et al. 2003), inhibition (Fontes et al. 2011a; Gruber et al. 2012a; Pope et al. 2003), and other aspects of executive functioning (Fontes et al. 2011a) as compared to those who initiate use later on. Further, episodic memory was poorer in those with an earlier onset of cannabis use in two studies (Pope et al. 2003; Solowij et al. 2011); however, another study failed to find this effect (Gruber et al. 2012a). Poorer performance on measures of inhibition (Battisti et al. 2010a; Gruber et al. 2012a) and impulsivity (Solowij et al. 2012) have also been associated with earlier age of onset. Moreover, Gruber and colleagues (2012b) reported that early-onset users made more errors and showed greater disruptions in brain activation patterns than late-onset users during an inhibition task. On the other hand, others have reported no differences between early and late-onset cannabis users (and healthy controls) on measures of working memory and attention (Ehrenreich et al. 1999; Gruber et al. 2012a; Pope et al. 2003), as well as on a task of visuospatial memory (Gruber et al. 2012a). The current evidence suggests that earlier onset of cannabis use is associated with poorer neurocognitive outcomes, but more research is needed to better determine how additional parameters of cannabis use (e.g., age of daily use, age of meeting cannabis use disorder), other

Table 1 Studies examining age of onset of cannabis use and neurocognitive functioning

Study	Age	Age of Onset		Healthy Controls	Length of Abstinence	Neurocognitive Domains Poorer in Early-Onset Cannabis Users	Neurocognitive Domains Intact in Early-Onset Cannabis Users
	M (SD)	*Early (n)*	*Late (n)*	*n*	*minimum*		
Battisti et al. 2010a	36.10 (11.11)	*Mean age*=15.0 (25)		19	12 h	Earlier onset associated with worse inhibition	–
Ehrenreich et al. 1999	23.25 *(unk)*	<16 (48)	≥16 (51)	49	2 h	Visual attention	Divided attention, flexibility in attention, working memory
Fontes et al. 2011a	30.21 *(unk)*	<15 (49)	≥15 (55)	44	Unknown	Executive functioning, inhibition	None
Gruber et al. 2012a	22.80 (6.57)	<16 (19)	≥16 (15)	28	12 h	Verbal fluency, inhibition	Attention, working memory, visuospatial & episodic memory
Gruber et al. 2012b	22.75 (2.82)	<16 (9)	≥16 (14)	16	12 h	None	Inhibition *(compared to the late-onset users)*
Pope et al. 2003	39.48 *(unk)*	<17 (69)	≥17 (53)	87	28 days	Verbal fluency, inhibition, episodic & visuospatial memory	Attention, working memory
Solowij et al. 2011	18.30 (0.63)	*Mean age*=16.5 (52)		62	12 h	Earlier onset associated with worse impulsivity	–
Solowij et al. 2012	18.30 (0.63)	*Mean age*=16.0 (48)		62	12 h	Earlier onset associated with worse episodic memory	–

All values are means and standard deviations unless otherwise noted

unk unknown, – no other domains evaluated

substance use, periods of rapid neurodevelopment, and sex (as discussed below) influence findings.

Sex Differences in Cannabis' Influence on Neurobehavioral Functioning

Neurodevelopmental Considerations

Accumulating evidence indicates sex-specific effects of cannabinoids. Neurodevelopmental trajectories vary by sex, such that female brains appear to undergo earlier maturation than male brains. Females' total brain size peaks between 10 and 11 years of age, while males' total brain size peaks at about 14 to 15 years of age (Lenroot et al. 2007). Similarly, females' prefrontal cortex gray matter volume peaks 1 to 2 years earlier than in males (Giedd et al. 1999). Therefore, if cannabis use is initiated in early to mid-adolescence, it is possible that males may be more vulnerable to neurobehavioral disturbances, especially functional and/or structural disruptions in the prefrontal cortex, compared to females.

In addition to differential rates of neuromaturation, CB1 density may also vary by sex, with animal studies citing greater CB1 receptor density among males across several brain regions (Burston et al. 2010; Mateos et al. 2011; Reich et al. 2009; Rubino et al. 2008). Whereas males either maintain or lose some CB1 binding sites in later adulthood (i.e., 45 to 70 years of age), adult female brains show increases in CB1 receptor density across the lifespan, eventually surpassing that of males (Van Laere et al. 2008). Furthermore, adolescent females evidence greater CB1 desensitization after exposure to THC in the prefrontal cortex, hippocampus, striatum, amygdala, and midbrain (Burston et al. 2010; Rubino et al. 2008). Given that endocannabinoid signaling plays a crucial role in establishing normal sex differences in the brain (Viveros et al. 2012), it is not surprising that disruption of this system may produce sex-specific differences in neurocognitive outcomes.

The interaction between sex and age of cannabis use onset has been examined in several animal studies, with somewhat mixed results, but generally suggesting the importance of considering these factors together in determining neurocognitive outcomes. Acute THC administration disrupted learning in adolescent female, adolescent male, and adult female rats, but did not disrupt learning in adult male rats (Cha et al. 2007). Chronic doses of THC administration did not affect learning in either adolescent or adult male and female rats (Cha et al. 2007), but others found that male rats evidenced worse novel object recognition than female rats (Mateos et al. 2011). In contrast, female rats administered chronic THC during adolescence perform worse on an object location task than female controls, while no differences emerged among male rats (Mateos et al. 2011). Although both male and female rats demonstrated deficits in spatial working memory after exposure to THC in adolescence (O'Shea et al. 2004, 2006; Rubino et al. 2009a, b), this exposure in adulthood had long-term impairments on memory in male rats, but not in female rats (O'Shea et al. 2004, 2006). Thus, cannabis use during adolescence may produce sex-specific alterations in neurodevelopment that may lead to enduring cognitive impairments.

Sex Hormones and Cannabinoids

Many recent studies have focused on the endocannabinoid system's bi-directional interactions with gonadal hormones (Lopez 2010). Cannabinoids affect the endocrine system, specifically the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes (which interact in their functioning), while gonadal hormones also modulate endocannabinoid activity and function (Lopez 2010). More specifically, evidence from animal studies suggest exogenous cannabinoids, like THC, have the ability to significantly alter pituitary function (Murphy et al. 1991a, b; Wenger et al. 1999) and may inhibit the HPG axis (Murphy et al. 1990, 1994, 1999; Steger et al. 1980; Steger et al. 1983), thereby dysregulating key motivational systems involved in drug-seeking behavior. Additionally, the endocannabinoid system plays an important role in regulating the neuroendocrine and behavioral response to stress, and evidence supports an association between disrupted endocannabinoid signaling and a blunted stress response (Gorzalka et al. 2008). However, hormones significantly influence the impact of cannabinoids on the HPG axis, as estrogen reduces the inhibitory effect of cannabinoids on HPG function (Scorticati et al. 2003, 2004). Furthermore, hormones play a key role in structural and functional changes in the endocannabinoid system, evidenced by fluctuations in endocannabinoid receptor (especially CB1) density across the estrus cycle (Bradshaw et al. 2006; Gonzalez et al. 2000; Rodriguez de Fonseca et al. 1994). Moreover, human studies have demonstrated that, during the follicular phase of the menstrual cycle (when estradiol is high and progesterone is low), females are more responsive to the effects of stimulants, such as cocaine (Sofuoglu et al. 1999) and nicotine (Newman and Mello 2009; Perkins et al. 2000); however, this relationship has not yet been explored with cannabis. It is presently unclear how these factors may differentially affect the neuropsychological functioning of male and female cannabis users; however, the potential detrimental downstream effects of cannabinoids on the HPA and HPG axes and how these alterations may differentially affect neuropsychological functioning in males and females warrant further investigation.

Behavioral, Tolerance, and Metabolic Considerations

Factors outside of the central nervous system may also play an important role in how cannabis use differently affects

neurocognition in males and females. Males are more likely to use cannabis than females (rates in 2010 were 11.2 % vs. 6.8 %, respectively; SAMSHA 2011) and initiate use at an earlier age (Gfroerer and Epstein 1999; Pope et al. 2003). However, similar to patterns observed in alcohol dependence, a telescoping effect (i.e., accelerated progression of a substance-use disorder) seems to occur. In this sense, females enter treatment for marijuana use disorders significantly sooner (i.e., after fewer years of use) and after less cumulative cannabis use compared to males (Hernandez-Avila et al. 2004). This may be due to various differences in the pharmacologic effects of THC in males and females. Preclinical studies have demonstrated that female rats preferentially metabolize THC to its most highly active metabolite, while male rats metabolize THC to multiple compounds (Narimatsu et al. 1991). Moreover, physiological data shows that when smoking a second cigarette, females have less tachycardia than males (Cocchetto et al. 1981), suggesting females may develop tolerance to cannabis more quickly than males, perhaps accelerating their escalation of use. Furthermore, some evidence indicates that females may feel greater hedonic reinforcement from cannabis compared to males, and that ovarian hormones (such as estrogen and progesterone) may facilitate stronger learned associations between drug effects and drug-related stimuli (Fattore et al. 2007). Taken together, these data suggest the potential for different behavioral, tolerance, and metabolic effects that influence patterns of use and abuse between males and females. Such differences may also indirectly influence the impact of cannabis use on the neurocognitive functioning of males and females. For example, it is possible that females may be more vulnerable to the negative effects of cannabis on frontal-limbic neurocircuitry, thus leading to an accelerated progression of cannabis use disorders. However, it remains unclear how factors like age of initiated use and amount of cannabis use may contribute to sex-specific neurocognitive outcomes among cannabis users.

Neurocognitive Sex Differences in Cannabis Users

When considering sex differences in cannabis' effects on neurocognition, it is first important to account for the sex differences in neurocognitive performance often reported among healthy human subjects. Males often perform better than females on measures of decision-making (Bolla et al. 2004; Overman et al. 2004; Reavis and Overman 2001), spatial processing, and psychomotor performance (Gur et al. 2012); whereas females perform better on measures of verbal memory (Kramer et al. 1988), visual recognition, attention, and reasoning abilities (Gur et al. 2012). In light of this and the aforementioned sex differences in neurodevelopment, endocannabinoid distribution and functioning, metabolism of THC, tolerance to THC, patterns of cannabis use, and cannabis' effects on hormonal systems, it seems reasonable to expect differences in how cannabis use may influence neuropsychological functioning in males and females. Nonetheless, this has been examined by only a few studies (see Table 2), but has promise to be a more significant component of the literature in coming years.

In one of the first studies to examine sex differences after THC administration, McDonald and colleagues (2003) found no differences in the effects of THC (0 mg, 7.5 mg, or 15 mg capsules) on measures of impulsivity between 18 male and 19 female recreational cannabis users. Similarly, 35 male and 35 female cannabis users did not demonstrate differential effects of smoked THC (joints with either 0 % THC or 2.9 % THC) in performance on measures of visuospatial processing, time estimation, and cognitive flexibility (Anderson et al. 2010). However, it is important to note that despite no differences found in subjective "high" scores in the aforementioned study, females discontinued smoking before males, but performed similarly. Rogers and colleagues (2007) found no sex differences in risk-taking performance between 7 male and 8 female cannabis users after administration of either 0 mg or 5 mg THC. Surprisingly, spatial working memory was enhanced in females (n=7), but not in males (n=12) after 0 mg or 8.5 mg of sublingual THC (Makela et al. 2006). Additionally, in all five sessions of a finger tapping task, males (n=12) had faster left-hand tapping than females (n=12) after 10 mg THC administration and for two sessions after THC and CBD combined administration (10 mg THC and 5.4 mg CBD), despite no differences in baseline performance (Roser et al. 2009). In summary, preliminary evidence suggests there may be little or no sex-specific effects of acute THC administration on neurocognition; however, studies are few and have relied on very small sample sizes.

In the few studies examining potential sex differences in the non-acute effects of cannabis on neuropsychological functioning, consistent evidence for sex-specific relationships are emerging. One of the first studies on this topic found that females who used cannabis heavily (i.e., median frequency of use was 29 out of the past 30 days) performed worse than light users (i.e., median frequency of use was 1 out of the past 30 days) on a visuospatial task—no differences were found between heavy and light male cannabis users, nor were any sex differences found on tasks of attention and inhibition

Table 2 Studies examining sex differences in cannabis users on neurocognitive functioning

Study	Age *M (SD)*	Female Users *n*	Female Controls *n*	Male Users *n*	Male Controls *n*	Length of Abstinence *minimum*	Findings Pertaining to Sex Differences
Acute Neurocognitive Studies							
Anderson et al. 2010	20.50 (2.70)	35	–	35	–	After smoking THC (2.9 %)	No difference on visuospatial processing, time estimation, and cognitive flexibility
Makela et al. 2006	21.80 (0.93)	–	7	–	12	After ingesting 8.5 mg THC	Spatial working memory was enhanced in females, but not males
McDonald et al. 2003	23.00 (4.48)	19	–	18	–	After ingesting 7.5 or 15 mg THC	No difference on impulsivity
Roser et al. 2009	27.90 (2.90)	–	12	–	12	After ingesting 10 mg THC or THC w/5.4 mg CBD	Males had faster left-hand tapping than females in both conditions
Non-Acute Neurocognitive Studies							
Clark et al. 2009	23.25 (*unk*)	10	7	5	12	Unk	Male users psychomotor performance < male controls; no difference among females
King et al. 2011	22.70 (*unk*)	14	14	16	16	12 h	Male users psychomotor performance and visuospatial organization < male controls; no difference among females
Pope et al. 1997	Unk	24	–	31	–	19 h	Heavy female visuospatial performance < light female; no difference among the males; or in attention & inhibition
Solowij et al. 2011	18.30 (0.63)	21	44	31	18	12 h	No interaction of group or sex on episodic memory
Tait et al. 2011	22.65 (*unk*)	586	239	493	181	*(baseline measures of 8 year study)*	No interaction of group or sex on episodic and working memory
Neuroimaging Studies							
McQueeny et al. 2011	17.81 (*unk*)	8	11	27	36	28 days	Female users right amygdalar volume > female controls, no difference among males
Medina et al. 2009	18.06 (*unk*)	4	6	12	10	28 days	Female users prefrontal cortex > female controls; male users prefrontal cortex < male controls

All values are means and standard deviations unless otherwise noted

unk unknown, *THC* tetrahydrocannabinol, *CBD* cannabidiol

(Pope et al. 1997). More recently, male cannabis users evidenced impairments on psychomotor performance (Clark et al. 2009; King et al. 2011) and visuospatial organization (King et al. 2011) compared to male healthy controls, but no differences were observed between cannabis-using females and their non-using counterparts (Clark et al. 2009; King et al. 2011). Preliminary evidence from our laboratory suggests a sex-specific dissociation in how amount of cumulative lifetime cannabis use relates to decision-making, but not episodic memory, among male (n=44) and female (n=25) young adult cannabis users (unpublished). Specifically, more lifetime cannabis use was associated with poorer decision-making performance for male cannabis users, but not female cannabis users. In contrast, more lifetime cannabis use was negatively associated with episodic memory performance in both male and female cannabis users. Other studies report no interaction effects of sex and cannabis use on episodic memory (Solowij et al. 2011; Tait et al. 2011) or working memory (Tait et al. 2011).

A few neuroimaging studies provide further preliminary evidence for sex-specific differences in the residual influence of cannabis use. After 28 days of abstinence, female adolescent chronic cannabis users had larger right amygdala volumes compared to female adolescent healthy controls, while there was no difference in amygdala volumes among adolescent male chronic cannabis users and controls (McQueeny et al. 2011). Female adolescent chronic cannabis users also evidenced larger prefrontal cortex volumes than female controls, whereas males showed the opposite pattern relative to a male control group (Medina et al. 2009). In this sample, smaller prefrontal cortex volume was associated with better executive functioning among the cannabis users, but larger prefrontal cortex volume was associated with better executive functioning among the controls.

Although still nascent, the current evidence points to sex differences in the impact of cannabis on neurocognitive functioning, but more so for non-acute than acute effects. However, the sex-dependent influence of cannabis appears to be domain specific (see Fig. 1), which may reflect some of the aforementioned differences in neurodevelopment, CB1 receptor density, hormones, and both the pharmacological and subjective effects of cannabis. Other factors not covered in this review may also contribute to possible sex differences. For example, one study found that stereotype threat (i.e., individuals' belief that they belong in a group that is seen as inferior) differentially affected neurocognitive measures among male and female cannabis users (Looby and Earleywine 2010). Although the emerging neuroimaging data suggest that some of the neurobehavioral differences may be driven by structural differences, the overall picture remains largely unstudied and likely involves a complex contribution of many factors.

Concluding Remarks

Accumulating research in the past 5 years has contributed considerable advances regarding cannabis' acute and non-acute effects on human cognition. These studies continue to demonstrate the negative effect of cannabis on learning and memory, in addition to deficits in attention, concentration, and abstract reasoning in both acute and non-acute studies. Given the acute and non-acute deficits in attention and concentration, it is possible that the cannabis-related impairments in episodic memory may be more influenced by encoding (through disruptions in the prefrontal cortex), rather than through temporal-lobe mediated storage and retrieval—or it may be a combination of both. However, the authors of a recent review on the acute effects of cannabis on memory function reported that deficits in learning and recall could not be attributed to cannabis' disruption of attentional processes; instead, acute cannabis intoxication may disrupt retrieval and not encoding (Ranganathan and D'Souza 2006). On the other hand, results from a recent study by our group found that poorer performances in delayed recall by cannabis users on an auditory episodic memory task did not persist after controlling for performance on immediate memory (Gonzalez et al. 2012b). Cannabis-related effects in other neurocognitive domains are often less consistent. Working memory is impaired during acute intoxication, but remains largely intact among recently abstinent adult cannabis users, while the data is mixed for recently abstinent adolescent cannabis users. The findings for measures of inhibition, motor impulsivity, and psychomotor control are mixed, whereas measures of decision-making and risk-taking remain intact during acute intoxication, but are impaired among cannabis users. Taken together with cannabinoid receptor distribution and evidence from neuroimaging data, it may be that cannabis' effects on prefrontal, striatal, and hippocampal structures may drive the observed neurocognitive profiles of cannabis users.

These new results have implications for clinical practice. For example, problems with decision-making, inhibition and/or risk-taking may serve as risk factors for the development of substance use disorders, as found in research on other drugs of abuse (de Wit 2009; Goldstein and Volkow 2002; Schepis et al. 2008), making it more difficult to resist the urge to continue using the drug even when its use is likely to be harmful (Bechara 2005). It is also possible that cannabis

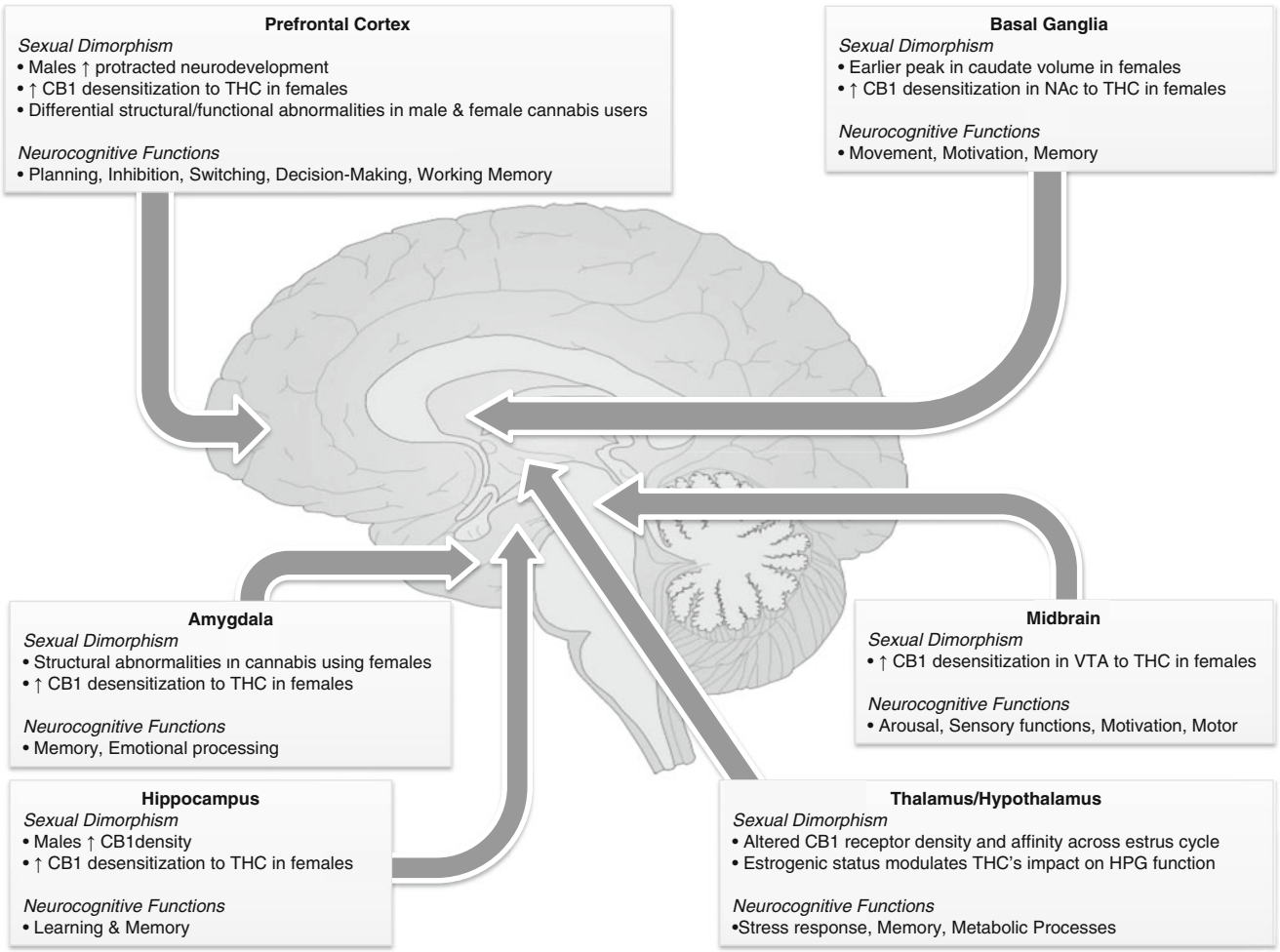

Fig. 1 Sexual dimorphism and neurocognitive functions of brain regions with high CB1 receptor density. This figure simplifies and summarizes some sexual dimorphisms relevant to the effects of cannabis on brain functioning in regions with high CB1 receptor density and some of the neurocognitive functions commonly ascribed to these regions. *Arrows* indicate the general location of the noted structures, although some lie outside of the shown midsaggital plane

negatively impacts these neurocognitive domains, especially if use is initiated during adolescence, when the prefrontal cortex is still developing. However, it is important to keep in mind the many pitfalls to interpreting and generalizing findings from studies presented in a systematic review. Many of these can be addressed with meta-analysis; however, despite the rapid growth in research, the last meta-analysis examining non-acute effects of cannabis on neurocognition was published almost a decade ago (Grant et al. 2003).

Importantly, many recent studies have also examined specific variables that may contribute to some of the discrepant findings pertaining to the neuropsychological profile of cannabis use. Here we suggest that neurodevelopmental factors and sex differences are important to consider when examining neurocognitive effects of longer term cannabis use. For example, onset of use during adolescence, as compared to later lifetime epochs, may be associated with disruption of normal neuromaturation and result in neurocognitive deficits. There is accumulating evidence that neurodevelopmental trajectories, regional CB1 densities, as well as endocrinological and behavioral contributions, are not uniform across sex, resulting in a sex-dependent impact of cannabis use on neurocognitive functioning.

Together, data reviewed in the current manuscript indicates that cannabis use may have a negative impact on some aspects of neurocognition, especially those mediated principally by frontal-limbic systems. However, there is a high degree of inconsistency related to the exact nature and chronicity or reversibility of these deficits. Future investigations that continue to employ longitudinal methodologies and capitalize on large sample sizes across the full range of cannabis use experience are critical to disentangle the temporal ordering of cognitive deficits and cannabis use. Additionally, more nuanced examinations that take into account individual difference variables are crucial in order

to develop a more stable understanding of how cannabis interferes with various domains of neuropsychological functioning. We suggest that a specific focus on pre-existing neurobehavioral factors and sex-differences, as well as their complex interactions, will be fruitful in understanding the subjective liability to the neurocognitive effects of cannabis.

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