



## Review

## Cannabinoid modulation of executive functions

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## ARTICLE INFO

## Article history:

Accepted 7 February 2008

Available online 18 March 2008

## Keywords:

Adolescence

Attention

Cannabinoid

Cognition

Decision-making

Flexibility

Inhibition

Prefrontal cortex

Time estimation

## ABSTRACT

Executive functions are higher-order cognitive processes such as attention, behavioural flexibility, decision-making, inhibitory control, planning, time estimation and working memory that exert top-down control over behaviour. In addition to the role of cannabinoid signaling in other cognitive functions such as mnemonic processes, interest in its involvement in executive functions has arisen more recently. Here, we will briefly review some of the recent findings indicating a modulatory role of cannabinoid action on executive functioning. In addition, a growing body of evidence suggests that in particular adolescents are more vulnerable for the deleterious effects of drugs of abuse such as cannabis on cognitive functioning. Therefore, in this paper we will also briefly discuss some recent developments in this research field.

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## 1. Introduction

Although *Cannabis sativa* and its products (e.g. marijuana, hashish) have been used for a long time for their medicinal and recreational properties, the molecular constituents of the brain endogenous cannabinoid system have only been elucidated in the early 1990s. The primary endogenous ligands for this system are anandamide and

2-arachidonylglycerol and, to date, at least two G-protein-coupled receptors for cannabinoid ligands have been cloned. Of these receptors, cannabinoid CB<sub>1</sub> receptors are thought to be primarily localized within the central nervous system, whereas cannabinoid CB<sub>2</sub> receptors appear restricted mainly to peripheral and immune tissues (for recent review, see Mackie and Stella, 2006; but see, Gong et al., 2006). Within the brain, cannabinoid CB<sub>1</sub> receptors are located presynaptically and activation of these receptors inhibits synaptic transmission. Thus, in this regard the endocannabinoid system can modulate neuronal activity of other transmitter systems, such as the dopaminergic, GABAergic and glutamatergic system. Consistent with this notion, the brain endocannabinoid system has been implicated in a wide variety of behavioural functions such as food intake (Di Marzo

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and Matias, 2005), nociception (Cravatt and Lichtman, 2004) as well as in modulating the reinforcing properties of drugs of abuse (De Vries and Schoffeleers, 2005). In addition, the endocannabinoid system has been shown to play an important role in various cognitive functions. Accordingly, endocannabinoid involvement in mnemonic processes including memory encoding, consolidation and extinction has been studied quite extensively (e.g. Marsicano et al., 2002; Robinson et al., 2007; Takahashi et al., 2005; Varvel et al., 2005; for review, see Riedel and Davies, 2005). More recently, its involvement in 'higher-order' cognitive or executive functions has received increasing interest. Executive functioning comprises cognitive processes such as attention, behavioral flexibility, decision-making, inhibitory control, planning, time estimation and working memory and is crucially involved in top-down control of behaviour. In this regard, recent reviews have addressed the role of the (endo)cannabinoid system in these processes based on clinical and preclinical data (Egerton et al., 2006; Solowij and Michie, 2007). Nonetheless, research in the cannabinoid field is rapidly expanding. Therefore, we will here focus on 1) several novel preclinical and clinical findings implicating the (endo)cannabinoid system in executive functioning and 2) briefly review some recent work considering the consequences of adolescent cannabis and marijuana use on executive functioning.

## 2. Neuroanatomical distribution of cannabinoid CB<sub>1</sub> receptors

Accumulating data has shown that most executive functions are mediated by frontostriatal brain areas in both humans as well as rodents with primary involvement of the medial prefrontal cortex (Dalley et al., 2004; Miller and Cohen, 2001). Consistent with the hypothesized role of the cannabinoid system in executive functions, high densities of cannabinoid CB<sub>1</sub> receptors have been found in frontal cortical, striatal and midbrain regions including the substantia nigra and ventral tegmental area in rodents (Egertova and Elphick, 2000; Tsou et al., 1998; for review, see Freund et al., 2003). Thus, the presence of cannabinoid CB<sub>1</sub> receptors in these brain areas may enable the cannabinoid system to modulate the release of other neurotransmitters that in turn may play crucial roles in executive functions. In support of this notion, cannabinoid CB<sub>1</sub> receptors have been identified on presynaptic terminals of GABAergic, glutamatergic, noradrenergic as well as serotonergic neurons throughout the brain including frontal cortical regions (e.g. Domenici et al., 2006; Haring et al., 2007; Hill et al., 2007; Hoffman and Lupica, 2000; Oropeza et al., 2007) suggesting control by the cannabinoid system of the release of these neurotransmitters. Furthermore, although cannabinoid CB<sub>1</sub> receptors have as yet not been found on nerve terminals of dopaminergic neurons, cannabinoid CB<sub>1</sub> receptor agonists such as Δ<sup>9</sup>-tetrahydrocannabinol and (R)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate salt (WIN55,212-2) have been reported to enhance dopamine transmission in the medial prefrontal cortex (Jentsch et al., 1997) and the nucleus accumbens (Cheer et al., 2004). These findings illustrate that the cannabinoid system may – in an indirect manner – modulate dopaminergic action, presumably through inhibition of GABAergic inhibition of dopamine neurons in the medial prefrontal cortex (Pistis et al., 2001) and ventral tegmental area (Lupica and Riegel, 2005; Szabo et al., 2002). This modulatory role on dopamine transmission may be of particular importance, since dopamine is crucially involved in executive functioning (for recent review, see Robbins, 2005).

Human imaging techniques, such as functional magnetic resonance imaging and positron emission tomography, have improved dramatically over the last decades and nowadays are applied widely in psychiatry and experimental psychology. Until recently, tracers for clinical use with high affinity for cannabinoid CB<sub>1</sub> receptors and low nonspecific binding were lacking, thereby hampering our understanding of the distribution of cannabinoid CB<sub>1</sub> receptors in the

human brain. Importantly, the recent development of the novel tracer N-[2-(3-cyanophenyl)-3-(4-(2-[<sup>18</sup>F]fluoroethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylpropanamide ([<sup>18</sup>F]MK-9470) has broadened our horizon in this regard and data obtained with this tracer indeed showed that the human brain also contains high densities of cannabinoid CB<sub>1</sub> receptors in frontal cortical regions (Burns et al., 2007).

## 3. Role of cannabinoids in executive functions

### 3.1. Attention

The ability to evaluate and allocate priority to invading environmental stimuli or possible behavioural response options to optimise behaviour requires attentional processing. One of the earliest observations that showed deleterious effects of cannabis on measures of attention was provided in an early study more than three decades ago (Caswell and Marks, 1973). Since then many other studies have reported that acute challenges with or prolonged use of cannabis and its products may impair attentional processing in humans (for review, see e.g. Solowij and Michie, 2007). These clinical findings have received support from recent preclinical studies, that have employed models to measure visuospatial attention in rodents such as the lateralized reaction time task and 5-choice serial reaction time task. Briefly, in these tasks rats have to attend to an intelligence panel containing different apertures (two for the lateralized reaction time task and five for the 5-choice serial reaction time task) and in one of these apertures a short visual stimulus is presented. Subsequently, rats then have to make a response into the corresponding illuminated aperture in order to obtain food reward. Indeed, using a lateralized reaction time task researchers have found that acute challenges with WIN55,212-2 impaired visuospatial attention (Arguello and Jentsch, 2004). However, in a similar dose range these findings were not replicated in the 5-choice serial reaction time task (Pattij et al., 2007a). Moreover, whereas the cannabinoid CB<sub>1</sub> receptor antagonist rimonabant did not alter visuospatial attention in the lateralized reaction time task (Arguello and Jentsch, 2004), the cannabinoid CB<sub>1</sub> receptor antagonist slightly improved attentional performance in the 5-choice serial reaction time task (Pattij et al., 2007a). These latter findings suggest that performance in the 5-choice serial reaction time task may activate the endocannabinoid system, which in turn may modulate visuospatial attention. In addition to acute challenges with cannabinoids, chronic intermittent treatment of rats with Δ<sup>9</sup>-tetrahydrocannabinol has also been demonstrated to impair visuospatial attention in a lateralized reaction time task (Verrico et al., 2004).

Both in humans as well as rodents, prefrontal cortical regions are critically involved in mediating attentional processes (for reviews, see e.g. Raz and Buhle, 2006; Robbins, 2002). Thus, the observed behavioural effects of cannabinoids on attention may possibly be mediated by their local effects on prefrontal cortical functioning.

### 3.2. Behavioural flexibility

Successful adaptation of behaviour to e.g. changing environments or – in laboratory settings – changing task demands, requires the capacity to adjust behavioural strategies and to suppress 'old' whilst initiating 'new' response patterns. Clinical observations suggest that behavioural flexibility in humans is modulated by the cannabinoid system. For instance, in a laboratory task requiring subjects to alternate between two response options in order to maximize monetary gains, marijuana has been found to dose-dependently impair the ability to switch their behavioural response, thereby resulting in loss of monetary gains (Lane and Cherek, 2002). Furthermore, heavy marijuana smoking in both adults as well as adolescents was shown to be associated with deficits in behavioural

flexibility as measured in a Wisconsin card sorting test (Bolla et al., 2002; Lane et al., 2007). Clearly, these findings implicate the cannabinoid system in behavioural flexibility, although the exact mechanisms responsible for these observed effects are as yet unclear.

To assess behavioural flexibility in rodents, several attentional set-shifting paradigms have been developed over the last years (Birrell and Brown, 2000; Floresco et al., 2006a). Briefly, in these tasks rats are required to make a choice between various response options in order to obtain food reward. Response options may vary from 'simple' intradimensional discrimination learning where correct decisions should be based on cues from a single perceptual dimension (e.g. olfaction), and in this regard reversal learning capacities are measured. Alternatively, the discrimination may also be based on cues from another modality and under these conditions successful decisions require extradimensional shifts, meaning that attention should be directed towards a different perceptual dimension (e.g. vision). While intradimensional reversal learning strategies largely depend on integrity of the orbitofrontal cortex (McAlonan and Brown, 2003; for review, see Murray et al., 2007), extradimensional shifts are mediated by the medial prefrontal cortex (Birrell and Brown, 2000; Floresco et al., 2006a). To date, few studies have examined the effects of cannabinoids on behavioural flexibility in rodents and findings are somewhat contradictory. Acute  $\Delta 9$ -tetrahydrocannabinol administration has been found to impair intradimensional, but not extradimensional reversal learning in rats (Egerton et al., 2005). Strikingly, in this study similar doses of  $\Delta 9$ -tetrahydrocannabinol were associated with decrements in expression of the immediate early gene *c-fos* in frontal cortical areas including the orbitofrontal and medial prefrontal cortices. In particular, the decreased *c-fos* expression in the orbitofrontal cortex is in agreement with the involvement of this brain region in intradimensional reversal learning, suggesting that these changes may underlie the observed behavioural impairments. In contrast to these findings, a more recent study has demonstrated that the cannabinoid CB<sub>1</sub> receptor agonist HU210 impairs and the cannabinoid CB<sub>1</sub> receptor antagonist 1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide (AM251) improves extradimensional reversal learning, whereas neither compound altered intradimensional reversal learning (Hill et al., 2006) thereby contrasting earlier findings (Egerton et al., 2005). Apart from these results obtained in attentional set-shifting tasks, mutant mice lacking cannabinoid CB<sub>1</sub> receptors displayed impaired reversal learning in a 'simple' water maze reversal learning task (Varvel and Lichtman, 2002), suggesting that the endocannabinoid system is indeed important in adjusting behavioural strategies.

Taken together, both in humans as well as rodents the (endo) cannabinoid system is involved in behavioural flexibility possibly through its modulatory role on prefrontal dopamine and glutamate action, as these neurotransmitters have been shown to importantly regulate set-shifting capacities (Floresco et al., 2006b; Ragozzino, 2002; Stefani et al., 2003).

### 3.3. Inhibitory control processes and decision-making

Decision-making and inhibitory control are essential cognitive processes in the selection of appropriate and the inhibition of inappropriate behavioural responses. Disturbances in these processes may underlie impulsive behaviour and pathological levels of impulsivity are key characteristics in the symptomatology of several psychiatric disorders including attention-deficit/hyperactivity disorder, addiction, mania and personality disorders (for review, see Moeller et al., 2001). To date, few studies have examined cannabinoid involvement in decision-making and inhibitory control subserving impulsivity. In human volunteers, acute challenges with  $\Delta 9$ -tetrahydrocannabinol and marijuana have been shown to increase impulsive responding in the stop-signal task (McDonald et al., 2003; Ramaekers et al., 2006), a task that measures response inhibition

defined as the ability to inhibit ongoing behaviour. Impulsivity in this task is reflected by a failure or deficit in the ability to inhibit ongoing behaviour. In contrast,  $\Delta 9$ -tetrahydrocannabinol did not affect decision-making (McDonald et al., 2003), at least as measured in a delay discounting paradigm, where subjects have to choose between immediate small reinforcement, and larger delayed reinforcement. Impulsive decisions in this task are reflected by an increased preference for the immediate reward, as the value of larger delayed reinforcers is thought to be discounted by impulsive individuals. Nonetheless, as discussed above, in a task where subjects have to choose between two response options in order to maximize monetary gains, marijuana increases the choice for response options associated with larger monetary loss (Lane and Cherek, 2002) and leads to more 'risk-taking' behaviour (Lane et al., 2005). Thus, these findings suggest a role for the cannabinoid system in a different type of 'risky' or 'impulsive' decisions.

To some extent, preclinical findings have supported the above-mentioned observations as WIN55,212-2 has been found to mildly impair response inhibition in the stop-signal task in rats (Pattij et al., 2007a), whereas it did not alter decision-making in a delay discounting task. Moreover, in a visuospatial attention task, namely the 5-choice serial reaction time task, rimonabant reduced impulsive responding suggesting a modulatory role of tonically activated cannabinoid CB<sub>1</sub> receptors by endocannabinoids on impulsivity (Pattij et al., 2007a). In this particular task, prematurely expressed responses – that is responses before the onset of a visual target stimulus – provide a measure of inhibitory control and disturbances in inhibitory control processes would therefore lead to increased premature responding.

How exactly cannabinoids alter decision-making and impair inhibitory control has as yet not been extensively studied. The modulatory role of the cannabinoid system on prefrontal cortical or accumbal dopamine action (e.g. Cheer et al., 2004; Jentsch et al., 1997) may seem a likely explanation, mainly because this neurotransmitter has been shown to play a cardinal role in decision-making (e.g. Van Gaalen et al., 2006a; Winstanley et al., 2003) as well as inhibitory control processes (e.g. De Wit et al., 2002; Cole and Robbins, 1987; Pattij et al., 2007b; Van Gaalen et al., 2006b).

### 3.4. Time estimation

The capacity to time and plan the temporal order of behavioural events is an essential cognitive function that allows individuals to successfully adapt behaviour (Meck and Benson, 2002). Accumulating clinical data have shown that cannabinoids alter this cognitive function and disturb the perception of time. Typically, the use of marijuana and  $\Delta 9$ -tetrahydrocannabinol in humans has been reported to result in an underestimation of time, that is subjectively time appears to pass more slowly (e.g. Hicks et al., 1984; Mathew et al., 1998; McDonald et al., 2003; Tinklenberg et al., 1972). Consistent with these human findings,  $\Delta 9$ -tetrahydrocannabinol and WIN55,212-2 have been found to alter time perception and in various experimental paradigms, such as a time discrimination procedure (Crystal et al., 2003) and a time estimation procedure (Han and Robinson, 2001), these compounds result in an underestimation of time. Furthermore, the behavioural effects of rimonabant have been found to result in an overestimation of time opposite to the behavioural effects of  $\Delta 9$ -tetrahydrocannabinol and WIN55,212-2 in the time estimation (Han and Robinson, 2001), but not time discrimination paradigm (Crystal et al., 2003). These findings thus suggest that tonic activation of cannabinoid CB<sub>1</sub> receptor by endocannabinoids plays a role in time estimation. The representation of time estimation is presumably modulated within the striatum and results from an interaction between afferent glutamatergic projections from the prefrontal cortex and afferent dopaminergic projections from the substantia nigra (Meck and Benson 2002). Indeed, recent studies have shown that drugs enhancing dopamine transmission such as methamphetamine

(Cheng et al., 2007a) and cocaine (Cheng et al., 2007b) may modulate timing behaviour. Furthermore, ineffective doses of the *N*-methyl-D-aspartate receptor antagonist ketamine were found to restore the effects of cocaine, supporting the notion of a glutamate-dopamine interaction in time estimation (Cheng et al., 2007b). As mentioned previously, the observations that cannabinoids modulate both cortical glutamatergic transmission as well as striatal dopaminergic transmission may well underlie their effects on time estimation processes.

### 3.5. Working memory

Involvement of cannabinoid signaling in working-memory processes, i.e. the temporary encoding of information, has been well documented. For over three decades, cannabis has been known to impair short-term working memory in both humans (e.g. Darley et al., 1973; Miller and Branconnier, 1983) as well as in rodents (e.g. Stiglick and Kalant, 1982, 1983). Following these initial observations, accumulating evidence has confirmed the notion that cannabinoids impair short-term and working memory (for reviews, see Egerton et al., 2006; Lichtman et al., 2002; Riedel and Davies, 2005). In search for the underlying neurobiological mechanisms, most preclinical studies have employed pharmacological approaches using systemic or intracranial application of cannabinoid CB<sub>1</sub> receptor agonists and antagonists. Such studies have demonstrated that the cannabinoid system may affect short-term and working memory by altering the mechanisms responsible for these processes within the hippocampus (e.g. Barna et al., 2007; Hampson et al., 2003; Robinson et al., 2007). More specifically, recent work has suggested that performance in a working memory task is associated with activation of the endocannabinoid system on a trial-by-trial basis (Deadwyler et al., 2007). This trial-dependent endocannabinoid tone may in turn affect working memory by reducing hippocampal encoding, since rimonabant was found to facilitate hippocampal encoding of working memory and subsequent behavioural performance (Deadwyler et al., 2007).

## 4. Adolescent cannabis use and executive functions

Finally, we would like to briefly address a topic that has recently been gaining more interest, namely adolescence as a neurodevelopmental period with potentially increased vulnerability to the adverse effects of cannabis exposure.

It is now well known that both in humans and rodents the brain continues to develop throughout adolescence, with processes such as synaptic pruning and myelination still occurring at a large scale during this period of life (for reviews, see e.g. Lenroot and Giedd, 2006; Spear, 2000). Importantly, it has been found that the frontal cortical areas of the brain, which control executive functions, are the last to reach full maturity (e.g. Gogtay et al., 2004). Within these frontal cortical brain regions, the endocannabinoid system also seems to continue to develop during adolescence, as dramatic decreases in cannabinoid binding capacities have been observed in rats during adolescence until early adulthood (Belue et al., 1995; Rodriguez de et al., 1993). In line with this, it was recently found in rats that the inhibitory synaptic function within the adolescent hippocampus shows a higher sensitivity to exogenously applied cannabinoids as compared to the adult hippocampus (Kang-Park et al., 2007).

In view of the ongoing maturation of particularly frontal regions of the brain and an increased sensitivity of the cannabinoid system during adolescence, this period of life might form a time window with increased vulnerability for lasting deficits in cognitive functioning due to exposure to exogenous cannabinoids. In a recent survey within the Netherlands, it was found that in 2003 the lifetime prevalence of cannabis use among 12–17 year-olds was 18%, with 40% of the cannabis users starting at age 13 or younger (Monshouwer et al., 2005). Similarly, nowadays almost 50% of 12th graders within the United States have tried marijuana, with 5% even reporting daily use

(Terry-McElrath et al., 2005). With such a high prevalence of cannabis use among teenagers, any lasting deficits will probably come at great cost for society, justifying the recently increased interest of scientists for this topic.

Indeed, there is now accumulating preclinical evidence of distinct long-lasting effects of cannabinoid exposure during adolescence, including disturbances in cognitive functioning. Particularly, lasting impairments of working memory as measured in an object recognition test were found in adolescent, but not adult  $\Delta$ 9-tetrahydrocannabinol-treated male rats when tested during adulthood (Quinn et al., 2007; Schneider and Koch, 2003). Nonetheless, these effects do not always appear robust, and absence of lasting residual effects on object recognition following repeated cannabinoid exposure during adolescence has also been reported (O'Shea et al., 2006). Interestingly, a similar treatment did impair working memory but only in adolescent-treated female rats (O'Shea et al., 2004), suggesting a sexual dimorphism in the adverse effects of cannabinoid exposure.

The behavioural changes observed following adolescent cannabinoid exposure are likely related to persistent molecular and neuronal adaptations. In support of this, it has been shown that exposure to cannabinoids during adolescence in rats resulted in lasting changes in, for instance, the mesolimbic dopamine pathway (Pistis et al., 2004) as well as in the opioid system (Ellgren et al., 2007). Moreover, repeated exposure to  $\Delta$ 9-tetrahydrocannabinol during adolescence was recently found to result in distinct changes in the hippocampal proteome (Quinn et al., 2007). Future preclinical studies might thus focus on lasting deficits of adolescent cannabinoid exposure on other cognitive functions as well as brain morphology and functioning.

The number of clinical studies investigating the effects of cannabis exposure during adolescence on cognition has also been rising over the last decade. There is considerable evidence of acute effects of  $\Delta$ 9-tetrahydrocannabinol on overall intelligence, processing speed, attention, and working memory (Ehrenreich et al., 1999; Fried et al., 2005; Kempel et al., 2003; Schwartz et al., 1989). In contrast, consensus is still lacking regarding the long-term effects of adolescent cannabis exposure. While some studies in adolescents or in adults that had started using cannabis during adolescence reported no lasting deficits in cognitive abilities such as overall intelligence quotient, processing speed, working memory, and attention (Fried et al., 2005; Jager et al., 2006), other studies found (subtle) long-lasting cognitive deficits following cannabis use during adolescence (Jacobsen et al., 2004; Medina et al., 2007; Pope et al., 2003; Schwartz et al., 1989). Importantly, it was shown in several studies that the cannabis-induced deficits were dependent on the age of onset of cannabis use, as results differed for early-onset cannabis smokers (before age 16 or 17) as compared to later-onset users (Ehrenreich et al., 1999; Kempel et al., 2003; Pope et al., 2003). These findings correlate well with a study showing that early-onset cannabis smokers had a smaller whole brain volume with a lower percentage of cortical grey matter and a higher percentage of white matter, as well as increased cerebral blood flow during rest as compared to late-onset users (Wilson et al., 2000). However, a major drawback in most of these studies on lasting cognitive deficits resulting from adolescent cannabis use is the lack of proper assessment of premorbid cognitive capacities of the subjects. Moreover, even if premorbid cognitive capacities would be known and cognitive deficits in early-onset cannabis smokers would be found, it can not be excluded that deficits were observed because early-onset cannabis use had influenced educational and social opportunities of the subjects to such an extent that it interfered with the testing rather than the deficits being due to cannabis-induced neuroplasticity. It is a challenge for future human studies to overcome these limitations in order to elucidate any long-lasting effects of cannabis use during adolescence. Preclinical studies are of particular importance in this respect, as it is much easier to control for environmental and premorbid factors in laboratory animals, and validated translational models are available for many different modalities of cognitive

functioning. Moreover, preclinical studies are better suited to elucidate the molecular and neuronal mechanisms underlying cannabinoid-induced effects.

## 5. Concluding remarks

In conclusion, when reviewing the expanding cannabinoid research field over the last decade, it becomes apparent that the endocannabinoid system is involved in various (if not all) executive functions. In this regard, most studies reported that cannabis as well as synthetic cannabinoid CB<sub>1</sub> receptor agonists impair the cognitive processes that subserve executive functioning. Although the neurobiological mechanisms mediating these deleterious effects are as yet largely unclear, accumulating preclinical data emphasize the importance of modulatory actions of the endocannabinoid system on prefrontal cortical and striatal dopamine and glutamate transmission. Finally, in addition to the behavioural effects of cannabis and related products on cognitive processes in adult users, a growing body of clinical and preclinical studies have suggested a particular vulnerability of the adolescent brain. Thus, adolescent cannabis use may on the long run be associated with lasting changes in cognitive functions and given the large number of adolescents using cannabis, this may pose a significant societal burden in the future.

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