Chapter 5

Influence of Drugs on Cognitive Functions

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71842

Abstract

Disorders related to the misuse of certain drugs represent not only a worldwide public health problem, but also an economic and social issue. Adolescents and children represent the most vulnerable population for drug consumption and addiction. At this early stage in life, a crucial phase of the neurodevelopmental process, substance abuse can induce brain plasticity mechanisms that may produce long-lasting changes in neural circuitry and ultimately behavior. One of the consequences of these changes is the impairment of cognitive functions, with academic negative impact in the acquisition of new knowledge. In this chapter, we will describe the effects of illicit substances of abuse, both stimulants and depressants as well as prescription drug misuse and its influence of on learning and memory processes. Recent evidence on the new so-called smart drugs is also discussed.

Keywords: abuse, cognition, performance, nootropic, smart, stimulants, depressant, memory, impairment, adolescent

1. Introduction

According to United Nations Office on drugs and Crime, in 2015, around a quarter of a billion people used drugs, and approximately 29.5 million showed drug use disorders, including dependence [1]. Drug abuse produces health disruption. Disorders related to the use of certain drugs are associated with an important worldwide rate of morbidity. A wide range of drug-induced neurobiological modifications have been described; some of which can affect learning and memory functions. Stimulant drugs, like nicotine and amphetamine, improve cognitive function at lower doses but impair memory performance at higher doses. Depressant drugs, like alcohol, can cause long-term effects on prefrontal cortex function, disrupting cognitive abilities.

Several studies have suggested that the influence of psychoactive drugs on learning and memory might be explained, at least in part, because of the shared neurobiological mechanisms involved in learning and memory processes and the drug-induced structural and functional changes in the brain. Anatomically, there is an important overlap between the neural substrates of learning and memory and those of addiction. Some of the areas that show overlap include the cerebral cortex, hippocampus, amygdala and striatum [2]; all of them are components of the mesolimbic dopaminergic system.

Adolescence is a sensitive period in brain development characterized by a decrease in gray matter and an increase in white matter. The diminution of gray matter is thought to be due, at least in part, to the process of synaptic pruning, which is the developmental refinement of brain circuits by removal of superfluous synapses [3]. Early drug exposure is associated with frontal lobe damage, low cognitive performance and emotional learning, as well as other behaviors. Moreover, it has been demonstrated that adolescent exposure to both prescription and social drugs impairs cognition, as well as other behaviors, in the adulthood [4].

There is a clear bidirectional relationship between abuse of drugs and poor academic achievement. It has been suggested that cognitive deficits could make adolescents more vulnerable to substance abuse than others; conversely, other proposals argue that substance abuse is the source of cognitive impairments [5–7]. Of course the two possibilities are not mutually exclusive; teenagers with poor academic performance may be more prone to abusing illicit drugs, which may impair their results at school even further. While the several social science theories have been proposed to try to explain each of these phenomena [6], in the following text, we will focus on the cognitive consequences of adolescent substance abuse on the functioning of the nervous system that may have a deleterious impact on cognitive abilities, academic achievement and long-term satisfaction with life in general.

2. Stimulant drugs

Memory is the natural counterpart of learning; both are necessary for behavioral change that precedes survival of species. Substance abuse has been demonstrated to exert detrimental impact upon learning and memory. According to the United Nations Office on Drugs and Crime through World Drug Report 2017, 29.5 million people globally suffer from drug use disorders [8]. Cognitive impairment is a well-established consequence of long-term substance abuse, with stimulants as nicotine, methamphetamine (MA) and cocaine leading deficits in the area of executive function. Stimulants are a class of illicit drugs that can have negative impact on individuals who use them, although this impact might be masked by the believed benefits (**Table 1**) [9].

2.1. Nicotine

Nicotine is the main psychoactive component of tobacco and the responsible agent of tobacco dependency. According to the World Health Organization, despite its severe health consequences, about one billion people smoke worldwide.

Drug	Cognitive process	Effect	Model	Reference
Stimulant drugs	Attention Vigilance Memory	*Acute*: Improving selective visuospatial attention, spatial working memory and associative memory	Monkey Rat Mice Zebrafish Human	[10, 11]
		Chronic: Tolerance Withdrawal syndrome Mild deficits in memory and inhibition response Disruption in prospective and visual memory, verbal ability, reasoning and decision making	Human Rat	[13, 25–27, 29]
Depressant drugs	Attention Memory	*Acute/low doses*: Facilitation in working memory, verbal fluency and executive functions Impaired working memory, verbal fluency and executive functions	Human	[37, 38, 41, 55–57]
		Chronic/high doses: Disruption in working and episodic memory, consolidation memory, attention and memory Also, presence of blackouts	Human	[39, 61–67]

Table 1. Effects of the stimulants and depressant drugs in cognitive functions.

When nicotine is administered acutely, it produces positive effects improving cognitive functions, including sustained attention, vigilance, visuospatial selective attention, spatial working memory and associative memory, both in animal models [10] and in humans [11]. Conversely, a vast amount of literature has showed that chronic nicotine use leads to tolerance, and 1 h after cessation of nicotine exposure, nicotine withdrawal syndrome emerges and it is characterized by mild cognitive deficits. In other words, nicotine tends to improve cognitive function at lower doses and impair performance at higher doses [12]. Furthermore, heavy smokers under acute abstinence from smoking experience decreased neurocognitive functions, including impairments in sustained attention, working memory and response inhibition [13]. Strong activation of memory-related brain regions that include the dorsolateral prefrontal cortex and hippocampus has been correlated with smoking-related cues in adult heavy smokers [14]. These areas are involved in emotional learning and reward-related learning.

Some reports have shown that nicotine and nicotinic agonists, as mecamylamine, evoked cognitive enhancement by potentiating the release of dopamine [12, 15]. Working memory is critically reliant on dopaminergic neurotransmission. In addition, rodent studies have revealed a direct relationship between dopamine release in the prefrontal cortex and on memory task accuracy [16]. Moreover, cholinergic systems and nicotinic receptors are essential for cognitive processes and have been implicated in diseases associated with cognitive impairment [17].

2.2. Methamphetamine (MA)

MA abuse represents a serious public health issue associated with a high likelihood of relapse. By 2008, nearly 25 million people worldwide were estimated to have used MA, with abuse being among younger age groups [18]. MA used is mainly for recreational purposes and it is known to induce a variety of desirable effects, including increased energy levels, positive mood, euphoria, reduced appetite, weight loss, enhanced mental acuity and social and sexual disinhibition [19]. In addition, MA-dependent individuals often claimed enhancement of cognitive function and ability to focus following drug administration. However, this drug induces long-term changes in the brain structure and function, changes in synaptic plasticity, cell death via apoptosis and neurotoxicity, and consequently, it causes dependence and withdrawal syndrome [20].

Anatomically, MA has a preferential neurotoxic effect on the frontostriatal systems that contributes to both emotion dysregulation and neurocognitive impairment [21]. For instance, MA addicts showed impaired performance on tests of cognitive flexibility, which measures the ability to modify behavior when presented with new information or changing outcomes. These deficits may impair MA addicts from altering their habitual drug abuse behavior, leading to an inability to initiate abstinence or resist relapse [22]. Cellular mechanism of this MA impairment has been associated with long-term downregulation of dopamine transporters, suggesting that there are structural changes in some of the dopamine nerve terminals [23]. Other findings suggest that MA use causes changes in the metabolism of the insula and striatum [24]. In a study in humans, MA-dependent participants had significantly lower results than control participants on memory tasks, including prospective memory and visual memory [25]. Accordingly, studies in young adult MA abusers have shown impaired verbal ability, deficits in psychomotor processing [26], reasoning deficits reflecting problematic decision-making abilities as well as retrospective memory task impairment [27].

The evidences pointed that acute administration of MA improves cognitive functions, while chronic consumption of MA deteriorates them.

2.3. Cocaine

Cocaine has long been one of the most common recreational stimulants, especially for adolescents. A recent estimate indicates that half a million of United States habitants use this drug weekly; in this sense, cocaine addiction represents a substantial burden for societies worldwide, linked to adverse outcomes such as violence, suicide and disability, as well as high rates of chronic relapse [28]. In the brain, crack cocaine use has been shown to cause toxic effects, particularly in the prefrontal cortex. These abnormalities are associated with neuropsychological impairments.

Abundant evidence has shown that cocaine withdrawal induces memory decline after its chronic use. It has been reported that chronic cocaine users showed significant harm on verbal memory and fluency as well as deficits in cognitive flexibility, but not in spatial memory, after acute withdrawal. Further, Briand and colleagues observed that object recognition was disturbed after withdrawal from chronic exposure to cocaine by an object recognition task in 2-week abstinent rats [29]. Several reports have shown that the insular and prefrontal cortices, involved in cognitive control, show reduced activity on selective attention and inhibitory

control tasks in cocaine addicts [30]. These brain areas may be involved in the maintenance and relapse of drug use [31]. Individuals with cocaine abuse and dependence show higher insula, frontal and/or striatum activation in response to cocaine-related cues, reflecting heightened attention in response to this drug [32, 33]. Furthermore, imaging data have revealed that gray matter volume loss over time is twice as fast among cocaine addicts as in healthy individuals. Given that gray matter volume in prefrontal cortex has been related to working memory performance, these findings are in keeping with the idea that long-term cocaine use may cause sustained deleterious effect on working memory.

3. Depressant drugs

Adolescence is the critical period for initiation of alcoholic beverage consumption. Epidemiologic studies reveal that alcohol use is remarkably common among teenagers, with increasing rates of alcohol abuse in the US including heavy episodic drinking [33]. After alcohol and tobacco, marijuana is the social drug most frequently consumed by this cohort. Additionally, a high percentage of alcohol abusers also consume marijuana [34]. Several studies have shown that both alcohol and marijuana tend to alter the structure and function of the brain and are associated with impaired decision-making, memory and impulsivity in young adults and adolescents (**Table 1**).

3.1. Ethanol

Evidence shows a direct correlation between early onset of alcohol intake and alcohol-related problems in adulthood, suggesting that adolescent exposure to the reinforcing properties of this drug increases the probability of its abuse later [35]. However, as for other addictive substances, the effect of exposure to alcohol depends to a great extent on how much and for how long it is consumed.

Acute alcohol intake has a biphasic effect on brain activity, causing excitation and euphoria at low blood concentration and depression as it increases [36]. However, regarding cognitive functions, experimental data have been inconsistent using a variety of cognitive tests. Thus, low or moderate doses of alcohol, relative to placebo, produced facilitation [37, 38], deficits [39] or no change [40] in memory performance at subtoxic amounts (<65 mg/dl). Moreover, it apparently does not produce adverse effects and may even slightly improve working memory in nonproblem drinkers, regardless of sex [41]. However, as the dose of alcohol increases, confusion, loss of awareness and selective attention begin to occur, significantly diminishing the execution of working memory and its long-term consolidation. The effect of alcohol on long-term memory formation is much greater than its impact on the capacity to remember previously consolidated memories or to retrieve short-term memory. It is well known that if subjects are asked to repeat newly acquired information following short delays (seconds) after its presentation while intoxicated, they often do fine [42]. Likewise, they are able to retrieve information acquired before acute intoxication. On the contrary, subjects perform very poorly using delays longer than 20 min, particularly if they are distracted between the stimulus presentation and testing [43].

As studies indicate that the extent of alcohol-induced memory deficits increases with the dose but maintains the same pattern (i.e., greater difficulty at forming new long-term memories than recalling the existing ones), it appears that this drug mostly affects memory consolidation.

Unfortunately, during adolescent life, repeated intoxication with high doses of alcohol becomes more frequent and memory impairments are more profound, commonly resulting in blackouts, that is, a complete incapability to remember all or part of a drinking event [44]. Heavy alcohol drinking associated with blackouts [45] does not necessarily involve loss of consciousness, but rather a failure to transfer information from short- to long-term memory [46]. Individuals with a history of blackouts show episodic memory impairments while intoxicated [47], particularly at retrieving the spatiotemporal context of events [48]. Moreover, long-term (3 years) heavy alcohol intake in adolescents between 15 and 19 years of age induced memory deficits [49] as well as volume reduction in subcortical and temporal regions [50].

The mechanisms underlying alcohol-induced memory disruption are still elusive. Throughout several decades, it was supposed that alcohol produces a nonspecific general depression of brain activity. Later, research led to assumption that alcohol depressed the activity of neurons by altering the fluidity of the neuronal membrane and consequently the activity of proteins, including ion channels that might, in turn, produce synaptic dysfunctions [51].

It was not until recently that new pharmacological information regarding the effects of alcohol on neural cells revealed that this drug has actually very selective effects on various neurotransmitter systems, both excitatory, e.g., glutamatergic and cholinergic, and inhibitory, such as GABAergic, glycinergic and serotonergic among others. Alcohol could alter the activity of specific receptor subtypes as well [52]. All these neurotransmission mechanisms have a deep impact on cognitive functions. Paradoxically, repeated alcohol exposure might promote the formation of a particular drug-reward–associated implicit memory that could underlay its addiction [53].

The main risk of alcohol ingestion early in life is that the adolescent brain is still in a maturation period and drug intoxication greatly affects its development and the individual's future life.

3.2. Cannabis

Recently, endocannabinoids, endogenous ligands that bind to and activate the same receptors as 9-delta-tetrahydrocannabinol (THC), the psychoactive component of cannabis, were found to play an important role in the diminution of gray matter [3]. Cannabis is the third most prevalent drug of abuse among teenagers, behind alcohol and tobacco [54]. Many studies in humans have shown that chronic cannabis consumption, especially when initiated early in life, correlates with a range of cognitive impairments in adulthood, including learning and memory deficits. Meanwhile, the evidence remained equivocal, partly due to the myriad of confounding factors, characteristic of human studies, as well as different methodology employed by the distinct studies, some unveiling clear effects, while others finding marginal or no effects [55]. However, in recent years, a clearer picture is emerging, which seems to suggest that teenage cannabis consumption may indeed have long-term detrimental effects on cognitive processes, including memory. The present section surveys the evidence linking adolescent cannabis consumption

and prevailing memory deficits. We will further discuss the present state of knowledge on such questions as how is it that cannabis consumption can affect memory? Is memory homogenously affected or are there certain types of memory more impaired? Also, if cannabis intake during adolescence affects brain function in the long-term, are such sequelae reversible?

First, as for the acute effects of marijuana consumption, impaired working memory during the acute phase of cannabis intoxication has been observed in several studies [55, 56]. For instance, randomized clinical trials with dronabinol, a synthetic derivate of THC, revealed impaired verbal fluency, working memory and executive functions in healthy subjects during and in the hours following intoxication [57]. On the other hand, other works on healthy subjects found that performance on verbal working memory was left unaffected but that the tasks elicited a higher activation of parahippocampal areas, which may indicate either "neurophysiological inefficiency" or alternate/compensatory neural mechanisms in these subjects [58]. This is consistent with another fMRI study that was conducted on otherwise healthy adults that were current marijuana users and that showed hyperactivation during a verbal working memory challenge, which the authors suggest may be related to suboptimal efficiency during cognitive challenge in this group [59]. Finally, another study by the same group showed that the frequency of cannabis use is positively correlated to blood oxygenation level–dependent signal in the left parahippocampal gyrus during a visual associative memory task, regardless of the age of onset (early vs. late adolescence) [60].

But beyond the acute intoxication phase, one obvious question is whether cannabis consumption produces long-term sequelae on cognition. Working memory performance appears to be especially sensitive to cannabis consumption in the early teenage years (before the age of 16–17). Testing 122 long-term heavy cannabis users on a corroborated 28-day abstinence period and 87 control subjects, Pope and collaborators showed that although adult-onset cannabis users hardly differed from controls, those that started before the age of 17 were impaired in a series of cognitive tests, most especially in verbal memory [61]. Further research has shown that the observed cannabis-induced deficits may prevail even after 6 weeks of discontinuation; although after 3 months of complete discontinuation, no difference was observed between previous heavy users and controls [62]. However, a more recent study in adolescents 18–20 years old with a history of chronic, heavy cannabis use, while performance in a verbal memory test was comparable to that of age-matched controls, a significant bilateral atrophy was observed, even after 6 months of supervised drug abstinence [63]. The putative detrimental effects of cannabis use appear to be dose-dependent. For example, performance in the Rey Auditory Verbal Learning Test correlated negatively with the number of years of cannabis misuse [64].

However, these results did not allow to determine whether cannabis had long-term detrimental effects on the cognitive abilities and brain functioning of these youths once they reached adulthood or whether a preexisting set of slight cognitive deficiencies such as lower verbal memory somewhat predisposed these youths to maladaptive behaviors including early-onset cannabis consumption. More to the point, as the authors pointed out, even if the toxic effects of cannabis were the culprit, it was impossible to determine in the light of these results, whether the observed differences were due to long-term effects of cannabis on these subjects or more short-term effects during adolescence that made them perform poorly at school and therefore made them less prone to develop these cognitive skills through adulthood.

In this regard, a recent widely reaching analysis from the Cannabis Cohorts Research Consortium using data from three distinct longitudinal studies started to shed light on this issue [57]. The study found that young adults that were cannabis users as teenagers were more likely to experience adverse outcomes as diverse as cannabis addiction, suicide attempt and high-school dropout. Importantly, the authors report that controlling for the potential confounding factors present, both before and during adolescence and spanning individual, parental and peer factors, failed to abolish most of the associations observed. Along with the fact that they also observed a dose-response relation, heavy users having the poorest outcomes as adults, the findings support the hypothesis that teenage marijuana consumption has long-term detrimental effects on cognition, memory and general well-being. Finally, preclinical research brought further support for a causal relationship between teenage cannabis consumption and adult cognitive impairments; chronic consumption of cannabis in rats during adolescence, but not adulthood, impaired spatial working memory when tested as adults [65, 66].

4. Prescription drugs

According to the Anxiety and Depression Association of America, mental disorders are common among children in the United States. Anxiety and major depression disorders are usually diagnosed in children between 8 and 15 years of age (National Health and Nutrition Examination Survey). The treatment of metal disorders in children and adolescents depends on the impairment degree. However, these treatments usually include drugs that affect cognitive functions. On the other hand, during childhood and adolescence, sports activities, especially at college levels, are frequently a cause of painful injuries that requires acute or chronic treatment of anti-inflammatory and/or analgesic drugs. All these treatments that are administered to school students could have an impact on cognitive functions and therefore on academic achievement. In this section, we will discuss the effects of nonsteroidal anti-inflammatory, anxiolytic and antidepressant drugs (**Table 2**).

4.1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are therapeutic agents commonly used in clinical practice for their analgesic, anti-inflammatory and antipyretic activity [67]. Although these chemical compounds are structurally different, they all inhibit both isoforms of the cyclooxygenase enzyme, COX-1 and COX-2, an enzyme responsible for inflammation and pain, which is necessary for prostaglandins and prostanoid synthesis [68]. Normally, COX-2 is expressed in dendritic spines of hippocampal and cortex neurons and has been implicated in synaptic modification, because its expression increases during long-term potentiation [69]. Moreover, astrocytes express prostaglandin E2 receptors (EP) and prostaglandin E2 (PGE2), which regulate membrane excitability, synaptic transmission and synaptic plasticity implicated in learning and memory processes [70]. Also, the administration of misoprostol, an agonist of PGE2 receptors, ameliorates the long-term deficits observed in Huntington disease R6/1 mice by increasing the branching in hippocampal neurons and stimulating the synthesis of brain-derived neurotrophic factor (BDNF) [71].

Drug	Cognitive process	Effect	Model	Reference
Prescription drugs	Spatial memory impairment	Acute administration: Neuroprotection Subchronic administration: improving cognitive functions Chronic administration: improve spatial memory impairment	Rat Mouse	[70–75]
	Cognitive and emotional alterations	Reestablishment of the deterioration in memory and spatial learning Diminish despair and memory impairment Chronic administration: increase cell proliferation in hippocampus Increase of BDNF levels	Human Rat	[78, 81–86]
	Memory and learning impairment	Restore cognitive impairment Improve executive function Increase spatial memory	Mouse	[88–90]
Cognition-enhancing drugs	Formation of memories and performing tasks	Enhancing cognitive performance in Alzheimer's disease patients Improve cognitive functions as: verbal memory, attention memory, information processing, executive function and memory mood	Human	[95, 96]
	Alertness and enhance cognition	Improves attention, memory and executive function in sleep-deprived individuals Limited effects in nonsleep deprived Mental performance of subjects with low baseline performance	Human	[101–105]
	Attention deficit/ hyperactivity disorder	Improve cognition processes as: working memory, speed of processing, verbal learning and memory and attention	Human Rat	[107–109, 111]

Table 2. Effects of the prescription and cognition-enhancing drugs in cognitive functions.

Furthermore, subchronic administration of acetylsalicylic and ascorbic acids increases expression of receptors related with cognitive function such as learning and memory, while chronic treatment of acetylsalicylic acid lessens the spatial memory impairment observed in an experimental model of Alzheimer's disease [72]. Several reports indicate that celecoxib, a selective COX-2 inhibitor, reduces oxidative stress in a model of hypoxia reoxygenation, reducing the activation of microglia and astrocytes in the neonatal rat brain and improving cognitive function, suggesting that celecoxib may have neuroprotective actions [73]. In addition, multiple exposures to sevoflurane, a model that mimics the neurotoxicity induced by anesthesia, produces an increase in proinflammatory cytokines and deterioration in cognitive function in young mice, effects that were attenuated by the administration of ketorolac [74]. Another

study showed that meloxicam ameliorated the depressive-like behavior, cognitive impairment and neuroinflammation in hippocampus caused by chronic unpredictable mild stress [75]. Then, NSAIDs indirectly could disrupt cognitive functions.

4.2. Antidepressant drugs

Major depression is a common mental disorder affecting adolescents in the United States. According to the National Institute of Mental Health, in 2015, an estimated of 3 million adolescents aged 12–17 in the United States had, at least, one major depressive episode. Major depressive disorder is a long-term disabling condition occurring with relapse and recurrences, which could become a chronic condition [76]. Among all the symptoms presented in this psychopathology, memory and attention deficits are considered an important clinical manifestation of major depressive disorder [77]. Furthermore, cognitive and emotional alterations observed in depressive patients have been associated with changes in neuronal activity of prefrontal cortex, cingulate cortex and hippocampus. In major depressive disorder, orbitofrontal, ventromedial and prefrontal cortices are hypoactive, and postmortem evidence indicates histopathological changes in orbitofrontal and prefrontal cortex [78]. Additionally, significant hyperactivity in anterior cingulated cortex, inferior frontal gyrus and occipitoparietal regions has been observed in adolescents with major depressive disorder [79]. Also, a reduction in the volume of the hippocampus was reported, which is related to the severity and the duration of the major depressive disorder [80]. All these alterations were shown to contribute to changes in cognitive and emotional processing in depressive patients. Nevertheless, antidepressant treatment contributed to reestablish mood and cognitive functions. For instance, the chronic administration of deprenyl, a monoamine-oxidase-B inhibitor, reestablished the deterioration in memory and spatial learning and also diminished the lipid peroxidation and the neuronal loss in prefrontal cortex, striatum and hippocampus [81]. Moreover, treatment with desipramine, a norepinephrine reuptake inhibitor, caused reestablished long-term potentiation and diminished despair and memory impairment, through activation of CREB in the hippocampus [82]. Similar effects were observed with fluoxetine (serotonin reuptake inhibitor); rats receiving a chronic treatment of fluoxetine increased cell proliferation and BDNF in hippocampus associated to a memory and learning improvement [83]. These studies suggest that antidepressants revert memory and learning deterioration observed in animal models of depression.

Regarding clinical studies, patients with major depressive disorder showed lower levels of BDNF in plasma, which correlates with memory function deficits; hence, BDNF levels increased after the antidepressant treatment [84]. Nevertheless, the impairment in psychomotor and memory processes observed in depressed treated patients has no significance for clinical purposes [85]. Moreover, some evidence has shown that conventional antidepressant treatment selectively diminishes cognitive dysfunction [86].

The involvement of antidepressant drugs in cognitive functions is not clear; however, animal model studies have shown that synaptic plasticity is increased in neuronal regions involved in mood and memory processing [81–84].

4.3. Anxiolytics

Cognitive impairments have been consistently reported in anxiety disorders. Benzodiazepine, which acts in a specific site of the GABA A receptor, has been, for many years, the first-line therapy for the treatment of anxiety disorders. Although benzodiazepines are attractive for their rapid therapeutic effect, these drugs have undesirable side effects both in the short term (e.g., sedation) and in the long-term (e.g., dependence and memory impairment [87]). Some reports have indicated that GABAergic neurotransmission in the hippocampus is involved in the modulation of learning and memory functions [88]. Also, the administration of an inverse agonist of α5 subtype GABA A receptors (RO4938581) enhances long-term potentiation in hippocampus, restores the cognitive impairment caused by the scopolamine treatment and improves the executive function in monkeys without affecting emotional state [89]. Furthermore, a partial inverse agonist of α5 subtype GABA A receptors increased spatial memory [90]. These studies indicate that GABAergic neurotransmission regulates memory and learning processes, which opens the possibility of designing new selective molecules with clinical utility, not just for treating anxiety disorders, but also for improving cognitive functions.

5. Cognition-enhancing drugs

The search for drugs that improve cognitive functions to treat several diseases, including Alzheimer disease (AD), attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), has derived a wide number of synthetic drugs that, in turn, increase learning, executive functions, or creativity in healthy people. These drugs, also named "smart drugs" or "nootropics," have different chemical origins and mechanisms and in general have showed little or no effect in improving learning and memory tasks. There is a growth in the consumption of these drugs by adolescents [91, 92], mainly due to academic demands and competitiveness [93]. According to the Federal Substance Abuse and Mental Health Services Administration, every year around 137,000 college students in the US begin to use psychostimulants. Furthermore, consumption of stimulant drugs of abuse increases in key academic dates (**Table 2**) [94].

Nootropics have focused their targets on modulation of neurotransmission, hormones, transduction systems and neuron metabolism. However, we will focus on legal stimulants commonly used by students to improve academic performance: acetylcholinesterase inhibitors, memantine, modafinil and methylphenidate.

5.1. Antidementia drugs

5.1.1. Acetylcholinesterase inhibitors (AChEIs)

Most of the drugs that are used to enhance cognitive functions, both in patients and in healthy volunteers, work through acetylcholine (ACh) neurotransmission. ACh is a neurotransmitter closely involved in synaptic transmission and also in the formation of memories and performing tasks. Donepezil, rivastigmine or galantamine had good results enhancing cognitive

performance in patients with mild to moderate AD, when compared with placebo [95]. However, diverse studies conducted in healthy volunteers have showed that AChEIs lightly improve verbal memory after semantic processing of words, attention memory, information processing, executive function and memory mood [96].

5.1.2. Memantine

Memantine is a psychostimulant used to treat moderate to severe AD. It acts on the glutamatergic system by antagonizing N-methyl-D-aspartate (NMDA) receptors. This drug has been showed to slightly improve cognitive functions as monotherapy of AD [97]. There are few studies about the cognitive-enhancing capacity of memantine on healthy volunteers. The studies published were tested with acute single dose of memantine, finding that this drug does not increase mental performance significantly [96].

5.2. Modafinil

Modafinil is a psychostimulant indicated in the treatment of narcolepsy, shift work sleep disorder and excessive daytime sleepiness [98]. Since approval by FDA, in 1998, modafinil has been widely used not only to treat wakefulness disorders, but also to increase alertness and enhance cognition. Modafinil exhibits advantages among other psychostimulants, including the lack of unwanted side effects (e.g., tolerance, abuse potential, sleep rebound and locomotor excitability) [99], and, in most countries, it is not a controlled substance; therefore, it can be easily purchased online. Modafinil exerts its actions through an unknown mechanism. Still, it is recognized that modafinil inhibits dopamine and noradrenaline uptake, elevates catecholamine's levels, therefore raises extracellular serotonin, glutamate, histamine and orexin and reduces GABA's concentration [100]. Although the effects of modafinil as a wakefulness promoter have been proven [101], its properties as cognitive enhancer are still controversial. In sleep-deprived individuals, modafinil improves attention, memory and executive function [102], while the effects of modafinil in non–sleep-deprived adolescents are limited [103]. Other reports have found that modafinil actually improves several cognitive functions [104]. Interestingly, modafinil has showed to enhance mental performance of subjects with low baseline performance or IQ on several tasks evaluated [105].

5.3. Methylphenidate (MPH)

MPH (Ritalin©) is a psychostimulant approved for the treatment of attention deficit/hyperactivity disorder (ADD/ADHD) [106]. Additionally, MPH is one of the most effective cognitive enhancers used by healthy people [107], because it acts through a mechanism analogous to that of cocaine: increases the levels of the catecholamines, dopamine, norepinephrine and serotonin, by blocking their transport [108]. This drug improves working memory, speed of processing, verbal learning and memory and attention [102]. Nevertheless, MPH effects are not restricted to spatial problems, since it also improves digit span test score [109]. Although MPH has demonstrated to be effective and safe in most of the patients when used in the short term, several side effects have been reported: decrease of appetite, insomnia, headache, irritability, weight loss, sadness, abdominal pain, nausea, somnolence, dizziness, among others.

Several studies have reported that MPH treatment during childhood produces "permanent" changes in behavioral responses to other psychostimulants [110]. Moreover, a recent study made on rats has showed that acute and long-term exposure of adolescents to MHP has important effects on reward-dependent learning and decision [111].

5.4. Considerations about use and misuse of cognition-enhancing drugs

There are some difficulties evaluating the efficacy of smart drugs, mainly due to the heterogeneity of subjects and the differences in the cognitive evaluation methods. Besides, the disparities in the design of the studies have been challenging the evaluation of smart drugs in healthy subjects. However, there are some studies that have used systematic methodology to analyze the literature published on healthy volunteers [96, 97]. According to these reviews, antidementia drugs, AChEIs and memantine enhance cognitive functions in patients with AD; nevertheless, their effects on healthy volunteers appear to be very poor [107]. Another aspect to consider is the interindividual variability of volunteers, because it could be an important reason that masks the cognitive effect of these drugs.

There are also several ethical considerations about the use of psychostimulants in healthy people. Currently, caffeine is the stimulant most commonly used to get alertness. However, the misuse of MPH and modafinil is growing among students, since these drugs are cheap and easy to obtain illegally.

6. Perspectives

Drug abuse and addiction to legal and illegal substances have become a major challenge in western developed and developing societies. Growing evidence has shown that the onset age of drug consumption is around 15 years. At this age, the central nervous system is still under maturation. Childhood and adolescence are critical stages for neural and social development. Therefore, worldwide increasing prevalence of drug abuse among teenagers will certainly have an effect on scholar performance. All the evidence described in the present review suggests that teenagers that consume drugs risk deleterious consequences in their academic growth, since the neural mechanisms targeted by these drugs may have long-term impacts on cognitive functions. Therefore, prevention initiatives and public health programs must be implemented in schools to protect children and teenagers from escalating drug use.

7. Conclusion

In summary, the evidence regarding the possible long-term detrimental effects of teenage drug consumption on learning and memory adds to the increased risk of developing mental disorders, and therefore it should be included in public health information campaigns that seek to encourage delaying and/or reducing drug consumption at this stage of life. The scientific information obtained from studies such as those described above will be of little use without adequate public policies aimed at alleviating this serious problem.

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References

[1] United Nations Office on Drugs and Crime through World Drug Report 2017. Available from: https://www.unodc.org/wdr2017/field/Booklet_1_EXSUM.pdf [Accessed: 2017-08-29]

[2] Kelley AE. Memory and addiction: Shared neural circuitry and molecular mechanisms. Neuron. 2004;**44**:161-179. DOI: 10.1016/j.neuron.2004.09.016

[3] Bossong MG, Niesink RJM. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Progress in Neurobiology. 2010;**92**(3):370-385. DOI: 10.1016/j.pneurobio.2010.06.010

[4] Robbins T, Everitt B, David N, editors. The neurobiology of addiction. 1st ed. The Royal Society; 2008. Available from: https://global.oup.com/academic/product/the-neurobiology-of-addiction-9780199562152?cc=mx&lang=en Accessed 2017-09-21

[5] Henry KL. Academic achievement and adolescent drug use: An examination of reciprocal effects and correlated growth trajectories. The Journal of School Health. 2010;**80**(1):38-43. DOI: 10.1111/j.1746-1561.2009.00455.x

[6] Bryant AL, Zimmerman MA. Examining the effects of academic beliefs and behaviors on changes in substance use among urban adolescents. Journal of Education & Psychology. 2002;**94**(3):621-637. DOI: 10.1037/0022-0663.94.3.621

[7] Crosnoe R. The connection between academic failure and adolescent drinking in secondary school. Sociology of Education. 2006;**79**(1):44-60 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834180/

[8] Jasper LE. Working Memory and Long-Term Abstinence from Substance Use. 2016. PhD Thesis, George Fox University

[9] Hall FS, Der-Avakian A, Gould TJ, Markou A, Shoaib M, Young JW. Negative affective states and cognitive impairments in nicotine dependence. Neuroscience and Biobehavioral Reviews. 2015;**58**:168-185. DOI: 10.1016/j.neubiorev.2015.06.004

[10] Grundey J, Amu R, Ambrus GG, Batsikadze G, Paulus W, Nitsche MA. Double dissociation of working memory and attentional processes in smokers and non-smokers with and without nicotine. Psychopharmacology. 2015;**232**(14):2491-2501. DOI: 10.1007/s00213-015-3880-7

[11] Jasinska AJ, Zorick T, Brody AL, Stein EA. Dual role of nicotine in addiction and cognition: A review of neuroimaging studies in humans. Neuropharmacology. 2014;**84**:111-122. DOI: 10.1016/j.neuropharm.2013.02.015

[12] Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: implications for nicotine dependence treatment. Neuropharmacology. 2014;**76**(Pt B):581-591. DOI: 10.1016/j.neuropharm.2013.04.034

[13] Gould TJ, Leach PT. Cellular, molecular, and genetic substrates underlying the impact of nicotine on learning. Neurobiology of Learning and Memory. 2014;**107**:108-132. DOI: 10.1016/j.nlm.2013.08.004

[14] Freedman R. Agonistas del receptor α7-nicotínico de la acetilcolina para la mejora cognitiva en la esquizofrenia. Revisión Anual de la Medicina. 2014;**65**:245-261. DOI: 10.1146/annurev-med-092112-142937

[15] Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: Monoaminergic modulation. Annual Review of Neuroscience. 2009;**32**:267-287. DOI: 10.1146/annurev.neuro.051508.135535

[16] Dineley KT, Pandya AA, Yakel JL. Nicotinic ACh receptors as therapeutic targets in CNS disorders. Trends in Pharmacological Sciences. 2015;**36**(2):96-108. DOI: 10.1016/j.tips.2014.12.002

[17] Harlé KM, Zhang S, Schiff M, Mackey S, Paulus MP, Yu AJ. Altered statistical learning and decision-making in methamphetamine dependence: Evidence from a two-armed bandit task. Frontiers in Psychology. 2015;**6**:1-14. DOI: 10.3389/fpsyg.2015.01910

[18] Dwoskin LP, Glaser PE, Bardo MT. Methamphetamine. In: Addiction Medicine. New York: Springer; 2010. pp. 1049-1061. DOI: 10.1007/978-1-4419-0338-9_52

[19] Bigdeli I, Nikfarjam-Haft Asia M, Miladi-Gorji H, Fadaei A. The spatial learningand memory performance in methamphetamine-sensitized and withdrawn rats. Iranian Journal of Basic Medical Sciences. 2015;**18**:234-239. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25945235 [Accessed: 29-08-2017]

[20] Casaletto KB, Obermeit L, Morgan EE, Weber E, Franklin DR, Grant I, Woods SP. Depression and executive dysfunction contribute to a metamemory deficit among individuals with methamphetamine use disorders. Addictive Behaviors. 2015;**0**:45-50. DOI: 10.1016/j.addbeh.2014.08.007

[21] Cox BM, Cope ZA, Parsegian A, Floresco SB, Aston-Jones G, See RE. Chronic methamphetamine self-administration alters cognitive flexibility in male rats. Psychopharmacology. 2016;**233**(12):2319-2327. DOI: 10.1007/s00213-016-4283-0

[22] Thanos PK, Kim R, Delis F, Rocco MJ, Cho J, Volkow ND. Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. Behavioural Brain Research. 2017;**320**:282-290. DOI: 10.1016/j.bbr.2016.12.010

[23] Stewart JL, Connolly CG, May AC, Tapert SF, Wittmann M, Paulus MP. Striatum and insula dysfunction during reinforcement learning differentiates abstinent and relapsed methamphetamine-dependent individuals. Addiction. 2014;**109**(3):460-471. DOI: 10.1111/add.12403

[24] Morgan EE, Woods SP, Poquette AJ, Vigil O, Heaton RK, Grant I. Visual memory in methamphetamine-dependent individuals: Deficient strategic control of encoding and retrieval. The Australian and New Zealand Journal of Psychiatry. 2012;**46**(2):141-152. DOI: 10.1177/0004867411433212

[25] Latvala A, Castaneda AE, Peräla J, Saarni SI, Aalto-Setäla T, Lönnqvist J, Kaprio J, Suvisaari J, Tuulio-Henriksson A. Cognitive functioning in substance abuse and dependence: A population-based study of young adultsadd. Addiction. 2009;**104**:1558-1568. DOI: 10.1111/j.1360-0443.2009.02656.x

[26] Rendell PG, Mazur M, Henry JD. Prospective memory impairment in former users of methamphetamine. Psychopharmacology. 2009;**203**:609-616. DOI: 10.1007/s00213-008-1408-0

[27] Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet. 2012;**379**:55-70. DOI: http://dx.doi.org/10.1016/S0140-6736(11)61138-0

[28] Amin B, Andalib S, Vaseghi G, Mesripour A. Learning and memory performance after withdrawal of agent abuse: A review. Iranian Journal of Psychiatry and Behavioral Sciences. 2016;**10**(2):e1822. DOI: 10.17795/ijpbs-1822

[29] Naqvi NH, Bechara A. The insula and drug addiction: An interoceptive view of pleasure, urges, and decision-making. Brain Structure & Function. 2010;**214**:435-450. DOI: 10.1016/j.pbb.2009.08.005

[30] Goldstein RZ, Craig AD, Bechara A, Garavan H, Childress AR, Paulus MP, Volkow ND. The neurocircuitry of impaired insight in drug addiction. Trends in Cognitive Sciences. 2009;**13**(9):372-380. DOI: 10.1016/j.tics.2009.06.004

[31] Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Brady KT. Prospective associations between brain activation to cocaine and no-go cues and cocaine relapse. Drug and Alcohol Dependence. 2013;**131**:44-49. DOI: 10.1016/j.drugalcdep.2013.04.008

[32] Prisciandaro JJ, McRae-Clark AL, Myrick H, Henderson S, Brady KT. Brain activation to cocaine cues and motivation/treatment status. Addiction Biology. 2014;**19**(2):240-249. DOI: 10.1111/j.1369-1600.2012.00446.x

[33] Stewart JL, Connolly CG, May AC, Tapert SF, Wittmann M, Paulus MP. Cocaine dependent individuals with attenuated striatal activation during reinforcement learning are

more susceptible to relapse. Psychiatry Research. 2014;**223**(2):129-139. DOI: 10.1016/j.pscychresns.2014.04.014

[34] Martin CS, Kaczynski NA, Maisto SA, Tarter RE. Polydrug use in adolescent drinkers with and without DSM-IV alcohol abuse and dependence. Alcoholism, Clinical and Experimental Research. 1996;**20**:1099-1108. DOI: 10.1111/j.1530-0277.1996.tb01953.x

[35] Vitali M, Napolitano C, Berman MO, Minuto SF, Battagliese G, Attilia ML, Braverman ER, Romeo M, Blum K, Ceccanti M. Neurophysiological measures and alcohol use disorder (AUD): Hypothesizing links between clinical severity index and molecular neurobiological patterns. Journal of Addiction Research & Therapy. 2016;**5**(2):1-17. DOI: 10.4172/2155-6105.1000181

[36] Harrison NL, Skelly MJ, Grosserode EK, Lowes DC, Zeric T, Phister S, Salling MC. Effects of acute alcohol on excitability in the CNS. Neuropharmacology. 2017;**122**:36-45. DOI: 10.1016/j.neuropharm.2017.04.007

[37] Gilbertson R, Ceballos NA, Prather R, Nixon SJ. Effects of acute alcohol consumption in older and younger adults: perceived impairment versus psychomotor performance. Journal of Studies on Alcohol and Drugs. 2009;**70**(2):242-252. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653610/pdf/jsad242.pdf Accessed: 2017-08-29

[38] Sklar AL, Gilbertson R, Boissoneault J, Prather R, Nixon SJ. Differential effects of moderate alcohol consumption on performance among older and younger adults. Alcoholism, Clinical and Experimental Research. 2012;**36**(12):2150-2156. DOI: 10.1111/j.1530-0277.2012.01833.x

[39] Friedman TW, Robinson SR, Yelland GW. Impaired perceptual judgment at low blood alcohol concentrations. Alcohol. 2011;**45**:711-718. DOI: 10.1016/j.alcohol.2010.10.007

[40] Dry MJ, Burns NR, Nettelbeck T, Farquharson AL, White JM. Dose-related effects of alcohol on cognitive functioning. PLoS One. 2012;**7**(11):e50977. DOI: 10.1371/journal.pone.0050977

[41] Hoffman L, Nixon SJ. Alcohol doesn't always compromise cognitive function: Exploring moderate. Doses in young adults. Journal of Studies on Alcohol and Drugs. 2015;**76**(6):952-956. DOI: 10.15288/jsad.2015.76.952

[42] Ryback RS. The continuum and specificity of the effects of alcohol on memory. A review. Quarterly Journal of Studies on Alcohol. 1971;**32**(4):995-1016

[43] Acheson SK, Stein RM, Swartzwelder HS. Impairment of semantic and figural memory by acute ethanol: Age-dependent effects. Alcoholism, Clinical and Experimental Research. 1998;**22**(7):1437-1442. DOI: 10.1111/j.1530-0277.1998.tb03932.x

[44] White AM, Jamieson-Drake DW, Swartzwelder HS. Prevalence and correlates of alcohol-induced blackouts among college students: Results of an e-mail survey. Journal of American College Health. 2002;**51**(3):117-119 (122-131). DOI: http://dx.doi.org/10.1080/07448480209596339

[45] Wetherill RR, Fromme K. Alcohol-induced blackouts: A review of recent clinical research with practical implications and recommendations for future studies. Alcoholism, Clinical and Experimental Research. 2016;**40**(5):922-935. DOI: 10.1111/acer.13051

[46] White AM. What happened? Alcohol, memory blackouts, and the brain. Alcohol Research & Health. 2003;**27**(2):186-196. Available from: https://pubs.niaaa.nih.gov/publications/arh27-2/186-196.pdf [Accessed: 29-08-2017]

[47] Wetherill RR, Fromme K. Acute alcohol effects on narrative recall and contextual memory: An examination of fragmentary blackouts. Addictive Behaviors. 2011;**36**(8):886-889. DOI: 10.1016/j.addbeh.2011.03.012

[48] Wetherill RR, Schnyer DM, Fromme K. Acute alcohol effects on contextual memory BOLD response: Differences based on fragmentary blackout history. Alcoholism, Clinical and Experimental Research. 2012;**36**(6):1108-1115. DOI: 10.1111/j.1530-0277.2011.01702.x

[49] Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: Influence of initiating heavy drinking. Journal of Studies on Alcohol and Drugs. 2012;**73**(5):749-760. DOI: https://doi.org/10.15288/jsad.2012.73.749

[50] Squeglia LM, Rinker DA, Bartsch H, Castro N, Chung Y, Dale AM, Jernigan TL, Tapert SF. Brain volume reductions in adolescent heavy drinkers. Developmental Cognitive Neuroscience. 2014 Jul;**9**:117-125. DOI: 10.1016/j.dcn.2014.02.005

[51] Chin JH, Goldstein DB. Effects of low concentrations of ethanol on the fluidity of spin-labeled erythrocyte and brain membranes. Molecular Pharmacology. 1977;**13**(3):435-441. Available from: http://molpharm.aspetjournals.org/content/13/3/435.long [Accessed: 30-08-2017]

[52] Criswell HE, Simson PE, Duncan GE, McCown TJ, Herbert JS, Morrow AL, Breese GR. Molecular basis for regionally specific action of ethanol on gamma-aminobutyric acid A receptors: Generalization to other ligand-gated ion channels. The Journal of Pharmacology and Experimental Therapeutics. 1993;**267**(1):522-537. Available from: http://jpet.aspetjournals.org/content/267/1/522.long [Accessed: 29-08-2017]

[53] Bernier BE, Whitaker LR, Morikawa H. Previous ethanol experience enhances synaptic plasticity of NMDA receptors in the ventral tegmental area. Journal of Neuroscience. 2011;**31**(14):5205-5212. DOI: 10.1523/JNEUROSCI.5282-10.2011

[54] Degenhardt L, Chiu WT, Sampson N, Kessler RC, Anthony JC, Angermeyer M, Bruffaerts R, de Girolamo G, Gureje O, Huang Y, Karam A, Kostyuchenko, Lepine JP, Medina Mora ME, Neumark Y, Ormel JH, Pinto Meza A, Posada-Villa J, Stein DJ, Takeshima T, Wells JE. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO world mental health surveys. PLoS Medicine. 2008;**5**(7):1053-1067. DOI: https://doi.org/10.1371/journal.pmed.0050141

[55] Schoeler T, Bhattacharyya S. The effect of cannabis use on memory function: An update. Substance Abuse and Rehabilitation. 2013;**4**(January):11-27. DOI: https://doi.org/10.2147/SAR.S25869

[56] Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. Journal of Addiction Medicine. 2011;**5**(1):1-8. DOI: https://doi.org/10.1097/ADM.0b013e31820c23fa.An

[57] Silins E, Horwood LJ, Patton GC, Fergusson DM, Olsson CA, Hutchinson DM, Spry E, Toumbourou JW, Degenhardt L, Swift W, Coffey C, Tait RJ, Letcher P, Copeland J, Mattick RP. Young adult sequelae of adolescent cannabis use: An integrative analysis. The Lancet Psychiatry. 2014;**1**(4):286-293. DOI: https://doi.org/10.1016/S2215-0366(14)70307-4

[58] Bossong MG, Jager G, Bhattacharyya S, Allen P. Acute and non-acute effects of cannabis on human memory function: A critical review of neuroimaging studies. Current Pharmaceutical Design. 2014;**20**(13):2114-2125. DOI: https://doi.org/10.2174/13816128113199990436

[59] Becker B, Wagner D, Gouzoulis-Mayfrank E, Spuentrup E, Daumann J. The impact of early-onset cannabis use on functional brain correlates of working memory. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2010b;**34**(6):83745. DOI: https://doi.org/10.1016/j.pnpbp.2010.03.032

[60] Becker B, Wagner D, Gouzoulis-Mayfrank E, Spuentrup E, Daumann J. Altered parahippocampal functioning in cannabis users is related to the frequency of use. Psychopharmacology. 2010a;**209**(4):361-374. DOI: https://doi.org/10.1007/s00213-010-1805-z

[61] Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: What is the nature of the association? Drug and Alcohol Dependence. 2003;**69**(3):303-310. DOI: https://doi.org/10.1016/S0376-8716(02)00334-4

[62] Schweinsburg AD, Brown SA, Tapert SF. The influence of marijuana use on neurocognitive functioning in adolescents. Current Drug Abuse Reviews. 2008;**1**(1):99-111. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19630709 [Accessed: 29-08-2017]

[63] Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S. Medial temporal structures and memory functions in adolescents with heavy cannabis use. Journal of Psychiatric Research. 2011;**45**(8):1055-1066. DOI: https://doi.org/10.1016/j.jpsychires.2011.01.004

[64] Auer R, Vittinghoff E, Yaffe K, Künzi A, Kertesz SG, Levine DA, Albanese E, Whitmer RA, Jacobs DR Jr, Sidney S, Glymour MM, Pletcher MJ. Association between lifetime marijuana use and cognitive function in middle age. JAMA Internal Medicine. 2016;**176**(3):352-361. DOI: https://doi.org/10.1001/jamainternmed.2015.7841

[65] Renard J, Krebs MO, Jay TM, Le Pen G. Long-term cognitive impairments induced by chronic cannabinoid exposure during adolescence in rats: A strain comparison. Psychopharmacology. 2013;**225**(4):781-790. DOI: https://doi.org/10.1007/s00213-012-2865-z

[66] Renard J, Rushlow WJ, Laviolette SR. What can rats tell us about adolescent cannabis exposure? Insights from preclinical research. Canadian Journal of Psychiatry. 2016;**61**(6):328-334. DOI: https://doi.org/10.1177/0706743716645288

[67] Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, Knaggs R, Martin D, Sampson L, Schofield P. British geriatric society. Guidance on the management of pain in older people. Age and Ageing. 2013;**42**:1-57. DOI: 10.1093/ageing/afs200

[68] Atkinson TJ, Fudin J, Jahn HL, Kubotera N, Rennick AL, Rhorer M. What's new in NSAID pharmacotherapy: Oral agents to injectables. Pain Medicine. 2013;**14**:S11-S17. DOI: 10.1111/pme.12278

[69] Yang H, Chen C. Cyclooxygenase-2 in synaptic signaling. Current Pharmaceutical Design. 2008;**14**:1443-1451. DOI: 10.2174/138161208784480144

[70] Furuyashiki T, Narumiya S. Stress responses: The contribution of prostaglandin E(2) and its receptors. Nature Reviews. Endocrinology. 2011;**7**:163-175. DOI: 10.1038/nrendo.2010.194

[71] Anglada-Huguet M, Vidal-Sancho L, Giralt A, García-Díaz Barriga G, Xifró X, Alberch J. Prostaglandin E2 EP2 activation reduces memory decline in R6/1 mouse model of Huntington's disease by the induction of BDNF-dependent synaptic plasticity. Neurobiology of Disease. 2016;**95**:22-34. DOI: 10.1016/j.nbd.2015.09.001

[72] DoostMohammadpour J, Hosseinmardi N, Janahmadi M, Fathollahi Y, Motamedi F, Rohampour K. Non-selective NSAIDs improve the amyloid-β-mediated suppression of memory and synaptic plasticity. Pharmacology, Biochemistry, and Behavior. 2015;**132**:33-41. DOI: 10.1016/j.pbb.2015.02.012

[73] Fan LW, Kaizaki A, Tien LT, Pang Y, Tanaka S, Numazawa S, Bhatt AJ, Cai Z. Celecoxib attenuates systemic lipopolysaccharide-induced brain inflammation and white matter injury in the neonatal rats. Neuroscience. 2013;**240**:27-38. DOI: 10.1016/j.neuroscience.2013.02.041

[74] Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology. 2013;**118**:502-515. DOI: 10.1097/ALN.0b013e3182834d77

[75] Luo Y, Kuang S, Li H, Ran D, Yang J. cAMP/PKA-CREB-BDNF signaling pathway in hippocampus mediates cyclooxygenase 2-induced learning/memory deficits of rats subjected to chronic unpredictable mild stress. Oncotarget. 2017;**8**:35558-35572. DOI: 10.18632/oncotarget.16009

[76] Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annual Review of Public Health. 2013;**34**:119-138. DOI: 10.1146/annurev-publhealth-031912-114409

[77] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: A systematic review and meta-analysis. Psychological Medicine. 2013;**44**:1-12. DOI: https://doi.org/ 10.1017/S0033291713002535

[78] Klauser P, Fornito A, Lorenzetti V, Davey CG, Dwyer DB, Allen NB, Yücel M. Cortico-limbic network abnormalities in individuals with current and past major depressive disorder. Journal of Affective Disorders. 2015;**173**:45-52. DOI: 10.1016/j.jad.2014.10.041

[79] Colich NL, Ho TC, Foland-Ross LC, Eggleston C, Ordaz SJ, Singh MK, Gotlib IH. Hyperactivation in cognitive control and visual attention brain regions during emotional interference in adolescent depression. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2017;**2**:388-395. DOI: 10.1016/j.bpsc.2016.09.001

[80] Zhao K, Liu H, Yan R, Hua L, Chen Y, Shi J, Lu Q, Yao Z. Cortical thickness and subcortical structure volume abnormalities in patients with major depression with and without anxious symptoms. Brain and Behavior: A Cognitive Neuroscience Perspective. 2017;**7**:e00754. DOI: 10.1002/brb3.754

[81] Kiray M, Bagriyanik HA, Pekcetin C, Ergur BU, Uysal N, Ozyurt D, Buldan Z. Deprenyl and the relationship between its effects on spatial memory, oxidant stress and hippocampal neurons in aged male rats. Physiological Research. 2006;**55**:205-212. Available from: http://www.biomed.cas.cz/physiolres/pdf/55/55_205.pdf [Accessed: 21-09-2017]

[82] Wang DD, Li J, LP Y, MN W, Sun LN, Qi JS. Desipramine improves depression-like behavior and working memory by up-regulating p-CREB in Alzheimer's disease associated mice. Journal of Integrative Neuroscience. 2016;**15**:247-260. DOI: 10.1142/S0219635216500140X

[83] Welbat JU, Sangrich P, Sirichoat A, Chaisawang P, Chaijaroonkhanarak W, Prachaney P, Pannangrong W, Wigmore P. Fluoxetine prevents the memory deficits and reduction in hippocampal cell proliferation caused by valproic acid. Journal of Chemical Neuroanatomy. 2016;**78**:112-118. DOI: 10.1016/j.jchemneu.2016.09.003

[84] Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, Voshaar RC, Elzinga BM. Serum levels of brain-derived neurotrophic factor in major depressive disorder: State-trait issues, clinical features and pharmacological treatment. Molecular Psychiatry. 2011;**16**:1088-1095. DOI: 10.1038/mp.2010.98

[85] Gorenstein C, de Carvalho SC, Artes R, Moreno RA, Marcourakis T. Cognitive performance in depressed patients after chronic use of antidepressants. Psychopharmacology. 2006;**185**:84-92. DOI: 10.1007/s00213-005-0274-2

[86] Bortolato B, Miskowiak KW, Köhler CA, Maes M, Fernandes BS, Berk M, Carvalho AF. Cognitive remission: A novel objective for the treatment of major depression? BMC Medicine. 2016;**14**:9. DOI: 10.1186/s12916-016-0560-3

[87] Rudolph U, Möhler H. GABAA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annual Review of Pharmacology and Toxicology. 2014;**54**:483-507. DOI: 10.1146/annurev-pharmtox-011613-135947

[88] Prut L, Prenosil G, Willadt S, Vogt K, Fritschy JM, Crestani F. A reduction in hippocampal GABAA receptor α5 subunits disrupts the memory for location of objects in mice. Genes, Brain, and Behavior. 2010;**9**:478-488. DOI: 10.1111/j.1601-183X.2010.00575.x

[89] Ballard TM, Knoflach F, Prinssen E, Borroni E, Vivian JA, Basile J, Gasser R, Moreau JL, Wettstein JG, Buettelmann B, Knust H, Thomas AW, Trube G, Hernandez MC. RO4938581, a novel cognitive enhancer acting at GABAA alpha5 subunit-containing receptors. Psychopharmacology. 2009;**202**:207-223. DOI: 10.1007/s00213-008-1357-7

[90] Navarro JF, Buron E, Martin-Lopez M. Anxiogenic-like activity of L-655,708, a selective ligand for the benzodiazepine site of GABAA receptors which contain the alpha-5 subunit, in the elevated plus-maze test. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2002;**26**:1389-1392. DOI: https://doi.org/10.1016/S0278-5846(02)00305-6

[91] Ott R, Biller-Andorno N. Neuroenhancement among swiss students—A comparison of users and non-users. Pharmacopsychiatry. 2014;**47**:22-28. DOI: 10.1055/s-0033-1358682

[92] Schulenberg JE, Johnston LD, O'Malley PM, Bachman JG, Miech RA, Patrick ME. Monitoring the Future National Survey Results on Drug Use, 1975-2016: Volume II, College Students and Adults Ages 19-55. Ann Arbor: Institute for Social Research, The University of Michigan, The University of Michigan; 2017. 445 pp. Available from: http://monitoringthefuture.org/pubs.html#monographs [Accessed: 2017-08-29]

[93] Garasic MD, Lavazza A. Moral and social reasons to acknowledge the use of cognitive enhancers in competitive-selective contexts. BMC Medical Ethics. 2016;**17**:18. DOI: 10.1186/s12910-016-0102-8

[94] Lipari R. The CBHSQ Report: Monthly Variation in Substance Use Initiation among Full-Time College Students Rockville. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality; 2015. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343537 Accessed 2017-09-21

[95] Birks J. Cholinesterase inhibitors for Alzheimer's disease. The Cochrane Database of Systematic Reviews. 2006;**1**:1-3. DOI: 10.1002/14651858.CD005593

[96] Repantis D, Laisney O, Heuser I. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review. Pharmacological Research. 2015;**61**(6):473-481. DOI: 10.1016/j.phrs.2010.02.009

[97] Matsunaga S, Kishi T, Iwata N. Memantine Monotherapy for Alzheimer's disease: A systematic review and meta-analysis. PLoS One. 2015a;**10**(4):e0123289. DOI: 10.1371/journal.pone.0123289

[98] Kumar R. Approved and investigational uses of modafinil: An evidence-based review. Drugs. 2008;**68**(13):1803-1839. DOI: 10.2165/00003495-200868130-00003

[99] Deroche-Gamonet V, Darnaudéry M, Bruins-Slot L, Piat F, Le Moal M, Piazza PV. Study of the addictive potential of modafinil in naive and cocaine-experienced rats. Psychopharmacology (Berl). 2002;**161**:387-395. DOI: 10.1007/s00213-002-1080-8

[100] WM Q, Huang ZL, XH X, Matsumoto N, Urade Y. Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. The Journal of Neuroscience. 2008;**28**:8462-8469. DOI: 10.1523/JNEUROSCI.1819-08.2008

[101] Westenson NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. Journal of Sleep Research. 2005;**14**:255-266. DOI: 10.1111/j.1365-2869.2005.00468.x

[102] Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. Pharmacological Research. 2010;**62**(3):187-206. DOI: 10.1016/j.phrs.2010.04.002

[103] Randall DC, Fleck NL, Shneerson JM, File SE. The cognitive-enhancing properties of modafinil are limited in non-sleep deprived middle-aged adolescents. Pharmacology Biochemistry & Behavior. 2004;**77**:547-555. DOI: 10.1016/j.pbb.2003.12.016

[104] Battleday RM, Brem AK. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. European Neuropsychopharmacology. 2015;**25**:1865-1881. DOI: 10.1016/j.euroneuro.2015.07.028

[105] Randall DC, Shneerson JM, File SE. Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacology Biochemistry & Behavior. 2005;**82**:133-139. DOI: 10.1016/j.pbb.2005.07.019

[106] Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia C, Holmskov M, Skoog M, Holmskov M, Rosendal S, Groth C, Magnusson FL, Moreira-Maia CR, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbol B, Simonsen E, Gluud C. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trialsequential analyses of randomised clinical trials. British Medical Journal. 2015;**351**:h5203. DOI: 10.1136/bmj.h5203

[107] Advokat C, Scheithauer M. Attention-deficit hyperactivity disorder (ADHD) stimulant medications as cognitive enhancers. Frontiers in Neuroscience. 2013;**7**:82. DOI: 10.3389/fnins.2013.00082

[108] Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: Comparison with amphetamine. Journal of Neurochemistry. 1997;**68**:2032-2037. DOI: 10.1046/j.1471-4159.1997.68052032.x

[109] Agay N, Yechiam E, Carmel Z, Levkovitz Y. Non-specific effects of methylphenidate (Ritalin) on cognitive ability and decision-making of ADHD and healthy adults. Psychopharmacology (Berl). 2010;**210**:511-529. DOI: 10.1007/s00213-010-1853-4

[110] Crowley NA, Cody PA, Davis MI, Lovinger DM, Mateo Y. Chronic methylphenidate exposure during adolescence reduces striatal synaptic responses to ethanol. The European Journal of Neuroscience. 2014;**39**(4):548-556. DOI: 10.1111/ejn.12426

[111] LR A, E J-B, MS MM, JD R. Acute and long-term effects of adolescent methylphenidate on decision-making and dopamine receptor mRNA expression in the orbitofrontal cortex. Behavioural Brain Research. 2017;**324**:100-108. DOI: 10.1016/j.bbr.2017.02.019

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