

NEUROENHANCEMENT: STATE OF THE ART AND FUTURE PERSPECTIVES

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Abstract

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Pharmacological neuroenhancement refers to the non-medical use of prescription drugs, alcohol, illegal drugs, or the so-called soft enhancers for the purpose of improving cognition, mood, pro-social behavior, or work and academic performance. This phenomenon is undoubtedly more frequent than previously supposed especially amongst university students.

The aim of the present paper was to carefully review and comment on the available literature on neuroenhancement, according to Prisma guidelines.

The results showed a great use of all prescribed drugs (benzodiazepines, antidepressants, antipsychotics, nootropic compounds, and especially stimulants) as neuroenhancers amongst healthy subjects, although probably the real prevalence is underestimated. The use of illicit drugs and soft enhancers is similarly quite common. Data on the improvement of cognition by other compounds, such as oxytocin and pheromones, or non-pharmacological techniques, specifically deep brain stimulation and transcranial magnetic stimulation, are still limited.

In any case, if it is true that human beings are embedded by the desire to overcome the limits of their intrinsic nature, neuroenhancement practices put into question the concept of authenticity. Therefore, the problem appears quite complex and requires to be deepened and analyzed with no prejudice, although within an ethical conceptual frame.

Key words: neuroenhancement, drugs, university students

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Introduction

Pharmacological neuroenhancement, or cognitive neuroenhancement, refers to the non-medical use of prescription drugs, alcohol or illegal drugs, or of the so-called soft enhancers, such as food supplements (e.g., herbal sedatives, vitamins and tonics), caffeine-containing products, energy drinks, and non-prescription drugs available in drug stores, to enhance cognition, mood, work or school performance, or to promote pro-social behavior (Gründer & Bartsch, 2014; Weiergräber et al., 2017). According to some authors (Middendorff et al., 2017), soft enhancers should not be included in the neuroenhancer category, although their use is quite common especially amongst students (Dietz et al., 2018; Micoulaud-Franchi et al., 2014).

Emotional enhancement is another category of neuroenhancement aiming at modifying an individual's emotions by amplifying and/or enhancing emotional states beyond normal levels of intensity by artificial means. It is noteworthy to underline that emotional enhancement does not induce actively specific emotions, but, on the contrary, it works by passively amplifying and enhancing

the genuine (positive or negative) emotions that usually a person feels before using the enhancer (Kraemer, 2011).

Some authors consider neuroenhancement a sort of an umbrella term referring to different types of interventions whose target is to improve human capacities beyond normal limits, and perhaps as means helping individuals to find their authenticity. According to this notion, it does not recognize any medical targets, because its purpose is to ameliorate wellbeing and consequently quality life of healthy individuals (Gordijn, 2015; Juengst, 1998).

Currently, there are no reliable data about the worldwide prevalence of neuroenhancement practice, for the real difficulties to describe and assess such a phenomenon. Generally, it is inferred from the consumption of non-medical use of prescription drugs, although to differentiate between occasional and more regular use may be quite challenging (Ragan et al., 2013). Students represent a population endowed with a particular risk for possible use of neuro-enhancing substances (Greely et al., 2008; Sahakian & Morein-Zamir, 2007). According to available data, between 5 and 35% of American or Canadian students use neuroenhancers and specifically 2-5% at least once a month and 1-3%

once a week (Outram, 2010), with a constant and progressive increase from high schools to college (McCabe et al., 2005; Wilens et al., 2008). Data in both Europe and Australia report a lower incidence than in the USA or Canada (Eickenhorst et al., 2012; Franke et al., 2011; Maier et al., 2013; Partridge et al., 2013). The difference between USA and European/Australian data is that North-American students have to cope with highly competitive academic contexts, and easily indulge to booster cognitive skills during exams, or to regulate mood, stress or anxiety symptoms that could indirectly impair performances (Lucke et al., 2018; Weyandt et al., 2009).

It should be noted, however, that studies on the prevalence of neuroenhancers show different limitations, so that the conclusions should be taken with cautions. First, most of them are carried out on volunteers, thus implying a selection bias: indeed, subjects using neuroenhancers tend to be too confident on their effects and might influence study outcomes. This gap between perceived benefits and results observed yawns even wider in real-life conditions: 70% of methylphenidate (MPH) users report a positive or very positive effect, so that, not surprisingly, the heavier consumers are those with highest satisfaction scores. Second, the studies are rarely double-blinded and placebo-controlled. Third, they tend to investigate the effect of a substance after a single dose, while information about a repeated use is lacking (National Consultative Ethics Committee for Health and Life Sciences, CCNE, 2013). This may be due to the fact that the prolonged administration of potentially dangerous substances to healthy subjects implies different ethical issues and the epidemiological studies are the only accepted (Heinz et al., 2012). Fourth, just a few studies investigated the reasons for taking the neuroenhancer. In any case, available data are considered unreliable and able to identify only the tip of the iceberg, given the under-reported consumption of neuroenhancers (Wilens et al., 2008).

Drugs that enhance one type of function might have a detrimental impact on another, or people who already function well might not experience any benefit, whereas those with less natural ability might experience only modest effects (Normann & Berger, 2008; Weiergräber et al., 2017). Another important issue is whether statistically significant improvements in cognitive functioning can be translated into practical or clinically significant benefits in real-world contexts. Notwithstanding these caveats, some proponents of neuroenhancement speculate that it will soon become a normal practice, although such a hypothesis is supported by limited evidence.

Furthermore, little is known about possible risk for health of neuroenhancers, being abuse and/or addiction one the major potential risk at least in vulnerable subjects, as neuroenhancers interact with the dopaminergic system (Heinze et al., 2012).

The aim of this paper is to review and comment on current literature on neuroenhancement and, to a lesser extent on emotional enhancement, with some personal and ethical considerations on this topic.

Materials and Methods

According to the PRISMA guidelines (Moher et al., 2009), the databases of PubMed, Scopus, Embase, PsycINFO and Google Scholar were accessed in order to research and collect articles that were published only in English language from 1980 to April 2020. Free text terms and MeSH headings were combined as it follows: “(neuroenhancement OR emotional enhancement) AND

(antidepressants OR benzodiazepines OR antipsychotics OR nootropics OR stimulants OR methylphenidate OR amphetamines OR modafinil OR atomoxetine OR piracetam OR acetyl-cholinesterase inhibitors OR cannabinoids OR hallucinogens OR alcohol OR caffeine OR ginkgo biloba OR hypericum OR oxytocin OR pheromones)”. All the authors agreed to include in the review conference abstracts, posters and case reports if published in indexed journals. The following inclusion criteria were adopted: studies carried out in clinical samples of adults; reliable diagnosis of psychiatric disorders according to structured interviews and standardized criteria; reliable assessment of outcome measures. All the authors equally contributed in identifying potential information specific to this topic amongst the titles and abstracts of the publications. The first selection excluded 10821 titles because: a) duplicates; b) not concerning the scope of the paper; c) not informative enough. The second selection excluded 509 abstracts after being read and reviewed, as the information reported did not fulfill the scope of our paper and/or the presented information did not seem relevant to the discussed topic. Subsequently, 293 more publications were excluded after being completely read and evaluated, as they did not provide enough information and/or resulted sufficiently in line with our review. Finally, 123 papers were included in the present review (figure 1).

Discussion

Neuroenhancement

As already underlined above, neuroenhancement is mostly pharmacological and includes the non-medical use of prescribed drugs, such as benzodiazepines (BDZ) antidepressants (ADs), antipsychotics, prescribed stimulants and nootropic compounds, and of smart or illegal drugs (de Jongh et al., 2008; Maier & Schaub, 2015). Non-pharmacological techniques, including deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) may also improve cognitive functions. Therefore, all these compounds and techniques will be described herein.

Benzodiazepines

Benzodiazepines are used as emotional enhancers thanks to their relaxant and anxiolytic activity. This class of drugs became extremely popular in the 1970s, since they represented a real advancement, as compared with barbiturates, given their relatively safety in overdose. In particular, diazepam (Valium) led to a so-called “Valium-mania”, as it was increasingly used not only for anxiety disorders, but also to deal with everyday life problems, so that it became the most prescribed drug of any types of the seventies (Calcaterra & Barrow, 2014). However, although their benefits remain unequivocal if correctly used, the popularity of BDZs slightly decreased after the mounting evidence of their adverse side effects, including severe seizures and withdrawal symptoms after abrupt discontinuation, or attention deficits, memory impairments, sleepiness and abuse/addiction in the long-term use (Panes et al., 2020; Pieters & Snelders, 2009).

In any case, different data indicate that BDZs are still quite used for their sedating properties for the purpose of neuroenhancement, as it is believed that a quieter and better sleep can improve cognitive performances, especially amongst students, as they are convinced that a relaxed brain is more efficient (Mache et al., 2012; Maier et al., 2013).

Antidepressants

Antidepressants are a class of drugs indicated not only for depression, but also for several other psychiatric conditions, including anxiety disorders, obsessive-compulsive (OCD) spectrum disorders, eating disorders, premenstrual syndrome, or pain syndromes, and several other (Cascade et al., 2007; Hofmeister & Bodden, 2016; Kennedy et al., 2016; Pratt et al., 2017). Not surprisingly they are also abused by an increasing number of healthy individuals (Normann & Berger, 2008).

Fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), was marketed in 1984 and, after a few years, it became known a sort of “miracle drug”, since it was thought as able to reduce negative feelings, induce a general state of psychic well-being and improve social performance even in non-depressed individuals. In 1994 Prozac was the second most-sold drug worldwide (“Prozac-mania”) (Elliott, 2000). According to the American psychiatrist Peter Kramer, Prozac was more than an AD, it was rather a drug that could help people to find their real self and, in other words and ultimately, authenticity (Kramer, 1993). However, Kramer himself underlined that the drug should be used only when necessary, that is to say in depressed patients, so that the ensuing mood increase was with no doubt useful in those individuals who could experience a real change in their life, as they were not suffering any more.

The evidence for the use of ADs in healthy control subjects is limited, even because this phenomenon is mainly hidden. Some studies indicate that ADs may influence emotional processing in healthy individuals by increasing recognition and recall of positive emotions and reducing salience of negative affects (Harmer et al., 2003a; Harmer et al., 2004). Indeed, ADs were found to attenuate the activity of subcortical limbic neural regions during exposition to negative emotional stimuli (Bigos et al., 2008; Del-Ben et al., 2005; Harmer et al., 2006; McKie et al., 2005; Takahashi et al., 2005). A study evaluated participants’ ability to correctly detect subtle expressions of sadness and the results showed that duloxetine (SNRI) might reduce accurate recognition of sadness (Bamford et al., 2015). In another study, volunteers who received a single dose (10 mg i.v) of citalopram (another SSRI) recognized more facial expressions of happiness and fear than those who had taken placebo, while no differences were observed in the recognition of other basic emotions (Harmer et al., 2003b). Subsequently, a 7-day double-blind trial carried out in healthy volunteers (n=42) treated with citalopram (20 mg/day), reboxetine (a norepinephrine-serotonin reuptake blocker) at a dose of 8 mg/day, SNRI, or placebo, highlighted that both citalopram and reboxetine decreased the identification of the negative facial expressions of anger and fear, while enhancing the relative recall of positive emotional material (Harmer et al., 2004). In any case, the available literature indicates that there is no evidence of any effect of ADs on the mood of healthy individuals (Normann & Berger, 2008). Furthermore, these compounds were found to cause emotional blunting, a syndrome which is totally different from apathy, in a significant percentages (30-40 %) of the cases in the long-term use (Marazziti, 2017; Price et al., 2009; Sansone & Sansone, 2010; Wongpakaran et al., 2007). Again, it is still an unresolved issue whether or not ADs, particularly SSRIs, may or may not impair or improve some cognitive domains (Marazziti et al., 2019). According to some authors, cognitive impairment would represent real side effects of SSRI (Fava et al., 2006; Popovic et al., 2015), although, a recent meta-analysis reported that all ADs would produce positive and significant

effects on control and executive functions (Rosenblat et al., 2015). However, further and focused studies are necessary to disentangle some AD side effects from effective symptom improvement that might be positive for patients (table 1).

Antipsychotics

Antipsychotics (As) are a class of psychotropic drugs primarily used in the treatment of psychoses, mainly schizophrenia and bipolar disorders, although they are increasingly being utilized for treatment of non-psychotic disorders (Huhn et al., 2019; Stahl, 2013). Due to their tranquilizer effects, their use amongst healthy individuals is not uncommon. It should be noted that the majority of data refers to first-generation antipsychotics (FGAs) (Gao et al., 2006; Pies, 2009), while information on second-generation antipsychotics (SGAs) is still limited (Miller, 2004). SGAs are often used with other illegal substances, being quetiapine the most abused, followed by olanzapine, risperidone and aripiprazole (Murphy et al., 2008; Reeves, 2007). Usually, antipsychotics are taken with opioids, cocaine and alcohol. Users reported combining As and other psychotropic compounds for different reasons, such as to recover from other drugs’ excessive effects, particularly excitation, or for their sedating effects, or simply as an experiment. Both positive and negative emotional effects are reported, such as feeling happy, friendly and sexy, as well as depressed, anxious and irritable (Malekshahi et al., 2015). (table 1).

Prescribed stimulants

Stimulants, such as methylphenidate (MPH), modafinil, dextroamphetamine and mixed-amphetamine salts (MAS), may increase vigilance, arousal and motivation, through their pharmacological effects on norepinephrine and dopamine systems. Methylphenidate is prescribed worldwide for ADHD. Modafinil is a wakefulness-promoting agent used to treat narcolepsy, sleep apnea and shift-work sleep disorder, and even ADHD in a limited number of cases. Dextroamphetamine and MAS are also used for ADHD and narcolepsy (Mucci et al., 2019; National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK, 2012; Sharbat Shoar et al., 2020; Thorpy & Bogan, 2020).

Not surprisingly, given their activating effects, stimulants are increasingly misused by healthy people, especially by youth and college students, or managers to enhance academic performances (McCabe et al., 2005). However, their abuse in these populations without ADHD diagnosis is a current concern, as it is estimated that about 30 % of specific prescriptions are used for neuroenhancement. The problem is particularly relevant in the USA, where, according to the National Surveys on Drug Use and Health between 2015 and 2016, 6.6% of the adult USA population (approximately 16.0 million) used prescription stimulants, with 1.9% reporting to misuse them, and 0.2% diagnosed with stimulant use disorder. Particularly, 31.2% of stimulant users referred to have misused stimulants at least once, over the preceding 12 months. Amongst motivations reported for misuse, the most common was to increase alertness and concentration (56.3%), followed by to help studying (21.9%) and to get high, adjust other drug effects, or just to experiment (15.5%), and weight loss (4.1%) (Compton et al., 2018).

These prevalence rates are quite astonishing while

Table 1. Use of antidepressants and antipsychotics as neuroenhancers

Authors and year	Type	N	Antidepressant	Method	Results
Bamford et al., 2015	Randomized controlled trial	40	Duloxetine	Generalised Anxiety Disorder Screener (GAD-7), visual analogue scales ranging, positive and negative affect, Cambridge Cognition Emotion Recognition Task	↓ accurate recognition of sadness
Harmer et al., 2003b	Clinical trial	24	Citalopram	The facial expression recognition task featured five basic emotions taken from the Ekman and Friesen Pictures of Affect Series	↑ recognition of facial expressions of happiness and fear ↔ for the other basic emotions
Harmer et al., 2004	Double-blind trial	42	Citalopram, reboxetine	Facial Expression Recognition, Emotional Categorization Task, Emotional Memory, Emotion-Potentiated Startle Response	↓ identification of the negative facial expressions of anger and fear ↑ relative recall of positive emotional material
Rosenblat et al., 2015	Systematic review and meta-analysis	-	Antidepressants	Trials published prior to April 15, 2015, were identified through searching the Cochrane Central Register of Controlled Trials, PubMed, Embase, PsychINFO	↑ control and executive functions
Reeves, 2007	Case-report	A 25-year old man with bipolar disorder	Olanzapine	Olanzapine abuse	
Murphy et al., 2008	Case report	A 29-year old man	Quetiapine	Abuse of quetiapine in a man with an unclear psychiatric history	
Miller, 2004	Cross-sectional	429 inpatients for addiction	Quetiapine, olanzapine, risperidone, aripiprazole	Lifetime abuse of antipsychotics (17%), past year abuse (9.1%); quetiapine (96.0%), olanzapine (28.0%), risperidone (20.0%) and aripiprazole (20.0%)	

considering that effective stimulating activity of stimulants on cognitive performances in healthy individuals are still a matter of debate. However, enhancer users tend to believe that stimulants improve both motivation and cognition, as reported in a study conducted amongst undergraduates of the University of Pennsylvania (n=40) with no history of ADHD (Ilieva & Farah, 2013). Indeed, although a few data indicated that MPH and modafinil might exert a certain positive influence on visuo-spatial memory and attention (Repantis et al., 2010), no direct effect on specific cognitive domains, such as memory or executive functions, has been yet demonstrated (Bagot & Kaminer, 2014; de Jongh et al., 2008; Wood et al., 2013). Interestingly, stimulants seem to increase cognitive performance in subjects with low baseline skills, while showing an opposite effect in those with higher baseline skills (Mattay et al., 2000; Mattay et al., 2003; Mehta et al., 2000; Müller et al., 2004; Randall et al., 2005). If MPH was found not to exert a significant effect on mood and emotions (Spencer et al., 2005), modafinil seems to produce a general mood elevating effect with a simultaneous increase of negative affect and increased reactivity to fearful faces (Schmidt et al., 2017).

In the UK, a study investigating the non-medical use of stimulants among college students of 23 universities of the Russell Group, found that lifetime prevalence use of modafinil, MPH and amphetamine-dextroamphetamine

was, respectively, 8%, 5.9%, and 3.2%, with 20% of the total sample reporting being interested in using stimulants for neuroenhancement. Although cognitive enhancement was the most common reason for using stimulants (approximately three quarters of cases), as expected, other reasons include tackling sleep deprivation, enhancing mood or simply for “curiosity” (Singh et al., 2014). Another study, conducted on a larger sample of academic students (n=6,725) of three different Swiss universities, reported that lifetime prevalence use of MPH and modafinil was 5.8% and 0.4%, respectively, the use for neuroenhancement was, respectively, of 4.1% and 0.3% (Maier et al., 2013). Lower prevalence of use of stimulants for non-medical purposes was reported among Dutch university students. Indeed, only 2.5% of the sample (n=1,572), reported to use MPH as cognitive enhancer, with 2.8% of participants using MPH for non-medical reasons. (Schelle et al., 2015). An Italian study conducted on university students from Northern Italy (n=899) found that 11.3% of the sample took stimulants for non-medical use (MPH or amphetamine) especially if younger, with no gender difference (Majori et al., 2017) (table 2).

Methylphenidate

A double-blind, placebo-controlled study was carried out in healthy volunteers (n=28, men) who were

Table 2. Stimulants - Reasons for use and impact on cognition

Authors and year	Type	N	Stimulant	Method	Results
<i>Reasons for use and college students</i>					
Hanson et al., 2013	Cross-sectional	-	Adderall	Tweets from likely students containing GPS data were identified with clusters of nearby colleges and universities for regional comparison	213633 tweets from 132099 unique user accounts mentioned "Adderall" Rates of Adderall tweeters were highest among college and university clusters in the northeast and south regions of the United States.
Singh et al., 2014	Cross-sectional	877	Adderall	Online survey	1.4% of participants with history of occasional Adderall use, 0.3% with past regular use, 0.3% current use
Palamar & Le, 2017	Cross-sectional	24740	Adderall, Amphetamine	Self-report survey	6.9% and 7.9% with past year use of Adderall and amphetamine, respectively
Lucke et al., 2018	Cross-sectional	1136	Atomoxetine, Modafinil, Adderall, Ritalin,	Online survey	Modafinil lifetime use 2.7%, past month use 1.5%, Adderall 2.9% and 1.0%, Ritalin 2.6% and 0.9%, Atomoxetine 0.1% and 0.0%, respectively
Teodorini et al., 2020	Cross-sectional	219	Modafinil	Online Survey	Most common reasons were "to increase attention", "to work long hours", "to get more done", "exam", "night work", "to think more clearly", and "other"
Ilieva & Farah, 2013	Cross-sectional	40	Adderall, Ritalin and other	Online survey	↑ perception of motivation and cognition
<i>Amphetamine-Dextroamphetamine</i>					
Weyandt et al., 2018	Double-blind, placebo-controlled, within subjects crossover design trial	13	30 mg	Digit Span Forward and Backward, Story Recall subtest from the Woodcock Johnson-III, Conners Continuous Performance Test Third Edition (CPT 3), The Behavior Rating Inventory of Executive Function, Adult version (BRIEF-A), Gray Oral Reading Tests-Fifth Edition (GORT-5), Perceived Drug Effect Self-Report (PDE-SR)	↑ attention ↓ working memory
<i>Atomoxetine</i>					
Chamberlain et al., 2006	Double-blind, placebo-controlled trial	60	60 mg	Go trials, Probabilistic learning task	↑ response inhibition; ↔ probabilistic learning
Graf et al., 2011	Double-blind, placebo-controlled trial	12	80 mg	Go/NoGo-Eriksen flanker paradigm fMRI	↑ neural sensitivity for error; ↓ inhibitory control
<i>Dextroamphetamine</i>					
Rapoport et al., 1980	Double-blind, crossover design trial	31	0.25-0.50 mg/kg	Activity test, Skin-conductance reaction time test, Rosvold's Continuous Performance Test (CPT)2, Learning task, Speech Communication Task	↑ vigilance, speech communication ↑ cues recall and free recall ↓ motor activity ↑ subjective euphoria and energy (dose-dependent effect).

Table 2. Continued

<i>Methylphenidate</i>					
Elliot et al., 1997	Double-blind, placebo-controlled trial	28	20 or 40 mg	CANTAB battery	↑ spatial function in novel performance ↓ impairment in consolidated performance ↔ attention and fluency
Rogers et al., 1999	Double-blind, placebo-controlled, trial	79	40 mg	Intra-/extra-dimensional shift (ID/ED) task	↑ learning about changing stimulus-reward associations, ↑ ability to shift an attentional bias ↓ response times
Volkow et al., 2004	Clinical trial	16	20 mg	Subjects underwent PET during a mathematical task and a neutral task	↑ extracellular dopamine in the striatum ↑ perceived motivation and interest
Linssen et al., 2012	Randomized, double-blind, placebo-controlled, four-way crossover design	19	20 or 40 mg	Visual verbal learning test, Set shifting task, stop signal task,	↑ declarative memory consolidation ↑ cognitive flexibility ↔ spatial working memory and planning
<i>Modafinil</i>					
Baranski & Pigeau, 2007	Randomized, double-blind, placebo-controlled trial	41	300 mg (MOD) 20 mg (d-AMP)	Visual judgement task Complex mental addition task	↓ self-monitoring (MOD) ↔ self-monitoring (d-AMP)
Muller et al., 2004	Randomized, double-blind, placebo-controlled, crossover design trial	16	200 mg	Cognitive task	↓ error rates in the visual-spatial task
Turner et al., 2003	Randomized, double-blind, placebo-controlled trial	60	100 or 200 mg	CANTAB battery	↑ recall, visual memory, spatial planning ↑ perceived alertness and energy
Marchant et al., 2009	Double-blind, placebo-controlled trial	24	200 mg	Attention shift task Prospective memory task	↑ attention-shifting tasks ↑ prospective memory

administered methylphenidate (20 or 40 mg) and tested using a CANTAB battery in two different moments (Elliott et al., 1997). Half of the participants took MPH at the first evaluation and placebo at the second, while others the reverse. The first group obtained significant improvement in spatial working memory tasks, and reported a lower number of errors than the second group. Furthermore, the first group obtained more accurate results in the Tower of London, while the second group experienced a decrease in performance accuracy and response latencies were decreased. These results demonstrated that MPH may enhance spatial function in novel performance, while impairs consolidated performance. Participants reported to feel significantly more alert and less tired. No impact of MPH on attention and fluency emerged, since there were no differences between the two groups in attentive set-shift tasks and verbal fluency subtests. Other controlled studies support the hypothesis that MPH can enhance cognitive ability. As demonstrated by a randomized, double-blind, placebo-controlled, crossover design study, MPH improved the capacity of detecting performance errors in healthy individuals, even after a single dose (30 mg)

(Elliott et al., 1997). Another trial on healthy volunteers reported that MPH (20 or 40 mg) might exert a positive impact on declarative memory consolidation, and improve set shifting and stop signal tasks performance, with no effect on spatial and working memory or planning (Linssen et al., 2012). Additionally, consistent evidence suggests that MPH increases motivation in healthy individuals (Volkow et al., 2004), or response latency shifts compared with placebo (Rogers et al., 1999).

Modafinil

Different studies explored whether or not modafinil might improve cognitive ability in healthy individuals. A double-blind, placebo-controlled study on 24 healthy university students demonstrated that modafinil (200 mg) might enhance attention-shifting tasks, with no impact on task implying unpredictable and infrequent disengagement of attention emerged, as well as prospective memory (Marchant et al., 2009). These results were partially confirmed by another research on adult male volunteers (n=60) administered with a single

dose of modafinil (100 or 200 mg), who showed a better performance than control subjects in tasks involving recall, visual memory, and spatial planning, and reported an increase in alertness, attention and energy (Turner et al., 2003). Again, a controlled study on healthy volunteers (n=16, aged 20-29 years), demonstrated that modafinil (200 mg), determined a significant decrease in error rates in the long delay condition of the visuo-spatial task and in the maintenance conditions, mainly in low baseline performance subjects (Müller et al., 2004). Additionally, it has been reported that modafinil can increase self-confidence in subjects with sleep deprivation. As emerged in a sample of 41 healthy volunteers undergoing visual-perceptual judgement task and complex mental addition task after sleep deprivation, modafinil significantly made subjects over-confident on their performance, notwithstanding a low performance accuracy (Baranski & Pigeau, 1997). The most frequent reasons reported for using modafinil concern boosting cognitive capacity, as well as being more performant. The results of an online survey carried out on 404 respondents of whom 219 were modafinil users (mostly male, American or British, university-educated, employed, with a mean age of 27), the most common motivation for misuse were “to increase attention”, “to work long hours”, “to get more done”, “exam”, “night work”, “to think more clearly”, and “other” (13%, n=28) (Teodorini et al., 2020).

Dextroamphetamine

Some data demonstrated that dextroamphetamine might improve cognitive ability in healthy adults. One of the first studies on adult population was carried out on a small sample of healthy college students (n=31, males aged 18-30). Participants, administered with different doses of dextroamphetamine (0.5 mg/kg, high dose group, or 0.25 mg/kg, low dose group), underwent different tasks to assess cognition, motor activity and mood. As far as cognitive abilities are concerned, high-dose subjects showed an increased vigilance and a significant improvement on cues recall and free recall. Even speech communication was increased, in particular the story telling, that resulted augmented more in the high-dose group, compared with low-dose participants. As for motor aspects, low-dose subjects exhibited a decrease in motor activity, while this effect did not occur in high-dose volunteers. However, the low-dose group appeared “more fidgety” to interviewers. With regard to mood, participants reported to feel euphoric, independently from amphetamine dose, and less tired in a dose-dependent way. Even psychophysiological measures were affected by dextroamphetamine. In particular the low-dose group showed a significant decrease in reaction time for long preparatory intervals and a reduction in skin conductance amplitude (Rapoport et al., 1980).

Amphetamine-dextroamphetamine (Adderall)

Adderall is a combination of amphetamine-dextroamphetamine used to treat ADHD and narcolepsy. Due to its property to improve cognitive performance in ADHD subjects, although it does not seem to be very effective in improving cognitive performance in healthy individuals, it seems that Adderall is one of the most used stimulants among college students as a neuroenhancer (Weyandt et al., 2018). Indeed, a double-blind, placebo-controlled study on a small sample of college students (n=13) demonstrated only a modest impact on cognitive processes. Particularly, it seemed to improve attention, although it worsened working

memory, with some components resulting less affected (perception of past cognitive and self-regulation in executive functioning in daily activities). Furthermore, participants reported no perception of the impact of the drug on their performance. Although this analysis may provide only an estimate of Adderall use in the USA, it turned out that 132,099 unique user accounts mentioned “Adderall”, with rates of tweet peaking during traditional college final exam periods, especially in the northeast and south US regions (Hanson et al., 2013). Another study on high school seniors (n=24,740) reported that 6.9% of participants showed a past-year use of Adderall for non-medical purposes (Palamar & Le, 2017). In the UK, Adderall seems less common, since a study on college students (n=877), reported that only 1.4 % of participants had a positive lifetime history of occasional use for cognitive enhancement, although lower percentages were reported for past regular use (0.3%) and current use (0.3%) (Singh et al., 2014).

Atomoxetine

Atomoxetine is a selective norepinephrine (NE) reuptake inhibitor, thereby augmenting NE intrasynaptic availability (Bymaster et al., 2002), approved in 2002 by the FDA for treatment of ADHD, in both children and adults (U.S. Food and Drug Administration, FDA, 2002).

To date, the impact of atomoxetine on healthy individuals remains unclear. According to a double-blind, placebo-controlled trial on healthy volunteers (n=60) receiving atomoxetine (60 mg), no impact on probabilistic learning task emerged (Chamberlain et al., 2006). Conversely, another double-blind, randomized, placebo-controlled study on healthy subjects (n=12), showed that a single dose of atomoxetine (80mg) might increase neural sensitivity for errors, as well as to decrease the inhibitory control, during the Go/NoGo-Eriksen flanker paradigm (Graf et al., 2011).

Atomoxetine does not seem to be appreciated among college students as neuroenhancers. An online survey on Australian college students (n=1,136) of three large universities highlighted that only 0.1% of participants had a lifetime use of atomoxetine for cognitive enhancement (Lucke et al., 2018).

(More details on the non-prescribed use of stimulants will be given in the next chapter on amphetamines and non-prescribed stimulants).

Prescribed nootropic drugs

The term “nootrope”, (from the ancient Greek words νόος “noos” mind and τροπεῖν “tropein” to turn) was first coined in 1972 to describe a novel psychotropic class able to increase cognitive skills initially in demented patients, with piracetam as the pioneer compound (Giurgea, 1973) soon followed by acetylcholinesterase inhibitors and memantine.

Nowadays there is an increasing use amongst the healthy population, as workers, soldiers and especially school and university students, in order to improve academic performance and to better manage stressful situations (Cakic, 2009; McDaniel et al., 2002). The prevalence of use is 16% and 35% amongst, respectively, European and USA students (Greely et al., 2008; Champagne et al., 2019) (**table 3**).

Piracetam

Piracetam (pyrrolidone acetamide) has a chemical structure resembling that of GABA: this suggests that

Table 3. Nootropics - Prevalence among college students and impact on cognition

Authors and year	Type	N Participants	Drugs	Method	Results
Maier et al., 2013	Cross-sectional study	6275	Anti-dementia agents	Online survey	0.1% of participants use anti-dementia drugs for neuroenhancement
Corazza et al., 2013	Systematic review	-	Piracetam	Systematic literature review carried out in PsychInfo and Pubmed Database and additional sources of unstructured information from the Internet was carried out between February 2012 and July 2013	Reason for use: Cognitive enhancement Recreational use
De Oliveira Cata Preta et al., 2020	Cross-sectional study	1865	Smart drugs	anonymous, self-administered questionnaire	Smart drugs use, 4.2% (within the last 12months) methylphenidate 99.0% of users, Modafinil and piracetam account for 1% of use
Lengvenyte et al., 2016	Cross-sectional	579	Nootropics and other cognitive enhancers	Anonymous questionnaires consisting of 13 items	Of the respondents, 8.1% indicated that they had used cognitive enhancers. Among those who had used these drugs, nootropics were the most frequently mentioned (59.6%)
<i>Memantine</i>					
Schugens et al., 1997	Double-blind placebo-controlled study	16	Memantine (30 mg)	Visual analogue mood rating scale, Benton test, Delay paradigm.	↔ effects of memantine on mood, attention, immediate and delayed verbal and visuospatial memory
Rammsayer, 2001	Double-blind, placebo-controlled, crossover design trial	40	Memantine (30 mg)	20 objects and 20 photographs were presented on a computer screen. After a retention interval of 80 min, the participants' task was to select the original objects and faces from a set of 80 items.	↓ Recognition performance for objects, ↔ performance on face recognition was not affected
Repantis et al., 2010	Systematic review	-	Memantine	MEDLINE and EMBASE databases were searched (MEDLINE: 1950 to 2007/07-week 2, EMBASE: 1989 to 2007/07).	Not conclusive results about the impact of memantine on healthy subjects
Barnes et al., 1996	Double-blind, placebo-controlled, crossover design trial	24	Memantine (30 mg/kg/day)	Electrophysiological and behavioural testing.	↑ tendency to show more selective spatial search patterns
Zoladz et al., 2006	Double blind, crossover design trial	40	Memantine and neramexane	Spatial memory task after intake of equimolar doses of memantine and neramexane.	↑ long-term memory
Wise & Lichtman, 2007	Preclinical study	24	Memantine, low doses (0.3 and 0.56 mg/kg) high doses (3 and 10 mg/kg) Donepezil Rimonabant	Radial-arm maze procedure	↓ number of errors committed during the retrieval test (low doses), disrupted maze running (high dose)

Table 3. Continued

<i>Acetylcholinesterase inhibitors</i>					
Yesavage et al., 2002	Randomized, double-blind, parallel group, placebo-controlled trial	18	Donepezil (5 mg) for 30 days	Flight simulator	↑ ability to retain the capacity to perform a set of complex simulator tasks, ↑ retention of training on complex aviation tasks in nondemented older adults
Grön et al., 2005	Randomized, double-blind parallel group placebo-controlled, repeated measures design trial	30	Donepezil (5 mg/day) for 30 days	Neuropsychological tests to assess cognitive status	↑ episodic memory in both the verbal and visual domain, and long-term visual episodic recall
FitzGerald et al., 2008	Double-blind crossover design trial	20	Donepezil (5 or 10 mg) for 6-week period	Levels of Processing task	↔ immediate and delayed recall of superficially processed, ↑ semantic processing and recall performance
Zaninotto et al., 2009	Double-blind, placebo controlled, parallel group design study	24	Donepezil (5 mg)	The test battery included tasks that tap cognitive domains that are sensitive to acetylcholine manipulations	↑ long-term recall of prose, objects recall, recall of spatial locations, and integration of objects with their locations.
Repantis et al., 2010	Systematic review	-	Donepezil	MEDLINE and EMBASE databases were searched (MEDLINE: 1950 to 2007/07-week 2, EMBASE: 1989 to 2007/07).	Not conclusive results about the impact of donepezil on healthy subjects
LaBerge et al., 2018	double-blind, placebo-controlled, crossover study	121	Galantamine (4 and 8 mg)	Mnemonic Induction of Lucid Dreams technique while returning to sleep.	↑ in lucid dreams in a dose-dependent way. ↑ dream recall, sensory vividness and complexity (p<0.05). ↑ Dream recall, cognitive clarity, control, positive emotion, vividness and self-reflection were increased during lucid compared to non-lucid dreams (p<0.0001).
Iglseider et al., 2018	Narrative review	-	Anti-dementia agents	Non systematic review of literature	↔ cognitive performance in healthy subjects
<i>Piracetam</i>					
Sannita et al., 1985	Double-blind, placebo-controlled, balanced order design trial	18	Piracetam (doses 800-4,800 mg)	EEG, Modified Abramson symptom questionnaire	↓ low-frequency components, ↑ power of the 8.5- to 12.0-Hz and of the fast-frequency components of EEG (anterior scalp areas)
Grossman et al., 2011	Preclinical study	336	Piracetam (mild dose 25-400mg/L, high dose 700 mg/L)	Novel tank and light–dark anxiety tests, Plus-maze test, The zebrafish novel tank test	↔ fish novel tank and light–dark box behavior at mild doses, and inhibition at high dose, ↔ inter-/intra-session habituation in the novel tank test for acute or chronic mild dose ↑ cued learning plus-maze test

Table 3. Continued

Samartgis et al., 2012	Preclinical study	1080	Piracetam 10 mg/kg	La Trobe University variant of the PAL task	↔ memory consolidation in the day-old chick with the passive avoidance learning task
Mindus et al., 1976	Double blind, intra-individual, crossover design study	18	Piracetam (4.8 g, three times a day for 4 weeks)	Digit Symbol Test, The Bourdon-Wiersma Test, The spoke test, Two-choice Reaction Time (2RT), Critical Flicker Fusion (CFF), Krakau Visual Acuity Test (KVAT), Tapping	↑ mental functioning in almost all tasks
Alkuraishy et al., 2014	Clinical trial	30	Piracetam (800 mg)	Computerized n-back test	↑ cognitive and working memory at all levels ↔ psychometric reaction time parameters except it ameliorate the total reaction time (TRT)

it probably acts as a GABA mimetic drug (Wisner et al., 2001). However, it has been proposed that its main pharmacological activity would consist in the activation of the glutamate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and as such, to increase their density and calcium uptake, possibly resulting in elevation of intracellular calcium levels (Ahmed & Oswald, 2010; Copani et al., 1992). As a result, piracetam would exert a neuroprotective action through improvement of brain membrane fluidity and neuroplasticity (Brandão et al., 1995).

Piracetam was and is still used to treat neurological disorders, such as early stages of Alzheimer's disease and memory impairment due to age (Waegemans et al., 2002). Possible cognitive enhancement and memory improvement are some of the reasons for its use amongst healthy subjects (Corazza et al., 2013). However, studies demonstrating that piracetam may effectively improve wakefulness and memory, were mainly conducted on animal models (Grossman et al., 2011; Samartgis et al., 2012), while information on healthy individuals is limited (Alkuraishy et al., 2014; Sannita et al., 1985). The first observations in healthy adults were carried out since the '70s. Amongst those, a double-blind, placebo-controlled, cross-over design study on a sample of normal elderly individuals (n=29), reported that piracetam exerted a significant effect on different cognitive tasks. Participants received a placebo for a week, then were divided in two halves, with one half receiving piracetam for a four-week period, while the other half placebo. After crossing-over, those subjects starting with piracetam received placebo and vice-versa. In general, when taking piracetam, individuals obtained better results in some different cognitive tasks (Mindus et al., 1976). The improving effect of piracetam (800 mg/die for four days) on memory and cognitive skills was supported by a more recent study conducted on healthy male volunteers (n=30). In particular, the drug exerted a significant effect on cognitive and working memory at all levels of computerized n-Back test ($p < 0.05$), although its impact on psychometric reaction time parameters was negligible, with the single exception of the total reaction time which resulted boosted (Alkuraishy et al., 2014).

Although the impact of piracetam on cognitive

ability is limited, it has become popular among college students. A cross-sectional survey study performed on students of two Lithuanian universities (n=579, response rate 95%) highlighted that 8% of the respondents had used nootropics, especially piracetam (59.6%) (Lengvenyte et al., 2016). However, as reported by a similar study on Brazilian college students (n=1865), piracetam accounted only for 1% of use (de Oliveira Cata Preta et al., 2020).

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (AChEIs) (donepezil, galantamine and rivastigmine) that improve cholinergic transmission by reducing ACh degradation, are commonly used in the treatment of both Alzheimer's and Parkinson's disease (Birks, 2006; Emre et al., 2004; Kandiah et al., 2017; McShane et al., 2006; Racchi et al., 2004; Rogan & Lippa, 2002; Sonkusare et al., 2005). Donepezil and galantamine are pure AChE inhibitors, while rivastigmine inhibits both AChE and butyrylcholinesterase (Weinstock, 1999). A few trials reported positive effects of these drugs on cognitive impairment of schizophrenia and drug abuse patients (Kishi et al., 2018; Ribeiz et al., 2010). Limited evidence would also indicate some efficacy of AChEIs to improve cognitive ability in healthy subjects. In a study, donepezil showed beneficial effects on maintaining complex aeronautical skills in retired healthy pilots (Yesavage et al., 2002). Again, this drug has been reported to improve both episodic and semantic memory (FitzGerald et al., 2008; Grön et al., 2005) and mood in healthy individuals (Zaninotto et al., 2009). Donepezil and galantamine were also shown to stimulate the lucid dreaming (LaBerge, 2000; LaBerge et al., 2018). Lucid dreaming is that particular state in which an individual is aware of the fact that he is dreaming, while actually being asleep (REM sleep phase). This is a phenomenon that some individuals find pleasurable, and it has been related to the ability of ACh and AChEIs to regulate REM sleep and to increase the number of REM sleep phases. Amongst students, AChEIs do not seem to be appreciated as neuroenhancers, since only 0.1 % reported to use them (Maier et al., 2013), or not to use them at all (Schelle et al., 2015). In any case, according to a recent review,

AChEIs would not be effective in healthy individuals (Iglseider, 2018).

Memantine

Memantine is used clinically in patients with moderate to severe Alzheimer's disease where it has been shown to be effective in reducing the level of cognitive impairment (Bullock, 2006; Reisberg et al., 2003). Memantine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist: the NMDA receptor influences neuronal plasticity, memory function and learning. Memantine may prevent neurotoxicity due to its low-affinity antagonism of glutamate, which has been linked to neurodegeneration and excitotoxicity (Lipton & Rosenberg, 1994).

Studies on animal models demonstrated the effectiveness of memantine in improving memory, in particular the processes of memory consolidation and reconsolidation, spatial memory and maintenance of hippocampus volume (Barnes et al., 1996; Wise & Lichtman, 2007; Zoladz et al., 2006). A trial conducted on young men and focused mainly on long-term visual memory, showed that memantine significantly increased recognition performance for objects (Rammsayer, 2001). However there is still no evidence indicating a possible cognitive- or mood-enhancing effect of these drugs in healthy subjects (Repantis et al., 2010; Schugens et al., 1997).

Alcohol

The anxiolytic action of alcohol is one of the main reasons for its wide use and abuse. Generally, alcohol is taken to reduce anxiety caused by social interactions, but it is well known that at high concentrations and/or chronic use it may impair attention, provoke ataxia, slow reactions and amnesia. When blood levels are >300 mg/dl, potentially fatal respiratory depression can occur (Nutt, 1999). Alcohol has an inhibitory GABAergic effect that, together with the inhibition of excitatory glutamatergic receptors, may provoke a depressant activity on the CNS. Alcohol shows an excitatory effect at the level of mu-opioid receptors involved in the reward system, and interacts with the serotonergic processes related to well-being and mood elevation (Costardi et al., 2015).

Alcohol can increase sensitivity to expressions of disgust and contempt (Felisberti & Terry, 2015), as well as facilitate the recognition of happy faces and increase emotional empathy ratings for positive stimuli (Dolder et al., 2017). Interestingly, although it does not increase sexual arousal, it was found to make pornographic images more enjoyable (Dolder et al., 2017).

In USA, several national survey studies investigating drinking habits of college students, the National Survey on Drug Use and Health (NSDUH), the annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), based on face-to-face interviews (67,500 individuals, aged 12 and older), that every year approximately 2,400 graduating seniors are questioned in subsequent years, in order to monitor ongoing trends in college drinking. Other relevant data derive from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), by surveying 46,500 adults with the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), and by The Harvard College Alcohol Study (CAS), although no longer active, that collected data from 15,000 college students. From these studies emerged that, in a given month, approximately 65% of college students used alcohol.

However, although from the '90s the total number of alcohol drinkers decreased, the total amount of frequent binge-drinkers increased (three or more binge-drinking episodes in a 2-week period). With regard to gender differences, although alcohol use was more frequent among males some decades ago, nowadays there is no difference, as reported in every country (White & Hingson, 2013).

It is estimated that more than 90% of college students consume alcohol for recreational use, given its easy availability and low costs. However, approximately 5% of academic students admit using alcohol even as a neuroenhancer, especially during the last month before an exam (Maier et al., 2013). Different reasons have been reported to explain the high prevalence of this phenomenon. Acute stress situations were found to increase selectively voluntary alcohol intake in undergraduate university students (Magrys & Olmstead, 2015). In addition, emotion dysregulation seems to play a critical role in alcohol-related problems of women attending college (Messman-Moore et al., 2010). A study carried out in a large sample of students (n=33,813) from 13 European countries, reported a social motivation, which was the most common reason for drinking, followed in this order by enhancement, coping and conformity motives in all countries involved except Finland (Kuntsche et al., 2014). The use of alcohol as a social enhancer is well described in an Australian study investigating the consumption of alcohol during "Schoolies", the immediate post-school celebration period lasting about four days. An online survey was administered to students in their senior year of school and participants anticipated that they would consume eight standard drinks a day and planned to spend substantial amounts of money on alcohol during Schoolies, demonstrating the importance of reducing the salience of alcohol in the course of this period (Jongenelis et al., 2017). Similarly, another research carried out through online questionnaires targeting 18-29 aged Irish university students showed that 81.6% of respondents were alcohol users and 44% of them declared an increase in consumption as they started university. A large part of them (66.4%) reported "to be sociable" as the primary reason for alcohol consumption, followed "enjoyment" (10.7%) and "relax" (6.4%) (Muli & Lagan, 2017). However, alcohol is used also to reduce anxiety due to academic performance, as confirmed by different studies. A Bosnian-Herzegovian investigation on 214 students found that almost a quarter of participants increased their consumption of alcohol during the last week before exams, with no correlation with anxiety symptoms (Kusturica et al., 2019). Furthermore, burn-out syndrome can be considered another risk factor for alcohol abuse or addiction, as reported in a sample of American medical students, who met the diagnostic criteria for such a condition in one third of cases, as educational debt further may increase the risk (Jackson et al., 2016). A dangerous and harmful use seems more likely in the male sex, while the most common reason related to alcohol use has been the social enhancement (Oliver et al., 2014).

To sum up, alcohol use among college students is widespread and often excessive. A significant number of them tend to use alcohol not only for recreational reasons, but also as a neuroenhancer, mostly to cope with anxiety during exams or stressful conditions that are frequent in academic life. However, students do not seem totally aware of the biological risks of drinking excessive quantities of alcohol and they tend to have too high expectations on its alleged impact on

cognition. All these motivations, coupled with the easy availability of alcoholic beverages is at the basis of the increased alcohol consumption worldwide amongst adolescents and students who are not aware of the long-term consequences on cognitive functions that may indeed result dramatically impaired (Brennan et al., 2020). In addition, the heavy alcohol use amongst university students requires the implementation of specific information about the risks of alcohol abuse, and appropriate prevention/intervention programs (table 4).

Illicit drugs

Illegal drugs, such as hallucinogens (mescaline, lysergic acid diethylamide, psilocybin), non-prescribed

stimulants, ecstasy, or other designer drugs, are widely used by healthy individuals as emotional enhancers (Normann & Berger, 2008) (table 5).

Hallucinogens

Hallucinogens were defined as “psychedelic” substances by the psychiatrist Humphrey Osmond in 1957, since they were thought to have a mind-revealing capability (from the Ancient Greek words *psychē* (ψυχή, "soul") and *dēloun* (δηλοῦν, "to make visible, to reveal") (Osmond, 1957), although they cause permanent hallucinatory symptoms.

Mescaline

Mescaline is a natural psychedelic alkaloid present

Table 4. Alcohol - Prevalence among college students, reasons for use and impact on cognition

Authors and year	Type	N	Methods	Results
Maier et al., 2013	Cross-sectional	6275	Questionnaire specifically designed at the Swiss Research Institute for Public Health and Addiction	Alcohol use, 90% Social reasons were the most common Use alcohol for neuroenhancement, 5%
White et al., 2013	Narrative review	50000	National Survey on Drug Use and Health (NSDUH), the annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), The Harvard College Alcohol Study (CAS)	Approximately 65% of college students used alcohol. Although from the '90s the total number of alcohol drinkers decreased, the total amount of frequent binge-drinkers increased
Kuntsche et al., 2014	Cross-sectional	33813	Drinking Motives Questionnaire Revised Short Form (DMQ-R SF)	The most common reasons for drinking were social motivation, enhancement, coping, and conformity
Messman-More et al., 2014	Cross-sectional	424	The Difficulties in Emotion Regulation Scale (DERS), Drinking Motives Questionnaire-Revised (DMQ-R), Alcohol Use Disorders Identification Test (AUDIT)	Emotion dysregulation predicted drinking coping motives
Oliver et al., 2014	Cross-sectional	349	Self-administered paper survey	Reasons for use: social motives were the most common. Coping and enhancement motives were more predictive of harmful or hazardous alcohol use (23.2% of students)
Felisberti et al., 2015	Placebo-controlled, repeated-measures design	18	Simula representing six emotions were used Alcohol high dose 0.6 g/kg for male, 0.52 g/kg for female, low dose, 0.2 g/kg for male and 0.17 g/kg for female	↑ sensitivity to expressions of disgust and contempt (not depending on stimulus duration)
Magrys et al., 2015	Randomized, placebo controlled trial	75	Trier Social Stress Test or no-stress protocol, 30-min free-drinking session (alcohol, placebo, or non-alcoholic beverage). The State-Trait Anxiety Inventory	Psychosocial stress ↑ voluntary intake of alcohol, but not placebo or non-alcoholic beverages
Jackson et al., 2016	Cross-sectional	4402	National survey	Burn out, depression, low mental or emotional QOL ↑ risk for alcohol abuse/dependence

Table 4. *Continued*

Dolder et al., 2017	Double-blind, random-order, crossover design trial	60	Face emotion recognition task (FERT), Multifaceted Empathy Test (MET), and Sexual Arousal Task (SAT), Visual analog scales (VASs).	↑ VAS ratings of stimulated, happy, talkative, open, and want to be with others. ↑ recognition of happy faces on the FERT, ↑ emotional empathy for positive stimuli on the MET
Jongenelis et al., 2017	Cross-sectional	187	<i>Ad hoc survey</i>	Students referred planning to consume 8 standard drinks a day
Muli et al., 2017	Cross-sectional	595	Online questionnaire	Alcohol users, 81.6% , ↑ consumption of alcohol after starting university, 44%. Reasons for use: “to be sociable”, 66.4%, “enjoyment”, 10.7%, and relax 6.4%
Kusturica et al., 2019	Cross-sectional	214	<i>Ad hoc questionnaire West-side test anxiety scale (WTAS)</i>	↑ consumption of alcohol during the last week before exams, with no correlation with anxiety symptoms
Brennan et al., 2020	Systematic review	-	Search MEDLINE, Embase and PsycINFO (January 2007 to April 2018) 27 cohort study included	↑ cognition among women with moderate alcohol consumption compared to current non-drinkers, ↔ for men. However, low level evidences

Table 5. *Illicit drugs - Prevalence among college students, reasons for use and impact on cognition*

Authors and year	Type	N	Method	Results
<i>micro-doses of psychedelics</i>				
Lea et al., 2020	Cross-sectional	1102	Online survey	Alternative treatment for mental health (40%), personal development and well-being (31%) and improvement of cognitive functions (18%)
Lea et al., 2019	Subreddit analysis	714	Online discussion forums	The third common motivation is to enhance cognitive performance
Hutten and al., 2019	Cross-sectional	1116	Online survey	LSD and psilocybin (the most used), improve performance (main motivation)
<i>MDMA</i>				
Maier, 2013	Cross-sectional	6275	Online survey	0.1% of academic students only use MDMA for neuroenhancement
<i>Stimulants</i>				
Teter et al., 2006	Cross-sectional	4580	Online survey	The most used stimulant in the past year was Adderall. Non-prescribed stimulants use was significantly more prevalent among Caucasian and Hispanic students. The more frequent reasons were to improve concentration, help study and increase alertness as well as recreational reasons including getting high and experimentation. Some sex differences were reported, with men using more NPS “to experiment”, and women to lose weight
De Santis et al., 2008	Cross-sectional	1811	Quantitative surveys and qualitative interviews	34% had used NPS and 63% of these had never taken NPS before college. The most common reasons were “stay awake to study” and “improve concentration”. The vast majority of NPS users get them from friends. On the whole, although students reported to use stimulants to face academic stress, they showed to not be adequately informed on the possible risk of using stimulants as neuroenhancers, but they consider the potential side effects acceptable
Weyandt et al., 2009	Cross-sectional	363	Brief Symptom Inventory, The Internal Restlessness Scale, the Sensation Seeking Scale, the Stimulant Survey Questionnaire	NPS users (7.5%). Different correlations emerged between the use of NPS and rates of psychological distress, internal restlessness, and sensation-seeking behaviour

Table 5. Continued

Hall et al., 2005	Cross-sectional	381	85-item questionnaire designed by the investigators on the basis of the survey prepared by Moline and Frankenberger	Only 14% of NPS users believe that stimulants may improve their academic performance in the long term	
Arria et al., 2008	Cross-sectional	1253	2-hour personal interview	Approximately 18% used stimulants for non-medical reasons. 33.3% of ADHD students referred to have overtaken their own stimulants or to have used someone else's stimulants for non-medical reasons at least once in their lifetime. Amphetamine and dextroamphetamine were used by the vast majority of NPS users	
<i>Cannabinoid compounds</i>					
Eickenhorst et al., 2012	Cross-sectional	1218 students	Web-based survey	Higher prevalence of cannabis use for neuroenhancement (14%), especially amongst men	
Kusturica, 2019	Cross-sectional	214 students	Westside Test Anxiety Scale and academic performance	Cannabis use tends to increase during the week before exams in 19% of students	
Schelle et al., 2015	Cross-sectional	1572	Online survey	1.3% of them used cannabinoids with the purpose of neuroenhancement	
Bonar et al., 2017	Longitudinal study	95	Baseline Timeline Follow-back (TLFB), Daily text message surveys	Significant correlations between the amount of cannabis used and the reason for its use, including social enhancement and/or coping	
Bravo et al., 2017	Cross-sectional	2129	Online survey	Positive association between marijuana use frequencies and coping strategies, expansion motives, and enhancement	
Glodosky et al., 2020	Cross-sectional	988	Online survey	Cannabis is frequently used against stress, depression, and anxiety, coping motives may be related to higher levels of depression, while expansion and conformity reasons to higher levels of anxiety	
Bae et al., 2019	Cross sectional	234710	Self-reported marijuana use	After recreational marijuana legalization (RML) policy cannabis use has increased among students in term of past month prevalence in RML and non RML exposed	
Olla et al., 2019	Observational study	22	Brief neurocognitive battery	Participants' cognitive performance remained stable or even improved during the acute intoxication phase	
Authors and year					
Type					
N					
Illicit					
Method					
Results					
<i>Mescaline</i>					
Halpern et al., 2005	Clinical trial	120	Mescaline	Screening interview, the Rand Mental Health Inventory (RMHI), neuropsychological tests of memory and attentional/executive functions	No evidence of psychological or cognitive deficits among Native Americans using peyote regularly
Papaseit et al., 2018	Observational study	16	Synthetic compounds showing mescaline-like	Visual analog scale (VAS), the Addiction Research Centre Inventory (ARCI), and the Evaluation of the Subjective Effects of Substances with Abuse Potential (VESSPA-SSE), The Hallucinogenic Rating Scale	Changes in VAS, ARCI, ↑ VESSPA-SSE
<i>Lysergic acid diethylamide (LSD)</i>					
Kaelen et al., 2015	Randomized, one-blind, placebo controlled trial	10	LSD 40, 50, 70, or 80 µg, placebo	Visual analogue scale (VAS) and the Geneva Emotional Music Scale (GEMS-9)	↑ emotional response to music

Table 5. Continued

Liechti et al., 2017	Placebo-controlled, double-blind, cross-over design	40	100 and 200 µg LSD	5 Dimensions of Altered States of Consciousness (5D-ASC), Mystical Experience Questionnaire (MEQ)	↑ mystical experience, changes in meaning of percepts, ↑ insightfulness
Pokorny et al., 2019	double-blind, randomized, placebo-controlled study	25	LSD (100 µg) ketanserin (40 mg) placebo	Intra/Extra-Dimensional shift task (IED), Spatial Working Memory task (SWM), and Cambridge Gambling Task (CGT) of the Cambridge Neuropsychological Test Automated Battery.	↓ executive functions, cognitive flexibility and spatial working memory
<i>Psilocybin</i>					
Hasler et al., 2004	Double-Blind, Placebo-Controlled Dose-Effect Study	8	Psilocybin 45, 155, 215, 315 microg/kg body weight PY, placebo	Altered States of Consciousness Rating Scale (5D-ASC), the Frankfurt Attention Inventory (FAIR), the Adjective Mood Rating Scale (AMRS)	↑ alterations in the self, perception, affection and attention
Pokorny et al., 2017	Double-blind randomized, placebo-controlled trial	32	Psilocybin 0.215 mg/kg p.o., placebo	Multifaceted Empathy Test (MET), the Moral Dilemma Task (MDT), The Altered States of Consciousness Rating Scale (5D-ASC), The Positive and Negative Affect Schedule (PANAS)	↑ emotional empathy associated with the change in meaning of perceptions. ↔ moral behavior
Carter et al., 2005	Double-blind, placebo-controlled study	8	Psilocybin 215 microg/kg, ketanserin 50mg, placebo	Attention—Multiple-object Tracking, Cambridge Neuropsychological Test Automated Battery (CANTAB), Spatial Span test, The Altered State of Consciousness (5D-ASC) rating scale	↓ attentional tracking ability, ↔ spatial working memory.
<i>Micro-doses of psychedelics</i>					
Anderson et al., 2019	Observational study	909	Microdoses (ng) of psychedelics	Online survey	↓ dysfunctional attitudes and negative emotionality, ↑ wisdom, creativity and open-mindedness
<i>Non-prescribed Stimulants</i>					
Hysek et al., 2013	Double-blind, placebo-controlled study	32	Single dose of MDMA (125 mg)	Multifaceted Empathy Test (MET), dynamic Face Emotion Recognition Task (FERT) and Social Value Orientation (SVO) test	↑ empathy at MET, and pro-social behavior, at the SVO test in men. ↔ cognitive empathy in the MET, ↓ identification of negative emotions in the FERT, particularly in women
Kuypers et al., 2017	Placebo-controlled study	118	MDMA (single dose, 75 or 125 mg)	Multifaceted Empathy Test (MET)	↑ emotional empathy for positive emotions at MET
Kirkpatrick et al., 2015	Randomized controlled trial	Study 1: 361 Study 2: 32	MDMA	Welfare Trade-Off Task (WTT)	↑ generosity towards others
<i>Cannabinoid compounds</i>					
Becker et al., 2014	Longitudinal study	70	Marijuana	Neurocognitive battery	↑ processing speeds than control subjects, ↑ cognitive deficits (verbal memory, spatial working memory, spatial planning and motivated decision-making)
LaFrance et al., 2017	Cross-sectional	721	Cannabis	Neuroticism, Extraversion, Openness to Experience Five Factor Inventory, Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory, Kaufman Domains of Creativity Survey, Creative Behaviors Inventory, Alternate Uses Test modified from the Uses of Objects Test, Remote Associates Test	Sober users ↑ creative and convergent thinking.

in high concentrations in the North American peyote cactus (El-Seedi et al., 2005), acting as a partial agonist at the level of the 5-HT_{2a} receptors (Nichols, 2004). After its administration, it induces important thinking alterations, distortions of the oneself's sense of time and reality perception, as well as an increase in suggestibility and a greater intensity of emotions (Grinspoon & Bakalar, 1997). To the best of our knowledge there are no clinical trials on healthy individuals on mescaline as neuroenhancer, with a single exception of a study conducted on Native Americans, who regularly ingest peyote for religious reasons, that did not highlight any psychological benefits or detrimental consequences (Halpern et al., 2005). However there are some studies on synthetic compounds with a mescaline-like structure, including as 2,5-dimethoxy-4-ethylphenethylamine (2C-E) and 2,5-dimethoxy-4-bromophenethylamine (2C-B), which have become popular as new psychoactive substance over the last decades. An observational study on a small sample of 2C-compound users (n=16, 8 female subjects) found that 2C-B determined statistical significant changes in almost all domains of the Visual Analogue Scale, particularly hallucinations (seeing animals, things, insects, or people or hearings of sounds or voices) (Papaseit et al., 2018). Also, significant changes in Addiction Research Center Inventory (ARCI) questionnaire emerged in those subscales measuring euphoria or dysphoria, somatic symptoms, intellectual efficiency and energy subscales (modest). Similarly, an increase in the Evaluation of the Subjective Effects of Substances with Abuse Potential (VESSPA-SSE) questionnaire emerged in pleasure and sociability, activity and energy, and sedation subscales (Papaseit et al., 2018). Particularly, a non-controlled, prospective, observational study on recreational drug users who had experienced 2C compounds at least once, reported that 2C-E induce significant changes in perceptions, as detected by Visual Analogue Scales (VAS) including "changes in colors", "changes in lights", "different body feeling", and "different surroundings" after four hours from substance consumption (Papaseit et al., 2020). In any case, there is no controlled study to assess the potential of mescaline as neuroenhancers in healthy subjects.

Lysergic acid diethylamide (LSD)

Lysergic acid diethylamide (LSD) is a unique molecule synthesized for the first time by the Swiss chemist Dr. Hoffman with the aim of studying the possible therapeutic uses of ergot derivatives (Hwang & Saadabadi, 2020). LSD potently binds to 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, dopamine D₂, and α ₂ adrenergic receptors and less potently to α ₁ adrenergic, D₁, and D₃ receptors (Rickli et al., 2015). Different studies reported that LSD impacts on sensorial perception by inducing a blissful state, synesthesia, derealization and depersonalization and increasing insightfulness. Similarly, it may boost emotional empathy, as well as to facilitate interpersonal relations (Carhart-Harris et al., 2016, Liechti, 2017). Furthermore, a study showed that subjects who had taken LSD before listening to music had an increased emotional response to music, compared to those who had taken placebo (Kaelen et al., 2015). Two placebo-controlled, double-blind, crossover studies conducted on two small sample of subjects administered with LSD (100 and 200 μ g, respectively) reported that this drug might induce mystical experience, although they were not frequent, and changes in

meaning of percepts, increase insightfulness and induce a blissful state, as measured by the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale. All these effects were dose-dependent (Liechti, 2017). With regard to cognitive effect of LSD, a study on healthy subjects taking LSD, placebo or LSD + ketanserin, a 5-HT_{2A} antagonist, showed how LSD significantly compromised executive functions, cognitive flexibility and spatial working memory, with no influence on the quality of decision-making and risk taking, while ketanserin normalized all cognitive deficits and effects (Pokorny et al., 2017). However there are no specific studies investigating LSD's role as neuroenhancer.

Psilocybin

Psilocybin is an alkaloid present in 200 of the so-called "magic mushrooms", as these are commonly called (Musshoff et al., 2000). From the pharmacological point of view, it binds with high affinity at 5-HT_{2A} and with less affinity at 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2C} (McKenna et al., 1990). A study exploring its effects versus placebo concluded that all subjects who had taken the active compound reported important alterations in the self, perception, affection and attention (Hasler et al., 2004). During intoxications, emotions can vary from pleasant and ecstatic to anxiety (Vollenweider et al., 1997). Another study noted that psilocybin significantly increases emotional empathy associated with the change in meaning of perceptions. By contrast, it did not seem to impair moral behavior (Pokorny et al., 2017). To evaluate the impact of psilocybin on healthy subjects, a sample of volunteers were recruited and evaluated after administration of psilocybin, placebo, ketanserin or psilocybin + placebo. Those who had taken psilocybin showed a significant reduction in attention tracking ability, but no effect on spatial working memory. Pre-treatment with ketanserin did not reduce the attention tracking ability deficit. The results suggest that there is a functional dissociation between the two tasks and that perhaps 5-HT_{1A} receptors are primarily involved in the observed deficit (Carter et al., 2005).

However, in recent years there has been a widespread interest in micro-doses of psychedelics to improve mental health, wellbeing and increase cognitive performance. An international study was conducted on an online sample of microdosing users, mainly of psilocybin and LSD. Its results showed that the main motivation for this practice was an alternative treatment for mental disorders (40%), followed by personal development and wellbeing (31%) and improvement of cognitive functions (18%) (Lea et al., 2020). An analysis conducted on discussion about microdosing of psychedelic compounds from an online forum showed that the third common motivation is to enhance cognitive performance in work and school, with the aim of improving concentration, productivity, creativity and problem solving (Lea et al., 2020). Another online questionnaire revealed that the most frequently used psychedelics were LSD and psilocybin and the main motivation was to increase performance. Interestingly, most users were not aware of the dose they were using (Hutten et al., 2019). Further, the results of an observational study showed that current and past microdosing users had lower scores on measures of dysfunctional attitudes and negative emotionality, and higher scores on wisdom, creativity and open-mindedness, than a control group (Anderson et al., 2019).

Amphetamines and non-prescribed stimulants

Amphetamines, and in particular the subtypes defined as “entactogen”, including the 3,4-methylenedioxy-N-methylamphetamine (MDMA, ecstasy), enhance empathy and social interactions, increase a sense of attachment towards the self and the others, as well as reduce social anxiety (Carlyle et al., 2019; Hysek et al., 2014; Nichols, 1986; Normann & Berger, 2008), although they are potent inducers of severe, treatment-resistant depressive episodes and psychoses (Glasner-Edwards & Mooney, 2014).

A double-blind, placebo-controlled study on healthy subjects (n=32, 16 women) taking a single dose of MDMA (125 mg) found that this drug increased empathy, as assessed by the Multifaceted Empathy Test (MET), in both sexes, and pro-social behavior, as measured by the Social Value Orientation (SVO) test in men only. Furthermore, MDMA did not affect cognitive empathy of the MET, and reduced the identification of negative emotions in the Face Emotion Recognition Test (FERT), particularly in women (Hysek et al., 2014). These results were subsequently confirmed by another placebo-controlled study on 118 healthy volunteers (with the only difference that MDMA doses were 75 or 125 mg). Similarly, MDMA administration determined an increase in emotional empathy for positive emotionally charged situations of the MET, while this effect was low for negative emotions (Kuypers et al., 2017). In line with the previous study, cognitive empathy resulted unchanged, while generosity towards others resulted increased (Kirkpatrick et al., 2015).

Stimulants are widely used among university students worldwide as neuroenhancers. As reported by a Swiss research on a large sample, it is estimated that 0.1% of academic students use MDMA for neuroenhancement (Maier et al., 2013). In studies carried out in the USA, its lifetime use resulted higher than that recorded in Switzerland. One of the largest American studies was conducted on a sample of 4580 college students. Participants, who were assessed by an online survey, reported a lifetime history of non-prescribed stimulants (NPS) use of 8.3% and of 5.9 % in the last year. In this case, the amphetamine-dextroamphetamine combination Adderall was the most used stimulant. The NPS use was significantly more prevalent among Caucasian and Hispanic students, who were three times more likely to consume stimulants, as compared with African-Americans and Asians. Different reasons were reported for using NPS, although the most frequent were the following: to improve concentration, to help study and to increase alertness, or recreational reasons including getting high (31.0%) and curiosity (29.9%). Furthermore, some sex differences were reported, with men using more NPS “to experiment”, and women to lose weight (Teter et al., 2006). A study conducted on undergraduates (n=1,811) from a southeastern USA university reported that 34% had used NPS, and 63% (n=368) of these had never taken NPS before going to the college. The most common reasons were “stay awake to study” and “improve concentration”, followed by “help memorize” and “stay awake to have fun”. Less frequent reasons include “feel high”, “reduce appetite” and “Attention-deficit hyperactivity disorder (ADHD) self-medication”. The vast majority of NPS users (87%) get them from friends, while only 4% of the overall sample from physicians for their ADHD. On the whole, although students reported to use stimulants to face academic stress, they showed to be poorly informed on their possible risk as neuroenhancers, as other students represent the main source of information.

In any case, they consider the potential side effects of NPS acceptable, while overestimating their possible advantages (DeSantis et al., 2008). Lower percentages of NPS users (7.5%) were found in another study conducted in a northeast USA university on a smaller sample of college students (n=363). Different correlations emerged between the use of NPS and rates of psychological distress, internal restlessness, and sensation-seeking behaviour, measured by different rating scales (Weyandt et al., 2009). Similar results were reported in a study conducted in a university of the Midwest, where only 14% of NPS users believed that stimulants may improve their academic performance in the long term (Hall et al., 2005).

In Spain, a study on 1253 first-year university students, demonstrated that approximately 18% of them was using stimulants for non-medical reasons. Furthermore, 33.3% of ADHD students referred to have overtaken their own stimulants, or to have used someone else's stimulants for non-medical reasons at least once in their lifetime. Stimulant-prescribed females turned out to be more prone to non-medical use of stimulants, compared with their male counterpart (37.5% vs 20.7%). Amphetamine and dextroamphetamine were the most used NPS (89.3%), followed by MPH, and MPH extended-release (Arria et al., 2008).

In conclusion, the abuse of NPS is an increasing phenomenon especially in highly competitive academic settings that should be not only carefully monitored, but also prevented through appropriate information campaigns.

Cannabinoid compounds

The United States Code (USC) indicates with the term “marihuana/cannabis” “all parts of the plant cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin”. Psychotropic and behavioral effects are due to the plant’s cannabinoid content, with Δ^9 -tetrahydrocannabinol (Δ^9 -THC), mainly found in leaves and flower buds, being the most active (ElSohly et al., 2017). The action of Δ^9 -THC is mediated by two major G-protein coupled receptors, cannabinoid receptor type 1 (CB1) and CB2, expressed within and outside the brain (Pertwee, 2014). Cannabis also contains cannabidiol, a non-psychotomimetic phytocannabinoid that seems to exert positive effects on several neuropsychiatric disorders and neurodegenerative diseases (Campos et al., 2016).

Given the wide consumption of cannabinoids worldwide, it is not surprising that they are also used as neuroenhancers, although at a lower rate than NPS. A German study on students (n=1,218) reported higher prevalence of cannabis use for neuroenhancement (14%), especially amongst men (Eickenhorst et al., 2012). Furthermore, it has been reported that cannabis use tends to increase during the week before exams in 19% of students (Kusturica et al., 2019). A Dutch study on university students (n=1,572) revealed that 1.3% of them used cannabinoids with the specific purpose of neuroenhancement (Schelle et al., 2015). A study on patients aged 18-25 years (n=95) recruited from an urban Emergency Department, found significant correlations between the amount of cannabis used and the reason for its use, including social enhancement and/or coping (Bonar et al., 2017). Similar results were reported in a study on a large sample (n=2,129) of college students of 11 different USA universities, reporting a positive association between marijuana use frequencies and

coping strategies, expansion motives, and enhancement (Bravo et al., 2017). In line with these findings, an analysis of a sample of 988 college students who were cannabis users, highlighted a moderator role of coping for the relationship between stress and depression, while expansion and conformity would play a significant role in the relationship between stress and anxiety. In other words, although cannabis is frequently used against stress, depression, and anxiety, coping reasons may be related to higher levels of depression, while expansion and conformity reasons to higher levels of anxiety (Glodosky & Cuttler, 2020). These results should be evaluated carefully, considering that, after recreational marijuana legalization (RML) policy in some American states, cannabis use has increased significantly amongst students in term of past month prevalence in RML and non RML exposed (Bae & Kerr, 2020).

With regard to the impact of cannabis on cognition, results are still controversial. On the one hand, a study considering 22 individuals with prescription marijuana from southwestern Ontario who were given a cognitive battery to assess cognitive performance, assuming they were adversely affected by acute intoxication, found that participants' cognitive performance remained stable or even improved during the acute intoxication phase (Olla et al., 2019). On the other hand, a controlled study was conducted on subjects aged between 18 and 20, of whom 35 were daily marijuana users who started using the drug before the age of 17, and 35 were healthy non-user control subjects. All subjects were assessed by a comprehensive neurocognitive battery. The results suggested that users showed relatively higher processing speeds than control subjects, but they had different cognitive deficits, especially in verbal memory, spatial working memory, spatial planning and motivated decision-making (Becker et al., 2014).

Another study was conducted to explore the possibility that cannabis might increase creativity, as suggested by previous research. However, the results showed that sober users were more creative and had better results with regard to convergent thinking, although these effects seem to be mainly related to the higher levels of expectation and openness to experience of cannabis users (LaFrance & Cuttler, 2017).

To summarize, on the basis of available data, cannabinoid compounds seem to exert no neuroenhancing effects.

Soft enhancers

The term “soft enhancer” refers to non-prescription drugs, food supplements, caffeine-containing products, herbal derivative, such as ginkgo biloba, that are used as neuroenhancers, especially by students (Dietz et al., 2018; Micoulaud-Franchi et al., 2014) (table 6).

Caffeine

Caffeine (1,3,7-trimethylxanthine) is the stimulant most used by man, especially as a component of tea, coffee, cola and energetic drinks (Nehlig, 2010). The main mechanisms of action of caffeine consist in the intracellular mobilization of calcium as ryanodine receptor agonist, inhibition of phosphodiesterases and antagonism of all types of adenosine receptors (AR): A1, A2A, A3 and A2B. However, at average levels of caffeine consumption (~210-238 mg/d), caffeine's main mechanism of action is antagonism of adenosine receptors (Dobson et al., 2015; Nehlig, 2010), thereby removing the endogenous adenosinergic tone, and affecting brain functions such as sleep, cognition,

learning and memory (Ribeiro & Sebastião, 2010). In the medical field, caffeine is used in the treatment of asthma and apnea in the newborns, in association with aspirin for headache, and in slimming compounds. Caffeine would inhibit lipid peroxidation and reduce the production of reactive oxygen species (ROS), so it would have a preventive role on neurodegenerative diseases (Devasagayam et al., 1996; Kolahdouzan & Hamadeh, 2017; Nehlig, 2010).

The properties of caffeine are still controversial. Indeed, if it seems to enhance working memory to a limited extent, especially in case of reduced alertness conditions, it can also impair this skill, so that it is concluded that caffeine does not improve recall and long-term memory (Nehlig, 2010). The only effect attributable to caffeine is the improvement of reaction time. With regard to emotional enhancement, low doses of caffeine may be of help in reducing anxiety and improving mood, while at high doses caffeine is associated with an increase in arousal, anxiety and nervousness. As a whole, therefore, caffeine should be considered a mild stimulant rather than a cognitive enhancer (Nehlig, 2010).

Ginkgo biloba

Ginkgo biloba extracts, whose active compounds are flavonoid glycosides and terpene lactones (Singh et al., 2014) seems to exert an antioxidant, anti-inflammatory action, as well as to play a modulating role in CNS (Zhang et al., 2017). Over the last decade, this compound has gained much attention, as different studies demonstrated that it might enhance cognitive functions in both animal models and healthy individuals (Abdel-Wahab & Abd El-Aziz, 2012; Alkuraishy et al., 2014). A study on 30 healthy subjects taking ginkgo biloba (60 mg/die for four days), found that it improved psychometric reaction time and cognitive central integrity, as assessed by the Leeds Psychomotor Tester and Critical fusion-flicker threshold, respectively, although memory resulted unchanged (Alkuraishy et al., 2014).

Hypericum perforatum

Hypericum perforatum, better known as St. John's wort, is commonly used to treat depression given its serotonergic activity (Calapai et al., 2001), however, its antidepressant efficacy is not wholly confirmed (Grobler et al., 2014). Similarly, its effects as cognitive enhancer, studied mainly in animal models, remain controversial (Ben-Eliezer & Yechiam, 2016; Valvassori et al., 2018).

Soft enhancers are widely used among students. Higher percentages of users were reported in a sample of students of German universities, with almost 90% of participants reporting to take caffeine as a non-prescription stimulant, both as caffeinated beverages and caffeine tablets (11.1%). Approximately a quarter of the participants consumed legal herbal drugs (valerian, ginkgo biloba, St. John's wort with the greater proportion of users being women ($p < 0.001$)) (Eickenhorst et al., 2012). Reasons reported for using this kind of neuroenhancers include improving performance, although about 60% of participants believed that neuroenhancers may have consequences on health, including psychological addiction (Eickenhorst et al., 2012). Similar prevalence rates were reported by a Dutch study on university students, with approximately 90% of the sample ($n=1,503$) reporting to use soft enhancers for non-medical use, and 45% specifically for cognitive enhancement (Schelle et al., 2015). Also, as reported by

Table 6. *Soft enhancers – Prevalence among college students, reasons for use and impact on cognition*

Authors and year	Type	N	Enhancer	Method	Results
<i>Reasons for use and college students</i>					
Perkin et al., 2002	Cross-sectional	1000	Nonvitamin, nonmineral supplements	15-item questionnaire	Lifetime use of dietary supplements (6.3%), with ginseng (29.7%), echinacea (27.8%), protein/amino acids (22.8%). Reason for use: improve energy 61.2%, promote weight loss 38%, to relieve stress and improve mood 24.7%, improve memory 17.5%
Gardiner et al., 2007	Cross-sectional	31044	Herbal dietary supplements	National Health Interview Survey	echinacea (45%), ginseng (34%), ginkgo biloba (22%), garlic (15%), St. John's wort (14%), peppermint (14%), ginger (10%), chamomile, (9%), kava kava (9%), and ephedra (7%)
Eickenhorst et al., 2012	Cross-sectional	1218	Caffeine beverages and pills, herbal drugs (valerian, ginkgo biloba, hypericum perforatum)	Online survey	Use of caffeine during study period, 89.3% (beverages), 11.7% (pills), herbal drugs 25.2%. Reason for use: improve concentration 55%, increase vigilance 49%, enhance cognitive potential 43%, cope with stress 38%.
Skewes et al., 2013	Cross-sectional	298	Energy drink	Paper-and-pencil self-report questionnaire	Use of energy drinks, 39.2% at least one a week. Social reasons, enhancement and coping were the most common reason for use
Shelle et al., 2015	Cross-sectional	1503	Lifestyle drugs (alcohol, nicotine, caffeine, over the counter pharmacy products)	Online survey	Use of lifestyle drugs as cognitive enhancers 45.6%
Malinauskas et al., 2016	Cross-sectional	496	Energy drink	Ad hoc 19-item questionnaire	Use of energy drink, 51%
Kusturica et al., 2019	Cross-sectional	214	Caffeine, energy drink, over the counter drugs	Ad hoc questionnaire West-side test anxiety scale (WTAS)	Emotion dysregulation predicted drinking coping motives
	Type	N	Method	Results	
<i>Caffeine</i>					
Neligh et al., 2010	Narrative review	-	Non systematic review of literature	↓ working memory, ↑ (in case reduced alertness), ↔ recall and long-term memory, ↓ reaction time. ↓ anxiety, ↑ mood (low doses), ↑ arousal, anxiety and nervousness (high doses)	
<i>Ginkgo biloba</i>					
Abdel-Wahab et al., 2012	Case-control preclinical study	80	Intermittent hypoxia (n=40), Room air (n040) Passive avoidance reflex test Biochemical assays	↓ memory impairment induced by hypoxia	
Al-Kuraishy et al., 2014	Clinical trial	30	Leeds psychomotor tester (CFFT) Critical fusion-flicker threshold, Computerized N-Back Task	↓ psychometric reaction time, ↑ cognitive central integrity p<0.05 ↔ working memory accuracy	
<i>Hypericum perforatum</i>					
Ben Eliezer et al., 2016	Meta-analysis	-	A Google Scholar structured search.No language, publication date, or publication status restrictions. 13 studies (published 2000–2014) were included.	reference memory and working memory ↑ healthy rodents, ↑ ↑ stress-impaired rodents.	

a study on Bosnian-Herzegovinian first-year university students, consumption of soft enhancers, that involved 31% of students, tended to increase during the week before the exams (Kusturica et al., 2019).

In the USA, a study conducted in Alaska on college students (n=298) reported that approximately 40% of participants consumed energy drinks at least once per week. Social reasons were the most frequent, although “enhancement” and “coping” were also common motives for energy drink use. A negative association emerged between age and energy beverages consumption (Skewes et al., 2013). Another study on 496 college students of central region university, reported that half of the participants (51%) consumed energy drink regularly (more than one each month), with a light prevalence amongst female sex (Malinauskas, 2007).

According to the National Health Interview Survey (NHIS), past year prevalence of herb dietary supplements (HDS) in the country was approximately 17% (n=31,044 NHIS respondents). This habit was more common among older, higher income, college-educated, non-Hispanic ethnicity participants. The most used HDS were echinacea (45%), ginseng (34%), ginkgo biloba (22%), garlic (15%), St. John’s wort (14%), peppermint (14%), ginger (10%), chamomile, (9%), kava kava (9%), and ephedra (7%) (Gardiner et al., 2007). Although HDS were used mostly to treat medical conditions, including anxiety and insomnia, they are common also among college students. Indeed, as emerged in a sample of 1000 college students, more than one quarter (26.3%) reported a lifetime use of dietary supplements, with Ginseng, echinacea, protein/amino acids being the most frequent used. Among HDS users, 61.2% reported taking them to “improve energy”, 38% to “promote weight loss”, 24.7% to “relieve stress and improve mood”, 17.5% to “improve memory”, 13.3% to “enhance sleep”. No ethnic, gender, health differences emerged amongst HDS users, although those who practice exercise more than three times per month and cigarette smoking were factors associated to HDS use (Perkin et al., 2002).

Non-invasive transcranial brain stimulation

Non-invasive brain stimulation, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), aims at modifying brain activity. Thanks to a magnetic current, TMS may influence neuronal activity in cortical regions, according to the variation of frequencies leading to a reduced or increased excitability for low and high frequency, respectively. The tDCS employs weak electrical current that alters neuronal excitability depending on the polarity of current. Both TMS and tDCS are used to treat resistant psychiatric and neurological disorders, although their use is still limited (Hamilton et al., 2011; Thibaut et al., 2014).

With regard to healthy individuals, available data, albeit limited, do not seem to indicate that such techniques may boost cognitive performance and/or modify emotional status (Knoch et al., 2006; Young et al., 2010) (table 7).

Neurofeedback

Neurofeedback is a type of biofeedback consisting in teaching a subject how to self-regulate his/her brain activity. Neurofeedback techniques include electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and spectroscopy. In particular EEG records cortical neuronal (Hammond, 2011), while fMRI shows activity of all cerebral regions (Weiskopf, 2012). Thanks to biofeedback techniques a subject can be aware of his/her neural activity and can learn how to modify it. So far, clinical indications of neurofeedback include ADHD and other developmental disorders, Parkinson’s disease, epilepsy, alcoholism, drug addictions, chronic pain, tinnitus, etc. (Hammond, 2011; Mihara et al., 2012; Weiskopf, 2012).

In healthy subjects, neurofeedback was found not only to improve cognitive performance, such as short term and working memory (Angelakis et al., 2007), learning, visuo-spatial skills or executive functions (Enriquez-Geppert et al., 2013), but also artistic performance (dancing, instrumental music, singing,

Table 7. Non-invasive transcranial brain stimulation and neurofeedback

Authors and year	Type	N	Technique	Method	Results
Knoch et al., 2006	Case-control study	52	Low-frequency repetitive transcranial magnetic stimulation (rTMS)	Ultimatum Game	Disruption of the right, but not the left, dorsolateral prefrontal cortex (DLPFC) by rTMS reduces subjects’ willingness to reject their partners’ intentionally unfair offers, which suggests that subjects are less able to resist the economic temptation to accept these offers
Young et al., 2010	Repeated measures design controlled trial	Experiment 1: 8 Experiment 2: 12	Transcranial magnetic stimulation (TMS) to disrupt neural activity in the right temporoparietal junction (RTPJ)	Experiment 1: TMS transiently before moral judgment (offline stimulation) Experiment 2: TMS during moral judgment (online stimulation)	Interfering with activity in the RTPJ disrupts the capacity to use mental states in moral judgment, especially in the case of attempted harms
Hamilton et al., 2011	Narrative review	-	Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)	Non systematic literature review	Preliminary results in healthy individuals suggest a possible role of TMS and tDCS on cognition, mood and social skills

Table 7. Continued

Authors and year	Type	N participants	Technique	Method	Results
Angelakis et al., 2007	Double-blind controlled design trial	6 elderly subjects	EEG peak alpha frequency (PAF)	State-Trait Personality Inventory (STPI), Digit Span (Wechsler, 1995), the Word List Memory Task (Welsh, Butters, Hughes, Mohs, & Heyman, 1991), the Stroop test (Stroop, 1935), the Passage Comprehension test, Raven's Standard Progressive Matrices, the Logical Memory, Faces, Verbal Paired Associates, Family Pictures, Visual Reproduction subtests of the Wechsler Memory Scale-III, "n-back" task and a "Go=No-Go" oddball task	↑ cognitive processing speed and executive function, but that it had no clear effect on memory
Hammond, 2011	Narrative review	-	EEG biofeedback	Non systematic review of literature	↑ cognitive performance in healthy individuals
Enriquez-Geppert et al., 2013	Narrative review	-	Computerized behavioral training, neurofeedback and transcranial electrostimulation	Non systematic literature review	↑ performance in task switching, memory updating, and dual tasks. Behavioral benefits in response inhibition, task switching, and memory updating

etc.) sports (golf, archery, etc.), and even surgery (Hammond, 2011). Beneficial effects of real-time fMRI neurofeedback (rt-fMRI-NF) have been reported, specifically increased positive emotion experiences in depressed and anxious patients (Linhartová et al., 2019).

However, the information on the possible neuroenhancing properties of neurofeedback is meager and should be considered preliminary.

Emotional enhancement

Emotional enhancement is that kind of neuroenhancement aiming at modifying an individual's emotions by amplifying and/or enhancing emotional states beyond normal levels of intensity by natural or artificial means. Although this is not the main topic of our review, in the next paragraphs our focus will be on oxytocin and pheromones, natural compounds with promising properties in this sense (table 8).

Oxytocin

Oxytocin is a small neuropeptide composed of nine amino acids. It is mainly synthesized centrally, in the paraventricular and supraoptic nuclei of the hypothalamus, but also in other sites in the central nervous system, such as the stria terminalis, the anterior commissural nucleus and spinal cord, and in non-neural tissues including ovary, testis, adrenal, thymus, and pancreas (Buijs et al., 1983; Jenkins & Nussey, 1991; Sofroniew, 1983). Oxytocin plays a role in different physiological functions including labor, uterine dilatation, lactation, sexual stimulation, stress regulation and social behaviors (Carter et al., 2001; Jenkins & Nussey, 1991; Zeeman et al., 1997). In general oxytocin is considered a pro-social hormone as it seems

to increase in-group trust, capacity of recognition of facial emotions, empathy, and to reduce anxiety and stress, while promoting health and wellbeing through its immunomodulatory effects (Domes et al., 2007; Heinrichs et al., 2003; Hurlmann et al., 2010; Kirsch et al., 2005; Marazziti et al., 2006; Shahrestani et al., 2013; Van IJzendoorn & Bakermans-Kranenburg, 2012). Not surprisingly, oxytocin has been hypothesized to be involved in the pathophysiology of different psychiatric disorders and to constitute a novel and natural treatment (Marazziti & Catena Dell'Osso, 2008). Indeed, nasal spray of oxytocin was found to improve social deficits in autism, by increasing eye contacts, decision-making and emotion understanding, and to achieve beneficial effects on repetitive behaviors and feelings of avoidance (Andari et al., 2010; Bernaerts et al., 2017; Bernaerts et al., 2020; Guastella et al., 2010; Yatawara et al., 2016). For its role in social bonding, over the last decades oxytocin has gained increasing attention until being regarded as a "love hormone" that might be helpful to resolve relationship problems, sexual difficulties or even to find a partner (Olf et al., 2013). Far from being a 'love potion', oxytocin may truly facilitate interpersonal intimacy or approach to partner, empathy and perhaps help to maintain a pair bond (Arueti et al., 2013; Heinrichs et al., 2003).

According to Wudarczyk et al. (2013), oxytocin should be used within a context of a structured treatment plan only if both partners agree to the treatment (Wudarczyk et al., 2013). However, we would underline that bond-promoting compounds involve the risk for excessive "medicalization" of human relationships and feelings, such as love, while scrambling their authenticity (Davis, 2010; Earp et al., 2015). Although data on the benefits of oxytocin are too limited before firm conclusions should be drawn, research in this field is active, so that these are questions that require to be answered soon.

Table 8. Emotional enhancement

Authors and year	Type	N participants	Emotional enhancer	Method	Results
<i>Oxytocin</i>					
Arueti et al., 2013	Double-blind placebo-controlled within-subject crossover design trial	42	Intranasal oxytocin (24 U.I.)	The "Etch-a-Sketch" Task	↑ paired performance up to the level of individual performance
Heinrichs et al., 2003	Randomized, double-blind, placebo-controlled trial	37	Intranasal oxytocin (24 U.I.)	Trier Social Stress Test	↓ salivary free cortisol levels in case social support in response to stress
<i>Pheromones</i>					
Kirk-Smith et al., 1978	Case-control study	24	Androstenol (0.3 mg)	16 photographs rated with nine-point bipolar category scales	Androstenol group rated the photographed women as sexier and more attractive
Benton, 1982	Randomized, double-blind, placebo-controlled trial	18	5 α -androst-16-en-3 α -ol (150 mg)	Menstrual distress questionnaire, Rating scales consisting about psychological distress	↔ ratings of being happy/depressed; lethargic/lively sexy/unsexy; irritable/good-tempered
Grosser et al., 2000	Double-blind randomized parallel 22 design at a rate of one or two per day trial	40	Androstadienone (100 pg) and 18 ng propylene glycol	Derogatis Inventory	↓ nervousness, tension and other negative feeling states
Jacob and McClintock, 2000	Experiment 1: randomized, double-blind, placebo-controlled, within-subject design trial Experiment 2: within-subjects design, with a randomized, double-blind treatment order	Experiment 1: 20 Experiment 2: 31	Experiment 1: Δ 4,16-androstadien-3-one (A; 0.00025 M concentration in propylene glycol or PG) and 1,3,5,(10),16-estratetraen-3-ol (E; 0.00025 M concentration in PG), or carrier odorant alone (PG) Experiment 2: 0.00025 M concentration of Δ 4,16-androstadien-3-one within a carrier odorant of 1% clove oil propylene glycol solution, or the 1% carrier odorant alone	The Profile of Mood States (POMS), The Addiction Research Center Inventory (ARCI), Visual Analog Scales (VAS)	Experiment 1: ↑ positive stimulated mood state in women but decreased it in men Experiment 2: Δ 4,16-androstadien-3-one modulated their general mood state, even when women were not aware of its odor.

Pheromones

The term pheromones, first used by Karlson and Lüscher in 1959, refers to a chemicals capable of convey information, triggering endocrine, behavioral and developmental reactions amongst conspecifics, including mammals (Brennan & Keverne, 2004; Karlson & Luscher, 1959). The vomeronasal organ (VNO), a specialized area of olfactory system that is also present in humans, is where pheromones are detected (Monti-Bloch et al., 1998; Rodriguez et al., 2000). Human pheromones include 4,16-androstadien-3-one (AND) and estra-1,3,5 (10),16-tetraen-3-ol (EST), whose chemical structure resemble sexual hormones (Monti-Bloch & Grosser, 1991), and that are secreted by apocrine glands in the axillary and pubic region (Grammer et al., 2005). According to different studies, pheromones may modulate physiological arousal (Bensafi et al., 2004; Wyart et al., 2007), mood (Bensafi et al., 2004; Benton, 1982; Jacob & McClintock, 2000; Kirk-Smith et al., 1978; Lundström

et al., 2003) and brain activity (Savic et al., 2005). In particular, androstadienone is thought to play a role in emotion regulation (Grosser et al., 2000). Indeed, both an increase in positive mood and a reduction in negative effects were found in women exposed to both male axillary extracts or purified androstadienone (Grosser et al., 2000; Jacob & McClintock, 2000; Marazziti et al., 2010; Preti et al., 2003; Wyart et al., 2007).

More recent findings suggest that a specific class of pheromones, the so-called appeasing pheromones (APs), might be useful in treatment of psychiatric disorders (Doucet et al., 2009). Although just a few case reports are reported in the literature, APs was found to improve symptoms of bipolar disorder, autism, OCD and reduce self-injuring behavior, social and separation anxiety (Piccinni et al., 2018). In any case, the role of pheromones in human (patho)physiology, that seems intriguing, is still controversial and requires to be deepened in future studies (Liebowitz et al., 2014; Winman, 2004; Wyart et al., 2007).

Table 8. Continued

Preti et al., 2003	Double-blind, repeated measures design trial	18	3-methyl-2-hexenoic acid (3M2H) (0.5 mg/ml), (male axillary extracts)	7-point, Likert-type, categorical scale	↓ tension, ↑ relaxation
Lündstrom et al., 2003	Experiment 1: randomized, double-blind, placebo-controlled, between-groups design trial Experiment 2: randomized, double-blind, placebo-controlled, within-groups design trial	Experiment 1: 38 Experiment 2: 40	Experiment 1: Androstadienone 250 M concentration of androstadienone (A) in mineral oil (M) with an odor mask consisting of 1% eugenol (E) Experiment 2: The same of experiment 1	Experiment 1: State Trait Anxiety Inventory-State (STAI-S) and the State Trait Anxiety Inventory-Trait (STAI-T)	Experiment 1: ↔ mood Experiment 2: ↔ mood scale change in the level of participant's trait anxiety
Bensafi et al., 2004	Randomized, placebo-controlled, between-subject design study	60	4,16-androstadien-3-one (Low concentration 2 mg, high concentration 50 mg)	16-item test	↑ positive mood and decreased negative mood in women compared to men (high concentrations)
Wyart et al., 2007	Double-blind, within-subjects repeated-measures design	21	4,16-androstadien-3-one (30 mg)	17-item scale	↑ mood, sexual arousal, and physiological arousal
Marazziti et al., 2010	Randomized, double-blind, placebo-controlled trial	24	Male axillary underarm extracts	The "Experiences in Close Relationships" questionnaire (ECR), the latest version of the Barratt Impulsiveness Scale (BIS-11), Structured Clinical Interview for Mood Spectrum, self-reported version (SCI-MOOD last month)	Impact on impulsiveness and romantic attachment

Conclusions: ethical implications

In spite of the limited evidence that some substances may improve cognitive functions in healthy subjects, there is an increasing worldwide use of the so-called neuroenhancers. If those included in the category of soft enhancers are not dangerous, as most of them produce placebo-like effects, it is astonishing how students and workers in competitive settings use active drugs, apparently neglecting or underestimating their detrimental side effects and potential risk of misuse, abuse and addiction. However, it is true that human beings are embedded by the wish to overcome their physical and cognitive constraint, and to expand their knowledge, mind and consciousness far beyond the nature-imposed limits. According to some authors, our history is mostly an improvement history (Buchanan, 2012), with a constant increase of human capacities and of quality of life (Caplan, 2003; Savulescu, 2006) that permitted to overcome difficulties of hostile environments, to evolve and to achieve a constant progression in artistic, technological and scientific domains

Taken to the extreme positions, however, this approach led transhumanists and posthumanists considering licit every natural, chemical or technological mean to expand human skills, abilities and opportunities

(Bostrom, 2003). On the other pole, the bioconservative approach is focused on preserving authenticity of human nature and considers neuroenhancers as a threat that can only result in unnatural outcomes (Fukuyama, 2002; Sandel, 2004). According to the "ethics of authenticity", theorized by the Canadian philosopher Charles Taylor, everyone should yearn to self-perfection and do its best to actualize its hidden potential (Taylor, 1991; Kraemer, 2011). Those who are not able to reach self-actualization are thought inadequate and unworthy of having a satisfying life (Elliott et al., 1997; Elliott, 2000; Taylor, 1991). In recent days, the concept of 'authenticity' has acquired a predominant role in ethical issues concerning 'human enhancement', as people tend to use enhancement in order to reach their personal authenticity. Obviously, the matter is complex, deeply debated, with most of its questions that remain largely unresolved.

With no doubt, more reliable studies carried out with no prejudice on effects of neuroenhancement in healthy subjects will be helpful in clarifying some, if not all issues. If it were licit or not to expand our cognitive and emotional abilities up to the point of scrambling our authenticity is a question requiring an integrated approach from specialists of different disciplines, from psychology to psychiatry, philosophy, religion, social and political science.

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