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Pharmacological Cognitive Enhancement among healthy university students: conceptual definitions, empirical aspects and ethical issues

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Introduction

Over the last two decades, considerable debate has arisen within the neuroscientific and bioethical communities with respect to an alleged increasing trend in the non-medical use of prescription psychostimulant pharmaceuticals (e.g. amphetamines, methylphenidate and modafinil) among cognitively healthy individuals in various contexts across societies.

In particular, this phenomenon has consistently been observed to be prominently pervasive and even growing in scope among otherwise healthy students in several colleges and universities in the world.

In fact, even though these psychostimulant drugs - also dubbed as "smart drugs" or "nootropics" - were originally developed for the treatment of cognitive deficits and impairments of patients suffering from various neuropsychiatric conditions (such as Alzheimer's disease, attention-deficit hyperactivity disorder, narcolepsy etc.), reports suggest that, in many countries, cognitively healthy undergraduates with no diagnosed neurological or psychiatric symptom whatsoever are increasingly turning to such prescription stimulants in the pursuit of enhanced cognitive abilities (such as memory, attention, alertness and learning), which would then enable them to achieve better academic performances.

This probably comes off as no surprise, given that students everywhere are exposed to increasingly keen peer competition in the academic context to increase their opportunities to successfully enter the globalised labour market and secure well-paying jobs – along with their associated socio-economic benefits and privileges in the global liberal market economy, which appears to be fundamentally and increasingly knowledge-based. Therefore, there is no wonder that their feeling constantly compelled to unfailingly achieve top-notch academic performances and to somehow gain a competitive edge over their colleagues provides breeding ground for the increasingly frequent use (or better, the misuse, and often even the abuse) of pharmaceutical cognition-enhancing substances not to treat cognitive disorders or illnesses and restore neuropsychiatric health but to merely try to enhance cognitive abilities beyond "normal standards" – a practice that may be summed up as "Pharmacological Cognitive Enhancement" (PCE) – in the hope of allaying their daily academic struggles and upgrading their cognitive-related achievements in the performance of academic tasks. However, despite having emerged almost two decades ago as a widespread practice among healthy university students, this phenomenon still seems to be very controversial under many factual and moral respects, raising dilemmas whose answers are, for the time being, yet to be fully cleared from the veil of doubt and uncertainty in which they are cloaked.

Three main contentious points in particular seem to persist as especially urgent in the neuroscientific literature, as well as in bioethical debates and, to a minor extent, in the public discussion of the topic:

1. Is the improvement of academic performance promised by PCE a concrete and effective possibility at hand for healthy university students worldwide, or is it just a mirage inflated by overly optimistic assessments of the developments in neuroscientific research about "smart drugs"? More simply put: are these psychoactive drugs actually able to determine appreciable

improvements in healthy individuals' "normal" cognitive abilities? And if yes, which is the extent and rate of such improvements, and which are the affected cognitive faculties?

2. What are the medical concerns raised by PCE among cognitively healthy students with regard to its safety risks and potential side effects? What is the actual risk-benefit ratio of PCE among cognitively healthy individuals?
3. Last, but not least: in the plausible prospect of this practice becoming increasingly pervasive and commonplace in the near future, what are the ethical and social implications (and the associated regulatory considerations) stirred by PCE use within academia?

The present dissertation is aimed precisely at shedding some light on these grey areas, without pretending, on the other hand, to provide conclusive answers on very specific empirical points of contention and on far-reaching ethical dilemmas, for the very reason that, in spite of the 20-year-long supposedly mounting societal prevalence of PCE and notwithstanding the fast-paced advances in neurocognitive sciences and in the bioethical discourse on the topic, it is still too early to make definitive statements with utter certainty – whatever their nature – on a reality which still has some way to go before it firmly takes hold across societies.

In order to satisfactorily fulfil this task, the present work intends to explore as comprehensively as possible the increasingly widespread phenomenon of PCE among cognitively healthy university students by both delving into its conceptual premises, providing an exhaustive overview of its empirical aspects and engaging in a timely discussion of the most urgent ethical, social and regulatory issues stemming from its eventual pervasive uptake in competitive academic contexts.

Here is how the work is outlined.

The first chapter is composed of two sections dealing with theoretical definitions and concepts surrounding the issue of Cognitive Enhancement (CE) in general terms.
In order to lay the groundwork for a clear, comprehensive and insightful assessment of the specific phenomenon of Pharmacological Cognitive Enhancement (PCE) among healthy university students in the subsequent chapters, a detailed and unambiguous working definition of CE is suggested preliminarily in the first section, so as to help readers dispel what is generally considered to be the main doubt regarding CE - namely, the fundamental distinction between downright cognitive enhancement and cognitive-enhancing therapy. In the second section, the chapter will then turn to broadly review the present-day state of knowledge in regard to the array of existing drugs, substances and technological devices which are currently resorted to and proposed for CE: however, for the purposes of this dissertation, attention will be drawn pre-eminently to the category of pharmaceutical drugs, while the other CE techniques will be glanced over more shortly.

The second chapter is comprised of four sections providing a comprehensive and thorough analysis – strictly empirical and scientific in nature - of the rife phenomenon of PCE use among cognitively healthy university and college students across the world. The first section of the second chapter presents a general review of updated empirical data on the current prevalence of PCE among healthy university students worldwide, whose self-reported reasons and deeper, underlying causes determinant to engage in the practice of PCE use are in turn explored in the second section. The last two sections, on the other hand, summarise the available scientific evidence on the actual risk-benefit ratio of PCE among cognitively healthy individuals: in particular, the third section reports the results of various studies on the actual efficacy of the off-label use of prescription drugs for CE purposes, while the fourth one sums up reliable scientific findings on the potential adverse effects and health risks that PCE may entail.

The third and final chapter is concerned with the discussion of the most pressing ethical and social concerns raised exclusively in the context of academic competition by this growing societal trend.
In fact, among the conspicuous range of ethical issues usually debated in the current CE literature, some of the most urgent ones concern the potentially deleterious social impact such cognition-enhancing interventions may have in the event of their eventual society-wide and deep-rooted uptake. Among them, those which realistically appear to be most relevant in current times relate to PCE - since pharmacological interventions are, at present, the most widely implemented and the most easily available ones for CE use among healthy people – and in particular to the phenomenon of university students using PCE as a means to better academic outcomes. In view of this practice taking deeper root and becoming much more pervasive than it is today, or even commonplace within educational institutions across societies, the third chapter provides an overview of what the current bioethical debate on CE realistically considers to be the most pressing ethical and social concerns raised by PCE among healthy university and college students with regard to circumstances of academic competition. These concerns are covered in the chapter to include first the potential configuration of PCE within academia as a form of cheating and its relation to doping in sports - both framed as issues of fairness in competition – and then the risk of indirect coercion to cognitively enhance oneself in competitive academic examinations, which is addressed mainly as a matter of personal autonomy in the larger framework of competitive fairness.

Let us now begin by delving into the theoretical aspects of CE in general and PCE in particular.

Chapter 1

Cognitive Enhancement: concepts, definitions and methods

1.1. A working definition of "Cognitive Enhancement"

At present, the expression "cognitive enhancement" is more or less straightforwardly and commonly employed in the scientific and bioethical literature to broadly refer to the use of a wide and often puzzling array of both already-existing and developing cutting-edge biomedical interventions[1] , either pharmacological or strictly technological in nature, aimed at improving the cognitive faculties of human beings[2].

However, the broad and unspecified meaning attributed to this expression has often proved to be not only quite confusing and divisive in the context of both public and academic debates on the public health and bioethical issues associated with cognitive enhancement, but also rather useless when aiming to gain some deeper conceptual understanding and sounder empirical knowledge of the matter intended as an increasingly documented phenomenon across human societies.

What makes it so disorienting and sometimes complicated to use in a clear-cut way in debates on the topic is its inherent, structural element of uncertainty as to whether it is always possible to refer to virtually any instance of a human being's mental faculties being improved through such interventions as a proper example of cognitive enhancement.

The legitimacy of such doubt becomes apparent when considering that, at the societal level at large, it is generally accepted that, as far as human cognitive faculties are concerned from a medical point of view, people can be roughly categorised as being either "cognitively healthy" – which is considered to be the standard for a "normal" person – or "cognitively impaired", respectively[3] , with the latter category comprising all the people suffering from neuro-psychiatric pathologies, which usually involve cognitive deficits and impairments of some sort.

Therefore, in light of such consideration, the issue at stake here clearly is whether both cognitively healthy people and the cognitively impaired ones can be equally considered to be "cognitively enhancing" themselves, without any distinction of sort in any meaningful way, when availing themselves of the abovementioned cognitive-improving interventions.

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[1] The expression as it is commonly used by the general public indeed refers primarily to the employment of actual and concrete biomedical tools and interventions, but it may also include a more comprehensive set of ordinary and quite conventional approaches aimed at maintaining and possibly improving mental agility, such as education, improved sleep and dietary patterns, intake of caffeine and/or caffeinated and stimulating dietary supplements or brain training via computer software games. However, discussion over these natural and/or conventional approaches is not included in the present work for a matter of focus, as interventions properly labelled as "cognitive enhancement" are usually intended to be biomedical in nature, (currently) not freely available and significantly more potent in action at neurological level than the former are. For further insight, see section 1.2, p. 7 below.

[2] Most such interventions have been previously tested on animals and introduced in animal models for scientific research purposes (e.g., Warwick, 2008) in order to be eventually established for use among human beings – as the majority of them has already been (e.g., Dubljević, 2013).

[3] See note 6 below.

In fact, the broad definition of cognitive enhancement (CE) as introduced at the very beginning of the chapter only makes an utterly generic reference to the improvement of human cognitive abilities: while such an improvement may obviously occur in both cognitively healthy and cognitively impaired people, it surely stands to reason that its very nature and extent vary substantially for the two categories of people, as they respectively experience said improvement beginning from very different cognitive baselines (for instance, due to the possible presence of impairing neuropsychiatric conditions) and correspondingly achieving very different final "cognitive outcomes".

Thus said, in order for the present dissertation to be as effective as possible in providing a clear, comprehensive and insightful overview of both the empirical aspects of the rampant phenomenon of Pharmacological Cognitive Enhancers (PCE) use at colleges and universities and the ethical concerns it raises in the competitive contexts of university exams in Chapters 2 and 3 respectively, a more detailed, specific and possibly univocal working definition of CE is surely needed to begin with as a conceptual foundation for the present dissertation as a whole to unfold and progressively delve into the various facets of the subject matter.

A reasonable way of approaching the challenging conceptual task of laying down an unambiguous definition of CE may be examining how the expression is predominantly used in the current scientific and bioethical literature on the topic.

At present, the expression "cognitive enhancement" is typically employed by the general public as a generic synonym for improvement in human cognitive faculties, which should consequentially lead to improved performances of cognitive-related tasks, with no further elucidations as regards the different empirical connotations it may take in practice and the various theoretical premises underlying the concept as a whole. On the other hand, the concept of CE tends to be characterised rather differently in distinct scientific and academic contexts - so that, for instance, public health inquiries usually focus on a specific type of CE method employed, often raising concerns regarding its medically appropriate use and the potential safety risks associated with its use (DeSantis et al., 2008; Franke & Lieb, 2010), while most neuro-scientific and bioethical literature displays a much keener and often optimist interest in their purported (and mostly scientifically unproved yet) benefits or in the ethical implications stemming from an eventually society-wide implementation of CE (Harris, 2011; Greely et al., 2008). Indeed, expert contributions on the topic in the academic literature do usually clarify even on a case-by-case basis the different and specific conceptual and factual connotations the subject matter assumes in their respective analyses.

However, whilst it is true that the state of the art as regards the general debate on CE is a long way from delivering, agreeing on and universally adopting an ultimate and unambiguous definition of what the expression "cognitive enhancement" exactly stands for and which cases are most suited for its proper usage, it is equally true that some sort of general consensus has somewhat implicitly been reached over time in the current associated literature, which by and large acknowledges as a most valid working definition any characterisation of CE whose meaning is consistent with the one expressed in an extensively quoted definition of CE as "interventions in humans that aim to improve mental functioning beyond what is necessary to sustain or restore good health" (Juengst, 1998)[4].

This pioneering definition of CE has paved the way for later ones, which are equally satisfactory for use in whichever context of discussion about the matter in that their conceptual foundations all rest upon a basic, fundamental distinction between *enhancement* and *therapy*.
Upon studying the etymology of the word "therapy", we find it originates from the ancient Greek *therapeía*, meaning "healing" (akin to *therápōn*, "attendant"). The Collins Concise English Dictionary defines it as "the treatment of physical, mental, or social disorders or disease"; to this meaning, the Word Reference Random House Unabridged Dictionary of American English 2020 adds "as by some remedial, rehabilitating, or curative process". This is the crux of the distinction: inherently, the notion of therapy necessarily entails the features of either prevention, rehabilitation from or mitigation of diseases, disorders or impairments. On the other hand, the word "enhancement" simply entails some sort of identifiable and measurable improvement, which in the biomedical sciences is taken to apply to healthy individuals[5] – thus, in contrast to the improvement expected in therapeutic treatments, which remedy to disadvantaged health conditions of patients by attempting to restore "normality" through palliation and rehabilitation from the medical conditions in question.

In relation to that, it must be pointed out how in much of the previous scientific research and academic literature the expression "cognitive enhancement" was usually connoted by a predominantly therapeutic meaning, as it was mostly used in reference to interventions aimed to either palliate, remedy or cure neuropsychiatric conditions such as developmental disorders (i.e. attention-deficit hyperactivity disorder) and neuro-degenerative diseases (i.e. Alzheimer's and Parkinson's diseases) entailing some more or less serious forms of cognitive impairment, deficit or disability that such CE interventions were intended to either try to reverse or at least make up for (Forlini et al., 2013). In these instances, the use of the expression "cognitive enhancement" clearly reflected efforts to improve the mental functioning of cognitively impaired patients insofar as it was both necessary and sufficient to at best restore or (more plausibly) simply sustain and try to prevent the irremediable deterioration of the normal functioning of their neural systems.

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[4] For further insight, see Hildt and Franke (2013): "Eric T. Juengst (1998) described the concept of enhancement to be a "moral boundary concept". Whereas on the descriptive level, enhancement serves to characterize a certain measurement to lead to some form of improvement, on the normative level, enhancement could be described as dwelling outside the field of medicine and beyond medical obligation, a measurement not legitimized by medical needs. In this distinction between treatment and enhancement, the concepts of health, disease and normality and the aims of medicine are crucial."
[5] For instance, see Hildt and Franke (2013): "Unlike medical treatments, enhancements aim at some kind of betterment in healthy individuals."

This understanding of CE in an exclusively therapeutic sense has been embraced rather uncritically by expert and lay people alike and remained unquestioned for quite some time, until people started to become aware of the latent and much more promising opportunities that such cognitive-enhancing interventions had to offer to cognitively healthy people as well.
For instance, unprecedented attempts at increasing or ameliorating cognitive functioning (e.g. through brain training with computer-based technologies, pharmaceutical drugs or stimulating devices) among the mentally elderly, in the sense of at least trying to slow down the cognitive and memory decline which physiologically occurs with age, have begun to be carried out in recent years under the label of CE, urged by the recent but widespread concern about developing dementia on the part of many ageing people (Harvey & Keefe, 2015; Taya et al., 2015).
Before long, these cognition-improving methods began to spark a great new deal of interest among neuroscientists and academics and to arouse much curiosity on the part of the general public, this time for enhancement use among cognitively healthy individuals wishing to better their intellectual performances – and no longer solely for therapeutic use targeted at cognitively impaired patients suffering from neuropsychiatric pathologies or at the elderly worrying about with looming dementia symptoms.

Against this background, the present dissertation finds its core conceptual foundation in this narrower configuration of CE, which strictly focuses on application to cognitively healthy individuals – as opposed to cognitive therapies, which comprise the entire range of methods and approaches intended to treat or at least relieve the burden of patients suffering from neuropsychiatric pathologies and cognitive impairments by trying to ameliorate their cognitive functioning. With this in mind, then, CE "is achieved when cognitive abilities are improved above what is considered to be 'normal range' functioning for human beings" (Blank, 2016).

Now, it is important to stress the fact that, at times, it may indeed prove very difficult to categorically discern the difference between a "normal functioning", cognitively healthy person and a cognitively impaired one (Ball & Wolbring, 2014) – particularly if we consider the increasing medicalisation[6] of

[6] Blank (2016) expresses a common, critical stance on this somewhat arbitrary distinction by asserting that "Where this distinction between 'cognitively disabled' and 'normal functioning' lies is unclear, and will likely become more ambiguous as our cognitive traits continue to be pathologized (Conrad & Horwitz, 2013; Coveney et al., 2011; Schanker, 2011). Furthermore, it can often be difficult to categorically determine whether an individual is 'normal', or suffering from a psychiatric condition requiring treatment, because many psychiatric diagnoses present as spectrum disorders. If we are going to posit differences between treatment and enhancement, we need a clear conceptualization of the point at which treatment becomes enhancement which, in turn, hinges on the definition of normal (Turner and Sahakian, 2008)". […] The concepts of disease and disorder themselves are also hard to pinpoint, especially with the tendency to regard more and more health states as diseases and, thus, more interventions as treatments (Nagel, 2010). Invariably, there will be borderline cases and disagreement among observers. From a sociological perspective, the distinction between therapy and enhancement is difficult to uphold because the concepts this distinction is based upon (i.e. normal, health, disease, etc.) are so difficult to establish and variable over time (Ball & Wolbring, 2014)".
Brühl and colleagues (2019) also note the presence of "the problem of defining normal compared to the usually better accepted definition of deficit in neuropsychiatric disorders (although this definition usually relies on a statistically defined normal performance, termed norms). These two definitions are often not clearly differentiated."

many cognitive behaviours and traits that have always been considered to be normal, ordinary or even quite common (Schanker, 2011; Conrad & Horwitz, 2013), or if we take into account the fact that some neuropsychiatric pathologies are recognised as spectrum disorders and are approached accordingly. These two factors may clearly make the boundary between traditional cognitive therapy and outright cognitive enhancement rather blurry to say the least, since the dividing line between the two notions lies on the conceptual point where cognitive disability becomes cognitive normalcy – two concepts which, in turn, depend on the distinction between disease, health and normality[7] (Turner & Sahakian, 2008; Ball & Wolbring, 2014; Blank, 2016).

Nonetheless, whilst trying to exactly tell CE from cognitive therapy may pose difficulties at times, this thesis will stick to the narrower connotation of CE as targeted to people who are commonly regarded as being cognitively healthy under a medical and broader sociological perspective.
Then, an appropriate working definition of CE here may refer to the recourse to biological interventions which are definitely not geared to ward off, alleviate or cure the symptoms of a neuropsychiatric condition, but, rather, are aimed to induce an improvement in cognitive faculties or in the execution of cognitive-related tasks on the part of individuals who are not suffering from any medically diagnosed mental pathology, but simply seek to achieve better intellectual performances (Schermer et al., 2009).

However, the selection of definitions suggested so far as most suitable for expressing the essential features of CE have mainly focused on emphasising the ultimate goal of CE – namely, the enhancement of human cognitive abilities – , perhaps to the slight detriment of the actual means resorted to in order to achieve such CE goal. Therefore, for the sake of a higher degree of specificity and clarity – as the following section will illustrate in detail – it is worth noting that some authors have deemed it sensible to flesh out and condense the concept of CE at one time by delineating it as "the use of pharmaceutical drugs or devices for non–health-related improvement of cognition" (Dubljević et al., 2015).

However, the very reason why it is so important to specify and unravel proper CE interventions as devoid of any therapeutic aim from treatments (i.e. preventive, curative, rehabilitative, and compensatory) of neuropsychiatric pathologies involving the use of the same methods and technologies is because, otherwise, the undiversified use of the expression in reference to both the therapeutic and the sheer enhancement aims turns out to be highly problematic in that it does not allow to grasp the range of serious medical, social, ethical and normative implications concerns raised exclusively by the concept of CE intended narrowly as unencumbered by therapeutic connotations of any kind. This more circumscribed definition does in fact usefully untangle circumstances which are socially accepted and fostered from similar ones which are, on the other hand, frowned upon, deterred or even forbidden (Dubljević et al., 2015). While, on the one hand, cognition-improving interventions in mentally disabled patients are

[7] See Blank (2016): "[…] the concept of 'normality' is itself elusive and may vary widely from place to place and time to time".

usually highly encouraged, supported and incentivised at the societal level at large on the basis of some generally accepted principles of equal opportunities and distributive justice[8] in providing for citizens' medical needs by compensating for their health impairments, on the other hand it must be pointed out that such biomedical interventions[9] would surely spark mixed and divergent reactions among lay and expert observers alike if their application to cognitively healthy people for mere enhancement purposes were to become common practice in societies across the world. In fact, as will be illustrated in Chapter 3in the context of universities and colleges, the recourse to biomedical cognitive-enhancing interventions on the part of cognitively healthy people may potentially be regarded as an unfair way to gain a cognitive edge over "normal", unenhanced people, thus stirring tricky ethical problems at the societal level (e.g. issues of cheating, coercion and inequality of access and opportunities).

Returning to the definition of CE suggested by Dubljević and colleagues (2015), the moral tension surrounding the bioethical contrast between conventional therapy and outright enhancement is further exacerbated when considering the scope of medical practice in relation to the fact that the pharmaceutical drugs or devices which are now used for "non–health-related improvement of cognition" were originally developed for the specific purpose of treating neuropsychiatric conditions. For instance, there have been and, indeed, there still may occur instances where some physicians may refuse to prescribe pharmaceutical drugs to healthy patients who so demand for enhancement purposes, based upon the fact that they deem their use for CE as immoral and beyond the scope of medicine per se, since CE does not have any preventive, rehabilitative or compensatory purpose under a medical perspective (Bergström & Lynöe, 2008; Banjo et al., 2010; Mendelsohn et al., 2010; Schelle et al., 2014). Some may even claim that the recourse to drugs or technological devices for CE should be regarded as illegal for various reasons (Bell et al., 2012): similar stances clearly entail normative consequences, because what is illegal should by definition be banned by the very law it infringes. Ultimately, the importance of normative discourse over the legal challenges associated to the issue of CE undoubtedly represents another foremost reason why the recourse to pharmaceutical drugs and technological devices for CE on the part of cognitively healthy individuals should be strictly differentiated from the therapeutic use of those same drugs and technologies for the treatment of neuropsychiatric conditions among cognitively disabled people.

[8] In this case, distributive justice as a moral principle is taken to mean fairness in allowing patients needing medical treatments to be cured in order to compensate for the deficits or impairments that they just happen to suffer from and that effectively deny them the possibility to conduct an active, meaningful or decent life or to take advantage of the same opportunities in life that healthy people do enjoy.

[9] For the time being, they basically include pharmaceutical drugs and technological devices, as according to the definition by Dubljević and colleagues (2015) cited in this page.

1.2. Different methods of CE

Now that a narrow and more adequate definition of CE has been set out, the next step is to specify what methods and technologies fall within the vast array of biomedical interventions that generally come under the heading of CE and that are currently resorted to and regarded as appropriate for this purpose.

To this end, this section will provide a general review of the broad range of existing approaches to CE in the present day. For the sake of simplicity, the array of interventions commonly clustered under the label of CE will be presented in this section in a consistent fashion with respect to the previously quoted definition[10] of CE suggested by Dubljević and colleagues (2015): that is to say, they will be reviewed as divided into the two broad categories of Pharmacological Cognitive Enhancement (PCE) and Non-Pharmacological Cognitive Enhancement (NPCE), respectively.

For a matter of focus, the overview presented in this section will not discuss commonly used and conventional lifestyle interventions (e.g. the so-called "environmental enrichments", education, healthy diet, physical exercise, meditation, proper sleep routine, caffeine or nicotine intake, natural dietary supplements, mnemonic strategies etc.) that, although generally safe, historically long-established and favourably accepted as morally legitimate across virtually any society in the world, are not usually regarded as proper CE strategies. In fact, although their lifestyle implementation is commonly - and rightly - deemed as beneficial for keeping the brains healthy and for maintaining and possibly improving mental agility, their "stimulating" action and enhancing effects on cognitive functions are extremely bland, or even null at times – thus, significantly different in extent from the effects of PCE. Most importantly, such ordinary "lifestyle interventions" are very hardly employed in a targeted way for CE purposes in particular, as compared to PCE and NPCE approaches (Garasic & Lavazza, 2016).
Also, although some scholars (Franke et al., 2014; Maier & Schaub, 2015) suggest also considering the use of some substances of abuse and illicit drugs (e.g. alcohol, cannabis, cocaine, ecstasy etc.) for CE purposes, these will not at all be dealt with here, because several studies have proved that these are most commonly used for recreative purposes - whereas the enhancement of cognitive function is the exception, rather than the rule.
Finally, the present section will not address some "futuristic" and still putative NPCE technologies such as nanotechnological neural implants, computer-based brain-machine interfaces (BMIs) or high-tech prosthetics, because they are either still in the research stage or a long way from being fine-tuned for CE purposes. In this respect, this review will not conjecture at all about which direction CE may take in the future as neuro-scientific research in the field progresses further with new biomedical developments in neuroscientific knowledge.
In fact, both conventional life-style interventions and developing technologies have already been the subject matter of extensive discussion and speculation elsewhere, whereas the present work is strictly

[10] Section 1.1, p. 5.

concerned with biomedical interventions which are actually resorted to for CE at present and are investigated in current empirical research to be explicitly marketed for CE use in the future.

Finally, it is important to stress that each different CE method/intervention is characterised by its own peculiar properties (e.g. pharmacological mechanisms of actions, risk-benefit ratio, technological manufacture etc.), and that is why each of them is being explored separately from the others (Coenen, 2008); however, the actual efficacy and the potential risks and adverse effects of the following CE methods will be delved into in detail in Chapter 2.

1.2.1. Pharmacological Cognitive Enhancement (PCE)

At present, the vast majority of scientific research, academic literature and bioethical debates on CE mostly focus their attention on PCE methods, because these represent the most common, documented and accessible strategy used among cognitively healthy individuals for boosting cognitive functioning to date (Banjo et al., 2010).

PCE interventions (which are often dubbed as "nootropics"[11] or "smart drugs") basically include chemical substances mainly coming under the form of pharmaceutical psychoactive drugs that were originally developed and marketed for the treatment of various neuropsychiatric conditions; such substances are used off-label for CE by cognitively healthy people, in the absence of diagnosed medical conditions, for the purpose of enhancing the performance of cognitive-related tasks beyond the usual standard levels. In fact, the general mechanism of action of pharmaceutical cognitive enhancers works by altering the balance of brain chemicals in order to induce some improvements in human cognitive faculties (Garasic & Lavazza, 2016).

Notwithstanding major differences in their chemical composition and pharmacology, the majority of PCE drugs known to date share some typical features:

1. They are prescription psychostimulant drugs which were originally developed as therapies for patients suffering from neuropsychiatric conditions such as developmental disorders (i.e. attention-deficit hyperactivity disorder) and neuro-degenerative diseases (i.e. Alzheimer's and Parkinson's diseases) (Singh, 2005; Husain & Mehta, 2011);
2. Their pharmacological mechanism of action is understood to work by augmenting the cerebral production and the synaptic action of neurotransmitters (dopamine and norepinephrine above all), promoting nerve development and increasing blood pressure, the flow of oxygen to the brain and glucose[12] utilisation.

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[11] For further insight on the origin of the word, see Petersen and colleagues (2018): "The term nootropics was coined in the 1970s by Giurgea and Salama (1977) to designate a new class of psychoactive substances (notably Piracetam) which can increase cognitive function (e.g., learning and memory) in the human brain. Giurgea's exact pharmacological definition is […] also explained in lay terms: "[Nootropics] are drugs, supplements, nutraceuticals, and functional foods that improve mental functions such as cognition, memory, intelligence, motivation, attention, and concentration."

[12] Oxygen (O) and glucose ($C_6H_{12}O_6$) are hereby mentioned as they basically function as the fuel which activates neuronal pathways and triggers the activity of neurotransmitters.

3. They are thought to exert a stimulating effect on the central nervous system, whereby they supposedly increase concentration, alertness, focus, attention, accuracy, memory, executive functioning, learning, perception and judgement; they are also understood to elevate mood, augment overall psychophysical sense of energy and reduce fatigue so as to boost work-prone motivation. (Talbot, 2009; Smith & Farah, 2011).
4. Scientific evidence demonstrating their actual efficacy as enhancers among cognitively healthy persons is still very sparse and mixed;
5. Significant safety concerns encompass unknown side effects, potential toxicity, risk of addiction and proneness to abuse;
6. They are used "off-label"[13] without medical prescription nor supervision in competitive-selective contexts (especially academia and workplaces) involving high-level cognitive performances and prolonged mental efforts (Garasic & Lavazza, 2015, 2016);
7. They all raise sweeping public health and ethical issues, especially if their use were to become widespread and generalised at the societal level (Bostrom & Sandberg, 2009; Blank, 2016; Jotterand & Dubljević, 2016; Brühl et al., 2019);
8. They are indeed being extensively and openly advertised by the media and through the Internet as nearly miraculous strategies to improve "normal" people's brain function with no prescription whatsoever, tickling the interest of a vast audience increasingly prone to "technological short cuts" to improve one's naturally-endowed features (Chatterjee, 2007).

In the following, a summary but comprehensive review of PCE drugs is provided.
However, the updated empirical evidence concerning the actual efficacy of PCE for the enhancement of intellectual performances in cognitively healthy individuals, the potential adverse effects and safety risks associated with their use will not be reviewed here: they will be addressed in further detail in Chapter 2 (in sections 2.3 and 2.4, respectively), within the overall empirical assessment of the phenomenon of PCE use among healthy university students – which also happens to be the empirical focal point of the present work as a whole.

[13] For the sake of simplicity and expositive clarity, the present dissertation will stick from now on through the very end to the definition of "off-label" use of prescription pharmaceutical drugs suggested by the National Institute of Drug Abuse (NIDA) in 2014 and reported by Drazdowski (2016) as follows: "[Off-label use] occurs when individuals either use medications that were not prescribed to them, use their prescribed medications in higher quantities or manners other than prescribed, or take medications for purposes other than prescribed". However, another similar and equally relevant definition is the one by Larriviere and colleagues (2009), read in the precise wording used by Blank (2016) to cite it: "Until medications are developed specifically for CE in a normal population, CE will be considered an 'off-label' use which includes: (1) prescribing drugs for conditions other than those for which they were approved; (2) prescribing drugs for patient groups other than those for which they were originally approved; and (3) varying from the approved dosage or method of administering drugs (Larriviere et al., 2009)."

1.2.1.1. Amphetamines

Amphetamines (whose enantiomers[14] are marketed as prescription drugs in the form of mixed salts) are a group of psychoactive drugs that produce a variety of stimulating effects on the central nervous system[15] and on the autonomic nervous system[16].

Mechanism of action

Amphetamines are defined as sympathomimetic amines, in that they mimic the effects produced by the actions of the sympathetic nervous system[17].

Amphetamines are reuptake modulators which inhibit reuptake of dopamine[18] norepinephrine[19] from the synapse (Iversen, 2006). They exert their primary effect on dopamine release from presynaptic storage vesicles and feature an indirect mechanism of action involving the presynaptic release of norepinephrine, increasing the activity rate of both neurotransmitters (Karoum et al., 1994; Sulzer et al., 2005; Wallace, 2012). The sympathomimetic response of amphetamines is very strong, because norepinephrine in particular is the primary neurotransmitter in the sympathetic nervous system.

Amphetamines do also act on the mesolimbic dopaminergic system[20] and on the nucleus accumbens[21], which are associated with behavioural stimulation and motor activity: this is the reason why, for instance, chronic amphetamine users can develop OCD like behaviours.

Their potency is due to the relative similarity[22] of the molecular structure of amphetamines to that of

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[14] For further insight, see Busch and Busch (2006): "Enantiomers are mirror-image isomers of a molecule whose physical and chemical properties are indistinguishable in an achiral environment".

[15] For further insight, see Daly and colleagues (2012): "The central nervous system (CNS) is a part of the nervous system that is divided into parts consisting of the brain and the spinal cord. The primary function of the CNS is to process the information received from the peripheral nervous system. Important neuroanatomical features of the CNS include neurons, glial cells, axons, membranes, and the neural tube and the ventricular system. The major subdivisions of the brain are the telencephalon, diencephalon, and brainstem. Additional components of the CNS include the cerebellum and spinal cord. Critical neurophysiological features of the CNS include neurons, synaptic transmission, and neurotransmitters. Behavioral aspects of the CNS include sensation and perception, motor system, cerebral lateralization, and language."

[16] For further insight, see Borst and colleagues (2007): "The autonomic nervous system (ANS) controls involuntary, vegetative, and visceral functions, including heart rate, blood pressure (BP), the motility and secretion of the digestive system, the urinary bladder, and aspects of sexual function. […] The responses of the ANS are involuntary."

[17] For further insight, see Lanese (2009): "The sympathetic nervous system makes up part of the autonomic nervous system, also known as the involuntary nervous system. […] The sympathetic nervous system directs the body's rapid involuntary response to dangerous or stressful situations. A flash flood of hormones boosts the body's alertness and heart rate, sending extra blood to the muscles. Breathing quickens, delivering fresh oxygen to the brain, and an infusion of glucose is shot into the bloodstream for a quick energy boost."

[18] For further insight, see Conrad (2008): "Dopamine serves as a neurotransmitter—a chemical released by neurons to transmit an electrical signal chemically between one neuron to the next to pass on a signal to and from the central nervous system. […] Dopamine plays important roles in executive function, motor control, motivation, arousal, reinforcement, and reward."

[19] For further insight, see Bylund and Bylund (2014): "Norepinephrine (also called noradrenaline) is a neurotransmitter in both the peripheral and central nervous systems. Norepinephrine produces many effects in the body, the most notable being those associated with the 'fight or flight' response to perceived danger." See also Aldred (2009): "[…] noradrenaline contributes to control of mood and arousal and can affect sleep patterns. Depletion of noradrenaline (norepinephrine) in the brain has been shown to cause a decrease in drive and motivation and might be linked to depression."

[20] For further insight, see Elsworth and Roth (2009): "The function of the mesolimbic dopaminergic system […] has been strongly implicated in goal-oriented (motivated) behaviors, in addition to reward, attention, and pharmacologically induced locomotion. Enhancement of DA transmission in this system has been linked with the addicting, reinforcing, and sensitizing effects of repeated exposure to psychostimulant drugs of abuse."

[21] For further insight, see Catterall (2009): "The nucleus accumbens is a primary site mediating reward behavior, and it is thought to be directly involved in reinforcing and addictive behaviors in response to drug use."

[22] They all present a phenyl group, an ethyl group and an amine group.

human neuromodulators and neurotransmitters such as dopamine and norepinephrine.

Therapeutic indications

Amphetamines have long been used to treat a variety of neural and psychiatric disorders: for instance, mixed salts of amphetamines (i.e. a mix of the two amphetamine enantiomers named d-amphetamine and l-amphetamine) marketed under various brand names are currently used as a treatment for attention deficit hyperactivity disorder (ADHD), as well as sleep disorders such as narcolepsy. Also, mixed amphetamine salts and even the amphetamine enantiomer d-amphetamine alone have historically been used for weight loss - which actually is still the primary use for the latter - as well as to fight fatigue and induce alertness and wakefulness.

Pharmacological effects

The pharmacological effects of amphetamines basically follow from the release of dopamine and norepinephrine from the presynaptic nerve terminals. Therapeutic doses of amphetamines induce stimulating effects on cognitive and emotional faculties (e.g. increased vigilance, concentration, learning, cognitive processing speed, motivation, arousal), decrease physical tiredness and fatigue, and improve psychomotor performance by increasing muscular energy, improving coordination and reducing reaction time (Knafo & Venero, 2015). Among the most common effects of amphetamines intake there is also an increased flight/fight/fright response, that is dose-related.

1.2.1.2. Methylphenidate

Methylphenidate (MPH) is a substitute phenethylamine[23] derivative. Much like amphetamines, MPH is a psychostimulant dopaminergic drug mainly acting on the catecholamine[24] neurotransmission in the central nervous system.

Four enantiomers of the drug exist, meaning there are four slightly different configurations of the molecule. Over time, the available formulation has come to include both d- and l-threo-methylphenidate enantiomers: of these, d-threo-methylphenidate (also known as dexmethylphenidate, much stronger[25] than l-threo-methylphenidate) is responsible for its action mainly as a dopamine reuptake inhibitor that also facilitates dopamine and, secondarily, norepinephrine release through pharmacologic mechanisms similar to those of amphetamines (Husain & Mehta, 2011; Dresler & Konrad, 2013).

Mechanism of action

The drug works by binding to dopamine and norepinephrine transporters and blocking the reuptake of these neurotransmitters: this leads to a boost in extracellular concentrations of both (with a bias towards dopamine) in the synapse and, consequently, to an increased rate of neurotransmitter activity (Heal & Pierce, 2006; Iversen, 2006).

Therapeutic indications

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[23] Phenethylamine (PEA) is an organic compound with CNS stimulating properties.
[24] Catecholamines – namely, dopamine, norepinephrine and epinephrine - are neurotransmitters.
[25] This is the reason why there are some medications which contain dexmethylphenidate only.

Methylphenidate was patented and marketed as a prescription drug for the first time in in the 1950s and its use was promoted for multiple neuropsychiatric conditions, such as ADHD, narcolepsy, behavioural problems, chronic fatigue and depression. One of the earliest common uses of the drug was in reversing the sedation caused by barbiturates. From the 1990s, it has progressively gotten more common to become the first-line treatment for ADHD. As it currently stands, MPH is a very common drug, with millions of adults and children using it for ADHD on a daily basis (Lange et al., 2010; Spencer et al., 2013). It is also resorted to for other applications, such as non-ADHD related hyperactivity in autism. Methylphenidate may also be prescribed for the treatment-resistant depression (Dell'Osso et al., 2014).

Pharmacological Effects

Thanks to its halting action on the reuptake of dopamine and norepinephrine, MPH induces effects similar to those of amphetamines (e.g. increased wakefulness, concentration, increased alertness, memory, physical energy, euphoria etc.) in ADHD patients. In particular, low doses of MPH improve vigilance levels, inhibitory control and working and episodic memory (Ilieva et al., 2015; Spencer et al., 2015).

1.2.1.3. Modafinil

Modafinil is a wake-promoting agent commonly marketed as prescription pharmaceutical drug under different brand names and prescribed almost exclusively - to date - for the treatment of narcolepsy (and associated cataplexy) and various other kinds of sleep disorders (Blank, 2016).

Mechanism of action

In spite of long-standing scientific research, the mechanism of action of modafinil is still unclear to date. However, while still being under discussion, it is understood to be somewhat similar to those of amphetamines and MPH in general terms, with some minor differences (Gerrard & Malcolm, 2007; Stahl, 2017). Several studies have suggested that modafinil acts as a weakly selective reuptake blocker, exerting a sympathomimetic stimulating effect on catecholamine neurotransmission in the central nervous system, especially with regard to the release of dopamine, norepinephrine and serotonin (Gerrard & Malcolm, 2007); other studies hypothesise "effects on γ-aminobutyric acid, glutamate, histamine, and orexin/hypocretin", leading to increased level of wakefulness, perception and arousal (Ishizuka et al., 2008; Knafo & Venero, 2015).

Therapeutic indications

Modafinil was first approved by the U.S. FDA[26] in 1998 for the treatment of narcolepsy and, at present, is also prescribed to treat obstructive sleep apnea, daytime hypersomnolence due to sleep-wake disorder, shift work sleep disorder and nocturnal sleep patterns disruption (Balloon & Feifel, 2006; Hashemian & Farhadi, 2020).

It is already used by military personnel, as evidenced in the Memorandum of the United States Air Force

[26] U.S. Food and Drug Administration. It is the U.S. Federal Agency in charge of enforcing and checking compliance with safety regulations on food, cosmetics, drugs, vaccines etc. For further information, see https://www.fda.gov/

(2 December 2003), which approves the use of modafinil for missions of great duration.

Pharmacological Effects

Modafinil helps alleviate excessive sleepiness by inducing heightened arousal, alertness and wakefulness; its use may lead to improvements mainly in attention, executive function and working memory, but there is still scarce proof of efficacy for these latter effects (Blank, 2016). Clinical trials are still being carried out to test it for use in ADHD, depression, stimulant addiction and neurodegenerative disorders (Gerrard & Malcolm, 2007).

As a result of its being employed for the treatment of hypersomnolence and disorders related to sleep disorders, the "off-label" use of modafinil has been reported to a significant extent by cognitively healthy (but often sleep-deprived) individuals, especially students and high-performance workers (e.g. surgeons, truckers, firemen), to try to stay awake, be more vigilant and focused, either in order to study longer or be more efficient at work. Interestingly, its use was approved for the military in the Memorandum of the United States Air Force (2003) in order to help soldiers and military staff to sustain prolonged mental efforts and evade fatigue and exhaustion during long missions.

1.2.1.4. Antidementia drugs

Antidementia drugs are pharmaceutical drugs prescribed to treat or at best try to slow down the symptoms of dementia associated to Alzheimer's disease and cognitive deterioration due to Parkinson's disease. Their active agents are either acetylcholinesterase inhibitors (AChEIs) or memantine[27]. The category of AChEIs-based drugs includes donepezil, galantamine, rivastigmine and tacrine – with the former being an acetylcholinesterase inhibitor and the last two being cholinesterase inhibitors. Their therapeutic use is indicated for the treatment of mild to severe cognitive and behavioural symptoms of Alzheimer's disease dementia and cognitive decline associated to Parkinson's disease (Racchi et al., 2004). Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist and are prescribed for the treatment of moderate to severe symptoms of Alzheimer's disease dementia (Sonkusare et al., 2005).

This specific category of also deserves a brief mention in that its use, although still not so widespread, is nonetheless steadily making its way into the compounds used as proper PCEs. Antidementia drugs are in fact being proposed for CE use by cognitively healthy individuals, as some clinical studies suggest they could induce faster response time in cognitive-related tasks (Dresler et al., 2013).

[27] For further insight, see Stella and colleagues (2015) and https://www.encyclopedia.com/caregiving/encyclopedias-almanacs-transcripts-and-maps/antidementia-drugs

1.2.2. Non-Pharmacological Cognitive Enhancement (NPCE)

While the literature on CE indeed displays a much stronger focus on pharmacological approaches to the improvement of cognitive faculties (Banjo et al., 2010), on the basis of the definitions laid out in section 1.1 non-pharmacological strategies may also prove successful in enhancing human cognition – not only in patients suffering from neuropsychiatric conditions, but also in otherwise healthy persons.

Currently existing non-pharmacological interventions for CE purposes comprise a range of cutting-edge brain stimulation technologies, both invasive and non-invasive ones, such as deep brain stimulation (DBS), direct vagus nerve stimulation (dVNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), among others.

Each practice differs from the others under several respects - the main ones being the technological device(s) used, the manufacture of its specific technological components, the conditions of use and the targeted brain area.

Although these innovative technologies are mainly resorted to as effective treatments to relieve symptoms of mild to moderate neurological and psychiatric conditions, since the 1990s there has been a steady surge in their diffusion in both medical and amateur contexts as CE strategies helping with the modulation of neuronal activity and the potential improvement of learning, memory, focus and alertness (Dayan et al., 2013). In particular, they are increasingly resorted to for CE in order to achieve better levels of brain function, or just for the purpose of training some specific cognitive capacities.

Let us now summarise the current state of knowledge about them in brief, also including their purported effects on cognitive functioning.

1.2.2.1. Deep brain stimulation (DBS)

DBS is a surgical brain stimulation keyhole procedure whereby two electrodes are implanted deep inside the interested areas of the brain, and a pacemaker like battery (IPG) is implanted beneath the skin just below the collar bone: then, implanted thin, soft, flexible wires connect the electrodes and the IPG. The IPG then generates small electrical high frequency impulses, which are delivered through the wires in order to reset distorted signals in the brain (in the case of Parkinson's disease) or simply modulate the activity of deep brain structures, through the electrical pulses provided to the fine probes inserted into the targeted brain areas under the scalp. In fact, the electrical current pulses do stimulate deep brain structures, whose activity is boosted with the purpose of increasing cognitive capacities (Hamani et al., 2008; Pacholczyk, 2011). DBS currently appears to have declarative learning enhancing potential by stimulating the hypothalamus and the entorhinal area (Hamani et al., 2008; Suthana et al., 2012; Suthana & Fried, 2014); however, it's not widely used yet as a CE method, but it is rather used quite effectively for the treatment of Parkinson's disease.

In fact, although DBS surgical procedure is generally safe and well tolerated, potential complications such as brain haemorrhage, ictus and cardiac events do surely have a strong deterrent effect for its use for

CE. Other potential adverse effects include stroke, sleep disorders, mnemonic difficulties, rapid mood swings, chronic headaches, and depressive tendencies (Mayo Clinic, 2014).

1.2.2.2. Direct vagus nerve stimulation (dVNS)

dVNS is another invasive technique for brain stimulation, similar to DBS but bound for afferent vagal nerves located in the neck. It works by surgically implanting a stimulator onto the vagus nerve and connecting it to a pacemaker-like battery implanted in the chest (just as in DBS). This brain stimulation method appears to involve modulation of brain stem activity through the left vagus nerve, stimulating the activity of the central nervous system (Krahl et al., 1998; Groves & Brown, 2005); however, little is known overall about how well it actually works, even though some studies have reported dVNS to enhance memory abilities (Clark et al., 1999). dVNS yields few side effects, but they're not very common nor severe; on the other hand, it must be stressed how both dVNS and DBS provide constant stimulation to the brain, as opposed to the non-invasive techniques (Dresler et al., 2013).

The major downside of both DBS and dVNS, however, is not merely their being invasive, but it also quite importantly includes their expensiveness, which undoubtedly poses significant challenges to their fair and equal distribution. (Ben-Menachem, 2001; Kuhn et al., 2010).

1.2.2.3. Transcranial magnetic stimulation (TMS)

TMS is a non-invasive, outpatient brain stimulation procedure whereby a magnetic coil is placed over the scalp and generates an electromagnetic field whose short but intense magnetic pulses then painlessly drive into the interested regions of the brain enough electric currents to cause the neurons at the surface of the brain to reach what may be called an action potential[28], thus stimulating underactive neural pathways and augmenting neural plasticity (Hsieh, 2015). A singular TMS session, for instance, practices such previously "idle" neural pathways from three to five thousand times more than the usual.

At present, TMS is mainly and successfully used for the therapeutic non-drug treatment[29] for adult patients aged 18 and above who are still suffering from depression after not having responded to antidepressant medication use. It's also being used to treat a number of different nervous system disorders and conditions like anxiety, PTSD and OCD, and research is finding the use of TMS to be beneficial with individuals dealing with substance abuse disorders as well as with some of the symptoms of pervasive development disorders such as Asperger's or autism.

However, despite the fact that TMS is currently being employed primarily to recover cognitive capacities lost because of cerebral trauma or neuropsychiatric conditions, it has recently been used also to enhance cognitive abilities in mentally healthy people, where studies have shown that reiterated sessions may have led to significant and long-lasting betterment in associative memory through hippocampal stimulation (Clark & Parasuraman, 2014; Nelson et al., 2014; Wang et al., 2014). So far, more than 60 studies of

[28] This means the neurons start to fire one after the other with a domino effect and form the connections that enable learning.
[29] Recently cleared by the U.S. FDA.

TMS sessions among cognitively healthy individuals have shown major (but only short-term) rapidity and precision enhancement in motor skills, visuospatial tasks and executive activities (Luber & Lisanby, 2014). TMS has also proved to accelerate memory processes (i.e. encoding, storage and retrieval) through prefrontal lobe stimulation (Gagnon et al., 2010).

Because it is a non-systemic, focal treatment, TMS doesn't have any of the typical side effects featured by traditional neuropsychiatric medications/treatments (e.g. memory difficulty, dry mouth, sedation, nausea etc.). The most common adverse effect of TMS is just a mild headache, which however disappears in the course of a few days. Most patients, however, report no side effects.

Finally, it must be pointed out that long-term effects of TMS are still unclear, with a major safety concern related to the potential serious risk for epilepsy seizures being triggered.

1.2.2.4. Transcranial direct current stimulation (tDCS)

tDCS is another type of neuro-modulatory, non-invasive transcranial brain stimulation technique whereby a weak electrical direct current (usually in the range of 0.5 to 2 mA) is delivered through the brain by means of two small electrodes positioned over designated areas of the scalp, in an attempt to modulate neural excitability in specific brain regions and increase neuroplasticity in a polarity-dependent fashion (Been et al., 2007; Maslen et al., 2014b). In the short term, the mechanism of action of this procedure involves triggering increased neuronal firing in surface regions of the brain, with the anode depolarising and stimulating neuronal activity under the scalp area where it is placed, and the cathode hyperpolarising and inhibiting the neurons located in the targeted brain area (Nitsche et al., 2008; Stagg and Nitsche, 2011); in the medium run, tDCS modifies the synaptic microenvironment in the brain; in the long run, this technique induces changes in neurotransmitters and increases neural plasticity (Stagg et al., 2009). The effects of tDCS can last up to four hours after the single tDCS session, which usually takes no more than 30 minutes (Nitsche et al., 2005).

To date, the most relevant field of application of tDCS has been the neurological one, especially in post-stroke rehabilitation to treat motor, cognitive ad speech deficits; in addition, it has frequently been used to treat patients suffering from Parkinson's disease, fibromyalgia and chronic migraine. On the other hand, its use has also been featured in the psychiatric field, as part of attempts to cure depression, OCD, PTSD, schizophrenia and disorders related to substance abuse and withdrawal.

tDCS has also been claimed to help enhance some cognitive functions in otherwise healthy individuals, such as attention, concentration and vigilance, depending on the targeted brain areas (Coffman et al., 2014). Improvements in verbal and motor learning, working memory and in memory consolidation have been reported as the most common ones following tDCS sessions in research settings (Kincses et al., 2003; Marshall et al., 2004; Fregni et al., 2005; Teo et al., 2011; Ohn et al., 2008; Chi et al., 2010; Fox, 2011; Clark et al., 2012; Javadi et al., 2012; Javadi & Walsh, 2012; Dubljević, 2014). In addition to that, mathematical skills and performance in verbal fluency tasks were found to have been ameliorated by tDCS in various studies (Iyer et al., 2005; Cohen Kadosh et al., 2010; Iuculano & Cohen Kadosh, 2013;

Knechtel et al., 2013).
Although the long-term safety of tDCS has yet to be established, scientific evidence for this brain stimulation technique suggests that it has not proven to be dangerous or problematic so far (Poreisz et al., 2007; Rossi et al., 2009; Hamilton et al., 2011).
The most common adverse effects reportedly include mild and only temporary tingling and a burning or itching sensation; nausea, headache and dizziness seldom occur. However, people undergoing tDCS must be aware that this procedure carries the serious (although very infrequent) potential risk for epilepsy seizures when the stimulation parameters are not regulated properly[30] (Brunoni et al., 2012).
Finally, a major cause for apprehension is represented by serious risks of misuse of tDCS devices by amateur users (e.g. video-gamers) in medically unsupervised contexts for cognitive "self-stimulation" purposes, enticed by overinflated, merely profit-oriented and misleading online advertising of relatively inexpensive and cure-all DIY tDCS devices to use at home to stimulate and "boost the brain" (Cohen Kadosh et al., 2012). In fact, tDCS devices are still not standardised worldwide: therefore, the main risks associated with the untrained performance of tDCS with DIY units are that such self-built equipment may not be properly manufactured, that it may be used inappropriately (thus causing unintended and detrimental effects to the brain) and that it may not even be tested to ensure compliance with satisfactory medical safety requirements (Maslen et al., 2014a, 2015).

[30] Differential physiological and adverse effect profiles depend on the electrodes size, their positioning, on the intensity and duration of the stimulation session, on the number of sessions per day and the interval between each session.

Chapter 2

Empirical assessment of PCE among cognitively healthy university students

Taking the cue from the definition of CE by Dubljević and colleagues (2015) quoted in Chapter 1[31], it has been illustrated throughout section 1.2 how the aim of enhancing cognition in the most general sense or, more specifically, the performance of cognition-related tasks in healthy human beings can be pursued through a range of both pharmacological and non-pharmacological means. However, the use of pharmacological psychostimulant substances for CE purposes – more succinctly termed "Pharmacological Cognitive Enhancement" (PCE) - represents, to date, the most widespread, popular, and accessible strategy to CE; consequently, it also happens to be the most investigated and discussed one in both scientific and bioethical literature on CE. Taking a look at the sheer magnitude of the body of studies and debates conducted over the last two decades in the field of CE, the whole concept of the CE endeavour is often even implicitly equated with outright PCE use only - with the discussion of NPCE rather being left aside, as it is deemed to be still very speculative for the time being, and somehow still too futuristic under many respects.

As matters stand today, the practice of PCE use among healthy individuals has been extensively and consistently documented by a sizeable amount of studies in different contexts across societies, with educational and high-performance professional settings being indeed the most common ones.

As it was anticipated since the very beginning, this work is strictly aimed at investigating the various features characterising PCE in particular, rather than CE in general, with a specific focus on the growing phenomenon of PCE use within academia in the world on the part of otherwise cognitively healthy students.

The rationale underlying this specific choice is better understood by considering the following reasons. First and foremost, academic contexts offer clear and widely recognised criteria and protocols with regard to how to observe and measure academic individual performance. Secondly, academic tests and exams justify a somewhat special attention in that, in such contexts, intellectual individual performance depends almost entirely on individual cognitive abilities (Kipke, 2013). Thirdly, cognitive enhancement in the context of academic competition does indeed give rise to peculiar and sweeping ethical and social issues related to said competition, namely, concerns related to the thorny question of "cheating" - in terms of the purported validity of tests and exams' results per se and with respect to other peer competitors, as the potential analogy with doping in sports may suggest - and the issue of the risk for implicit coercion due to widespread PCE use at universities. Lastly, academic contexts are, to date, the most widely studied

[31] Section 1.1.

ones as part of empirical research on PCE and, therefore, the available data on PCE use within universities is much greater as compared to other contexts. To illustrate this, although a great deal of research has actually recorded PCE use in several diverse workplaces[32] (e.g. Dietz et al., 2016; Wolff et al., 2016), the majority of evidence is mainly of university students steadily resorting to PCE to a greater extent in key academic periods, such as during the run up to admission tests, midterms and final exams (Bennett & Holloway, 2017).

Let us now delve in more detail into the empirical aspects of PCE use in academia by healthy students, with a view to present a definite and comprehensive picture of this mounting phenomenon.

2.1. Current prevalence of PCE among cognitively healthy university students worldwide

A great deal of empirical research has been conducted, especially over the last decade, with the aim to gauge the extent of the phenomenon of PCE use in universities and colleges in the world. However, trying to exactly determine the actual social relevance of the practice of PCE among healthy university students by pulling together valid empirical data has proved to be not at all a straightforward task, notwithstanding the apparently definitive and compelling "evidence" (which is mainly anecdotal) spread by the popular media and the Internet with regard to the "widespread" and even "increasing" use of prescription drugs among healthy university students for the purpose of improving their academic performances.
To date, the reality is slightly different and more complex than what these facile media claims purport. In fact, although PCE is currently widely discussed in the scientific and bioethical literature, the numerous contributions on the topic are a long way from delivering valid and extensive empirical data about its actual prevalence rates. In fact, apart from scattered (but plentiful and perhaps a bit inflated) anecdotal evidence, there has been indeed insufficient statistical and empirical research of the phenomenon in question (Brukamp, 2013). No nationwide research on PCE across campuses has been carried out so far, and the amount of information gathered to date is rather meagre, somewhat speculative and scattered across disparate studies, which are also highly inconsistent among themselves (Varga, 2012).

In fact, attempting to map out an accurate, clear-cut and sufficiently reliable picture of the prevalence rates of PCE across universities on a more or less international level is actually a much more complex challenge than one may think.
The difficulty experienced in assessing estimates of prevalence is primarily due to methodological shortcomings: the inconsistencies detected in the various sampling approaches to the selection of study

[32] For instance, see section 1.2.1.3. under heading "Pharmacological effects". For further insight, see Ilieva and Farah (2013): "[…] people persist in using stimulants to enhance schoolwork and, according to anecdotal evidence, other cognitively demanding duties such as stock trading, entrepreneurship, surgery, and professional academic work (Sahakian & Morein-Zamir, 2007; Franke et al., 2013; Kolker, 2013)".

subjects, the measures, protocols and criteria used, the investigated substances[33], demographic factors[34] and the specific contexts of data collection, all together do substantially contribute to determine a highly variable, rather mixed, inconsistent and even contradictory portrayal of scientific evidence on the issue.

For instance, according to an extensive literature review of numerous surveys carried out in North America by Wilens and colleagues (2008), the range in prevalence rates estimates concerning prescription stimulant drugs use for non-medical reasons in healthy college populations varied from 5% up to 35% - although, according to Smith and Farah (2011), the range spans from 5% to 29%. Various independent studies have also assessed the levels of stimulant abuse on campuses. Surprisingly, such studies suggest comparable percentages of students self-reporting their illicit use: averaging the respective percentages, the campus subpopulation abusing prescription stimulants is reported account for an approximate 20% of the overall student population (Babcock & Byrne, 2000; Hall et al., 2005; McCabe et al., 2006; White et al., 2006).

This seems to be suggested by the dramatic escalation in prescriptions of psychostimulant medications to undergraduate university students over the past 20 years (e.g. from 1990 to 1999, methylphenidate prescriptions in the U.S. have risen up to five times; prescriptions for psychostimulants in general have witnessed a 368.5% increase from 1992 to 2002, according to a 2002 report by the Drug Enforcement Agency), which bears as an indirect consequence a correspondingly significant increase in their non-medical usage (Advokat, 2010; Advokat & Vinci, 2012; Varga, 2012; Emanuel et al., 2013). Another comprehensive review of 28 epidemiological studies undertaken by Smith and Farah in 2011 reports the prevalence rates of PCE use (at least once in their lifetime) to span from 5.3% up to 55% among American and Canadian students. Even a small/much more circumscribed study such as the one conducted by Brandt and colleagues in 2014 at a small liberal arts college in the U.S. North-East brings up similar percentages: about 27% of the 303 students surveyed reported that they had used prescription stimulants non-medically as a study aid at least once in their life. Other comparable percentages are offered by several independent investigations assessing the non-medical use of prescription stimulant medications among students, which reveal an average of 20% prevalence of such practice across campuses (Babcock & Byrne, 2000; Hall et al., 2005; McCabe et al., 2006; White et al., 2006).

Such high percentages in a European context were confirmed, although in a very circumscribed and unsystematic study, by Castaldi and colleagues in 2012 via a paper-and-pencil survey reporting that a considerable 16% of the 77 sampled undergraduate students enrolled in the Faculty of Medicine at the University of Milan admitted having used prescription drugs non-medically for the purpose of cognitive enhancement. In 2014, the assessment of 10 studies by Franke and colleagues resulted in estimates of

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[33] Blank (2016): "[…] it is likely that some respondents might be reluctant to admit using prescription medications for non-medical reasons, especially prescription stimulants, which are FDA Schedule II controlled substances."

[34] Blank (2016): "Whether involving drugs or devices, the prevalence of CE will undoubtedly differ sharply according to age, gender, occupation, geographic region and other demographic variables, complicating the task of assessing prevalence (Farah et al., 2014) and making any generalizations from small samples dangerous."

prescription drugs use for enhancing purposes among healthy subjects falling within a range of 1% up to more than 20%.

However, such a variability in the range of prevalence rates estimates seems far too high to be regarded as plausible. In fact, the more realistic prevalence rates of off-label use of prescription stimulants for the targeted purpose of boosting cognitive performances at university are much more likely to span from 3% to 11%. In light of this, it is most easy to guess how difficult it is to obtain an exhaustive overview of the scope of such phenomenon.

In the majority of such studies, major inconsistencies and variability among their respective results stem from an uncritical lack of distinction among different categories of substances used for cognition-enhancing reasons. In fact, many surveys and polls conducted so far (such as the abovementioned one by Franke and colleagues in 2014) for the purposes of studying PCE have yielded prevalence rates of PCE use by clustering under the label of PCE the use of "any psychoactive drug with the purpose of enhancing cognition": therefore, most such studies, while conducting research on PCE prevalence among healthy subject, have actually conducted their investigations on prevalence rates of both *illegal* drugs, prescription psychostimulant drugs and the so-called "soft enhancers" (e.g. caffeinated products, ginkgo biloba, natural dietary supplements and other over-the-counter products) altogether. Such studies have been clearly focused more on the aim itself of enhancing cognition and less on the critical distinction between substances: they have not been strictly aimed to investigate PCE in particular, but rather to explore the use of substances for cognition-enhancing purposes by healthy individuals or students in general - whether they be illicit street drugs, proper pharmaceutical drugs subject to medical prescription or mere dietary supplements (which often do not have any cognitive effect at all, neither good nor adverse ones).

Some advances in this sense have been made thanks to an apparently emerging consensus in the scientific and bioethical literature on PCE, which increasingly seems to agree on distinguishing between, on the one hand, prescription pharmaceutical drugs (e.g. amphetamines, methylphenidate etc.) as proper PCE and, on the other hand, off-the-counter products and illicit drugs as respectively legal and illegal psychostimulant substances which are not regarded as PCE. In fact, this definite differentiation and categorisation of psychostimulant substances has proved helpful to stem the variability of estimate prevalence rates (Franke et al., 2014; Maier & Schaub, 2015). In the light of this approach, more valid, consistent and refined prevalence rate estimates on PCE use by healthy students in universities and colleges in various countries in the world have been obtained – in accordance with a more plausible range of prevalence percentages going from 3% to 11%.

The first instance of this differentiating approach to empirical research on PCE dates to 2001 and was quite ahead of its time back then, as regards both the extent and the careful design of the study: in fact, McCabe and colleagues surveyed a sample of 10'904 cognitively healthy American university students enrolled in 119 different universities and colleges in the U.S. and, according to the estimates, 6.9% of them declared having used prescription stimulants off-label at least once in their lives, while 4.1% of them had done so in the last year (McCabe et al., 2005). This investigation also highlighted that, overall, male research subjects (especially fraternity members) with a low GPA from the most competitive academia in the North-East showed the highest prevalence rates, perhaps suggesting some sort of generalised pattern whereby the rates of reported PCE use among students may vary depending on factors such as gender, starting GPA, type of academic institution and type of students researched . However, although this constitutes, to date, the most extensive and accurate investigation on PCE use among healthy undergraduates for the purpose of improving academic performances, another large survey was undertaken in 2013 in Switzerland: using a sample of more than 6000 Swiss university students, Maier and colleagues estimated that 7,6% of the sampled research subjects had used prescription drugs non-medically for cognitive enhancement purposes; such study has also found methylphenidate, (4,1%), sedatives (2,7%) and betablockers to be the most commonly used means of PCE among the students in. Another subsequent online survey involving Swiss undergraduates from the University of Zurich suggested a 4.7% prevalence rate for the use of prescription stimulants to achieve better academic performance in the absence of diagnosed mental illnesses (Ott & Biller-Andorno, 2014). Again, in 2014 Wolff and colleagues estimated a prevalence rate of 5.8% for PCE use (at least once in their lifetime) among about 1000 German university students. Such findings were also shown to be lower in magnitude when the research subjects were asked to report their current use of prescription drugs: the prevalence rate percentage dropped to 3%.

A 2015 investigation carried out by Schelle and colleagues on a sample of 1600 Dutch university students estimated even more modest prevalence rates: in this case, only 1.7% of the sampled students admitted the off-label use of prescription medications. The results of this study seem to be in line with an earlier research undertaken by Partridge and colleagues in 2012, where only 2.4% of the sampled 1265 participants reported non-medical use of prescription medication for cognition-enhancing purposes. Lastly, a systematic online survey administered in 2015 to a sample of 2359 students from the whole of Roma Tre University in Italy found that 4.2% of the sampled students reported having used prescription drugs (sedatives, anti-depressants, methylphenidate and mixed amphetamine salts) non-medically at least once in their lifetime either to quell anxiety or increase concentration and alertness for the sake of enhanced academic performances: 1.6% of them did so in the 12 months preceding the survey, while 0.3% in the last month before participating in the research (Mallia & Lucidi, 2016).

Generally speaking, it may seem obvious, perhaps, to stress how the high variability and inconsistency of the empirical data drawn from the literature and reported above is further exacerbated especially by the degree of anonymity (i.e. online vs. face-to-face surveys), and by the social desirability bias[35] that may affect the answers given by research subjects. In fact, it has proved very common to observe that a lower

[35] See also note 3.

the degree of anonymity and social desirability of the peculiar behavioural phenomenon, which is investigated in a given study usually yields lower prevalence rates of PCE use due to a lower willingness of participants to declare their engagement in practices such as the off-label use of prescription stimulants for non-health related reasons. These factors tend to result in answers – and, eventually, aggregate "empirical" data – which are not valid and realistic in their purported representation of the actual state of affairs with regard to the issue under assessment, and therefore contribute to both an even higher degree of variability and inconsistency across research studies in the field and, consequently, to under or overestimations of the phenomenon in question. In this respect, the use of a research method which is already well-established and has proved successful in studies on the use of doping substances in sports (e.g. Pitsch, 2016) has begun to be considered by researchers recently for application to research studies on PCE – namely, the Randomized Response Technique (RRT), which allows to maintain a high anonymity standard with regard to sensitive information. A paper-and-pencil questionnaire administered by Dietz and colleagues (2013) to a sample of 2569 German students at the University of Mainz was the first one ever to be designed on the basis of the RRT: according to the results, a great 20% of the surveyed students reported having used PCE in the last year. Also, consistently with other studies such as the U.S. national survey mentioned above (McCabe et al., 2005), this research too seems to suggest that, overall, male respondents display higher prevalence rates of PCE use as compared to their female counterparts (which report a prevalence rate of 7% only), again hinting at the potential impact of gendered factors on the prevalence rates of PCE use among healthy students.

A final observation may also be remarked about the generally higher tendency for North American undergraduates to report the use of prescription drugs[36] to improve their cognitive faculties and performances in academic tasks as compared to university students elsewhere in the world, as well as about the significant pattern of higher diffusion of PCE in the U.S.A relative to Europe (Maier & Schaub, 2015).

2.2. Reasons and motivations for healthy undergraduates to resort to PCE

In order to figure out why the controversial practice of resorting to PCE is becoming increasingly frequent and pervasive especially among otherwise healthy university and college students, it is essential to at least try to get a deeper understanding and awareness of the factors underlying the psychological mechanisms which actively determine the growing prevalence of this behaviour.

More importantly, assessing the determinants which compel undergraduates to engage in the off-label misuse of psychostimulant medications may prove instrumental in providing an essential aid to define and design preventive measures and interventions tailored to address the needs and the potential problems encountered by PCE users (and abusers) - because, as will be expounded in section 2.4 of this chapter,

[36] This factor may constitute an hindrance to the comparability of international empirical data on PCE prevalence rates among healthy university and college students.

one of the health risks posed by long-term and high-dose PCE use to healthy individual is the potential for developing addictive habits and engaging in substance abuse patterns in the long run.

To date, the amount of existing research dedicated exclusively to the collection of the self-reported reasons to use PCE and to the analysis of the subtended, more latent motivations prompting so many undergraduates towards the off-label use of prescription stimulants without any medical need in the conventional sense is still rather scarce - as compared, for instance, to the variety of scientific studies on the actual effectiveness of psychostimulants used as cognitive enhancers by cognitively healthy individuals in general. In fact, the body of research on the reasons behind the growing spread of PCE among university students mainly consists of brief and rather summary assessments usually coming as part of introductory sections of more comprehensive contributions on the topic. It has also proved to be quite disorderly in its design, as the vast majority of the empirical investigations on PCE undertaken so far have analysed the use of different types of substances and drugs by different groups of students, whose reasons to do so have been worded slightly differently in each study, resorting to diverse research methods. Nonetheless, rare systematic reviews synthesising the meagre body of empirical findings on the reasons behind the use of prescription stimulant drugs by healthy university students have been conducted and have yielded quite significant conclusions so far. In fact, they have demonstrated that the findings of the sparse studies seem to be rather consistent with each other on the whole. Two recent systematic literature reviews by Benson and colleagues (2015) and Drazdowski (2016) have used qualitative methods to assess the most commonly endorsed motives behind the off-label use of prescription stimulants among healthy university students, and have showed that the most frequent self-reported reasons were strictly academic in nature, with users citing "to concentrate better while studying", "to improve study skills", "to stay awake to study longer" and "to improve concentration" as the major motives for the non-medical use of stimulant medications. The only quantitative meta-analysis undertaken so far on the empirical literature concerning the motives underlying university students' choice to resort to PCE is the one by Bennett and Holloway (2017), who, upon pooling the findings of 29 studies reporting prevalence data on the most common motives and specifically covering prescription stimulant use among undergraduates, reported that the most frequently cited motives for the off-label use of psychostimulants were to enhance 'academic outcomes' and 'to stay awake', whose respective prevalence rate percentages of 60% and 48% were significantly higher than those for other motives (i.e. "to experiment", "to party", "to get high" etc.).

By and large, single research studies have delivered uniform findings which are consistent with the ones mentioned above, even though they are differently phrased each time.
Teter and colleagues (2005) reported that the undergraduates surveyed in their study cited two main reasons for engaging in PCE, namely, "to help with concentration" and "to increase alertness".
According to Advokat and colleagues (2008), undergraduate students usually resort to the non-medical

use of prescription psychostimulants to enhance their academic performance, specifically by augmenting focus, concentration and the capacity to stay awake longer to study. Rabiner and colleagues (2009) surveyed online more than 3400 undergraduates from two U.S. south-eastern universities and found that the main rationale among healthy college students for using ADHD prescription pharmaceuticals off-label was to enhance their ability to maintain sustained attention and “to concentrate better while studying”, as they perceived their short attention span and self-reported lack of prolonged concentration to be major obstacles to successful academic achievements. Franke and colleagues (2011) found, in a sample of German university students, that the major reason motivating users to engage in the off-label use of prescription stimulants was in fact to achieve some sort of cognition-enhancing effect to increase their ability to study longer. Ghandour and colleagues (2012) investigated a sample of cognitively healthy Lebanese students, and found that those who reported using prescription stimulants most prevalently did so with a view to benefiting from the effects for which they are usually prescribed to actual patients (e.g., to stay focused over extended periods, improve concentration and increase wakefulness), although applied to academic goals: this suggest that such students were plausibly sort of seeking a means to treat their self-perceived attention problems, in the hope this practice would enhance their ability to study Dennhardt and Murphy (2013) and Gallucci (2013) also indicated that the most prevalent reasons for university students to use prescription psychostimulants non-medically were “to help concentration” and “to increase and sustain alertness”, both for the sake of improving academic performance. Once again, some sort of pattern suggesting a correlation between self-reported concentration problems and the use of PCE to help in the pursuit of better academic results was detected.

Therefore, it seems reasonable to conclude that the whole range of empirical research studies undertaken so far on the topic unanimously suggest that the off-label use of prescription stimulant medication among cognitively healthy individuals in collegiate contexts is mainly fostered by students’ inclination to experience the stimulating effects of said medications in the belief that these will produce some enhancement of cognitive faculties such as to increase attention, concentration, focus and alertness and to prolong or maintain an efficient and productive level of wakefulness.

In fact, as compared to other social groups, university students do seem particularly attracted by the idea of availing themselves of alternative aids to enhance their naturally endowed cognitive faculties, for the very reason that, generally speaking, they reportedly perceive a strong need to study better and longer, in order to be more efficient and to perform better on tests and exams – to put it briefly, to enhance their academic performances.

Whilst this semi-ubiquitous necessity felt by such a large number of university and college students in the world may indeed be considered the major cause behind their propensity to conceive of prescription stimulant drugs as a viable means to CE, it is perhaps quite evident that it does not hold up as the one and only cause for the occurrence of PCE among so many healthy undergraduates. It must necessarily be determined, in turn, by even deeper root causes, such as subtle psychological processes and contextual determinants related to the family background of these students and to the social settings where engage in PCE. In fact, it is reasonable to believe that attempts to devise effective prevention and treatment programmes for those needing them would most likely be pointless if they targeted and sought to counteract this specific cause only.

To date, the only comprehensive assessment of the key predictive factors bringing about the need experienced by such a considerable number of students to try to achieve the utmost possible level of productivity and academic excellence – often via some sort of technological "shortcut" or external "support", as CE may also be conceived of - has been provided by Varga in 2012. According to his literature review, the overall range of underlying factors with the true potential for compelling university students to consider resorting to the use of prescription stimulants in the belief that these actually benefit their academic pursuits may be broadly grouped in four main categories – respectively, "pressure to succeed", "socio-cultural expectations", "collegiate lifestyle" and "accessibility to prescription stimulants".

First and foremost, university and college undergraduates do presently face more pressures than ever before, mainly due to "increased parental expectations", but also in relation with the heightened level of the required minimum standards for university admission, increasingly keen peer competition in the academic milieu and for scholarship programmes, individual ambition and tendency to perfectionism (Howe & Strauss, 2000; Bishop, 2003; Kohn, 2003; Sax, 2003; Kadison & Digeronimo, 2004; Taylor et al., 2002; *Chronicle of Higher Education*, 2005; Farrell, 2006; Stoeber & Hotham, 2016). Other factors determining the growing incidence of PCE among undergraduates for the purposes of boosting academic performance are socio-cultural in nature and include, for instance, "growing up with multiple friends on prescription stimulants" and, more generally, an implicit, favourable public scrutiny on the use of PCE as compared to the use of illicit drugs: "Overall, pressure to succeed contributes to [PCE] abuse; however, sociocultural acceptance of its abuse poses a greater, potentially more dangerous threat (Quintero et al., 2006). College students typically perceive […] prescription drug use […] as acceptable compared to the use of other drugs" (Varga, 2012). Furthermore, the "collegiate lifestyle" itself may strongly spur students to engage in the non-medical intake of prescription medications even in the absence of diagnosed mental illnesses: psychostimulants may in fact support them in coping with the inevitable academic stress and physical fatigue often experienced when trying to succeed in juggling courses, exams, extracurricular activities, social life and work all at the same time (Babcock & Byrne, 2000; Brooks, 2001; Kadison & Digeronimo, 2004; Dworkin, 2005; Labig et al., 2005; Law, 2007; Quintero et al., 2006). Finally, students are simply finding it increasingly easier to get prescription stimulants, considering both the high rate of prescription drug diversion on the part of their peers who actually have a valid prescription and the ease with which they can be found and purchased online without prescription (CASA, 2005; Kadison & Digeronimo, 2004).

The common denominator of all these diverse pressures lies in that they are either implicitly or explicitly linked with a latent but quintessential, constant feature that is increasingly seen as taking precedence over other salient aspects of university students' experience of life– namely, competition in the struggle to obtain better academic results than those achieved by the other colleagues. Ultimately, such competition is based on each "contestant's" strive to display better cognitive abilities than the others, in order to increase one's chances to reap relatively scarce and unequally distributed socio-economic benefits once in the job market. This dynamic is based on three common assumptions taken as unmistakably characterising modern liberal societies and economies - namely, the goal of efficient productivity, "the competition-based allocation of work, income and opportunity"[37] (Wagner, 2013), and the "societal focus on cognitive/neuro abilities" (Jotterand & Dubljević, 2016), which are the very abilities enabling contestants to take part in said productivity-oriented competition (Tomažič & Čelofiga, 2019). In fact, cognitive abilities such as memory, attention, accuracy and learning play an increasingly important role in virtually any socio-economic sphere, insofar as such abilities "are the basis of, and permeate many of the preferences and actions that have shaped society in the past and will shape society in the future. Exhibiting certain abilities is at the root of power to access privileges such as income, political influence, and employment, and having power allows one to influence which abilities are seen as essential. […] Cognition is one example of a cherished ability; the ableism of cognition (meaning that certain cognitive abilities are seen as essential) is often used as a tool to give one social group power over another" (Jotterand & Dubljević, 2016). Therefore, an excellent final degree score at the end of the academic career is often considered as the essential key to obtain employment in high-paying and prestigious jobs, which constitute only a small percentage of any given society's labour supply.

Thus, the keen emphasis which is increasingly put on cognition-based and productivity-oriented competition as the criterion to award socio-economic privileges in the civil society can be considered to be the very primordial element which, by insinuating progressively earlier and ever more pervasively in educational settings (i.e. even in high schools[38]) creates fertile soil for the use and, sometimes, the abuse of prescription psychostimulants by healthy students seeking a viable external shortcut to enhance their cognitive abilities and make them better than the others' for the sake of being as much "competitive" as possible. It then seems that undergraduates are in general constantly pressured not only to progressively improve their own standards of performance but also to improve far enough as to perform better than their colleagues, and in order to do so they must be willing to "value and take advantage of every moment to study" (Babcock & Byrne, 2000). However, they are highly likely to eventually find themselves unable to sustain such pressing and implicit societal demands by relying on their own "natural" psychophysical resources only, and many students who try to avoid "external aid" such as PCE often find themselves in a

[37] For further insight, see Wagner (2013), and the competitive socio-economic background introducing the ethical discourse in Chapter 3 of the present dissertation.
[38] For further insight, see Varga (2012).

study vicious circle such as one peculiar case mentioned by Varga (2012): "He obsessed over earning high marks and […] stayed up to the wee hours of the morning studying. […] By studying too much and too long, Ted was soon studying less and less efficiently. This increased his need to study more, setting up a dangerous cycle". Even if this is a rather extreme example, it has been consistently demonstrated that many students may eventually suffer from considerable stress upon realising that they are unable to actually study longer and better. There is no wonder, then, if they seek external help to cope with such expectations and find it in PCE: in fact, many undergraduates turn to the off-label use of prescription stimulants just to have that much psychophysical energy and wakefulness enabling them to be more productive, even in the absence of neuropsychiatric conditions of their own.

Several empirical studies seem to have demonstrated the validity of claims regarding PCE among healthy students as a function of academic stress: for instance, an extensive study by DeSantis and colleagues (2008) involving 1811 undergraduates highlighted a strong positive association between prescription stimulants use and academic stress, with a significant peak use during finals and exam periods. Sattler and Wiegel (2013) also investigated the prevalence of PCE among German university students and noticed that the use of prescription stimulants among healthy students increased during the six months preceding anxiety-inducing tests. In line with these findings, Moore and colleagues (2014) confirmed that "evidence was found to suggest an increase in psychostimulant use during periods of stress, with significant differences found from self-report data between the first week and midterms and from chemical data between these same two assessment periods as well as between the first week of classes and finals. Brandt and colleagues (2014) further corroborated such results by stressing how the findings of their own study on university students also indicated that the vast majority of the users surveyed resorted to prescription stimulant medication especially in the run-up of midterm and final exams. Quite importantly, other studies such as those by Bavarian and colleagues (2013) and Ponnet and colleagues (2015) have consistently shown that the heightened stress perceived in these specific times of the academic year is often aggravated by students' self-reported procrastination and poor time-management skills.

Further light has been shed on the motives for engaging in PCE on the part of otherwise healthy university and college students. Based on the research results reviewed so far, it can be concluded that, among the many factors contributing to PCE, there is a more important, definite and understandable rationale behind healthy undergraduates' turning to prescription stimulants to ameliorate their academic performance: the intense psychophysical stress often associated with due to persisting high-level academic competition between students, based on their making the most of their cognitive abilities in order to achieve top-notch performance and outdo other peers. This aspect should indeed be given much more consideration in the CE debate than it has ever been, in that it bears considerable normative implications both for public health policies in general and for prevention and intervention measures specifically addressing the well-being of students struggling with PCE abuse due to lack of stress-reducing and study-time management capacities. To use the words of Ross and colleagues (2018), "these findings highlight the need to […] help college students develop study and time management skills, as well as healthy ways of dealing with academic pressures and other responsibilities".

2.3. Actual efficacy of PCE in cognitively healthy individuals

Let us now move to what is, perhaps, the most basic as well as the thorniest empirical question surrounding CE methods in general and PCE in particular.

In fact, virtually any critical observer has come to wonder, at some stage, whether "the pharmacological premises of the entire CE endeavor" (Blank, 2016) actually hold up, whether the whole CE undertaking really is viable and able to deliver fruitful, appreciable and replicable results in healthy individuals or, on the other hand, is still grounded mainly on wishful thinking. In more concrete terms, the fundamental question revolves around whether the means which are, at present, most widely resorted to for the purpose of enhancing one's cognitive faculties (i.e. pharmaceutical drugs, also dubbed "nootropics" or "smart pills") do actually live up to the extremely high hype they have been attracting so far. In fact, how well do they work? Or better still: do they even work at all with regard to their alleged capacity to enhance cognition in healthy individuals? Are their promised benefits actually tangible in real-life situations? Finally, as far as the topic addressed throughout the whole dissertation is concerned, can university students reliably expect their academic pursuits to be made more easily achievable and better in outcomes by resorting to prescription psychostimulants so often touted as cognitive enhancers?

Setting the record straight, evidence has been found to largely suggest that there's an appreciable discrepancy (at best) between the clinically proven effectiveness of prescription stimulant medications in the treatment of the targeted neuro-psychiatric disorders (e.g. ADHD) and their purported cognition-enhancing effects in healthy individuals (Advokat & Scheithauer, 2013).

In fact, the most reasonable and responsible conclusion that may overall be drawn from the scientific findings available to date[39] on the actual efficacy of PCE in healthy subjects is that its alleged power to boost human cognitive faculties is still highly dubious. At present, there really appears to be no empirical evidence proving a definite cognition-enhancing capacity of PCE with any certainty. On the contrary, if anything can be asserted with a fair degree of confidence is that the widespread, enthusiastic expectations regarding the efficacy of the non-medical use of prescription stimulants for CE are, to date, largely unmet and far greater than the extent of their actual effects as tested so far in healthy research subjects in laboratories.

For instance, the Foresight Report "Drug Futures 2025?" (2010) analysed 17 stimulant pharmaceuticals acting on neuronal pathways and synaptic plasticity, and failed to detect any remarkable enhancement of cognitive abilities in healthy individuals owed to the pharmacological mechanisms of action of said psychostimulants. In 2010, Repantis and colleagues also undertook a systematic literature review, which

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[39] However, it must me stressed that these are mainly coming from scientific research conducted in controlled laboratory settings, not in real-life ones.

highlighted how two of the most popular PCE agents – namely, methylphenidate and modafinil - demonstrated only limited effectiveness upon testing on healthy users: besides a slight enhancement in memory, methylphenidate was not found to have other relevant cognition-improving effects; although modafinil was shown to have attention-enhancing effects on non-sleep-deprived individuals and to significantly help sustain alertness, wakefulness and executive memory in sleep-deprived research subjects, it could not avert cognitive performance decline in situations of severe sleep deprivation (Repantis et al., 2010b). Such findings were further corroborated in 2014 by Farah and colleagues, who, upon having reviewed more than 50 experiments, reported that the use of amphetamines and methylphenidate by healthy individuals for CE had only limited positive effects on learning faculties, and that these were neither uniform, consistent nor unfailingly manifest in all 50 experiments under assessment.

In 2013, Ilieva and colleagues had also conducted an extensive and thorough double-blind, placebo-controlled experiment to learn more on the psycho-stimulating effects of mixed amphetamine salts-based ADHD medication in cognitively healthy youth: upon completion of 13 tests involving the performance of different cognitive-related tasks (e.g. to test executive memory, intelligence, creativity, etc.) over 7 research sessions, they failed to detect any improvement whatsoever – not even a moderate/medium one, which the test was adequately designed to spot - in the performance of any one of the tasks assessed in the investigation, apart from minimal enhancement in executive function and learning measures only among those with lower baselines[40]. Therefore, they concluded that the prescription stimulants under assessment have "no more than small effects on cognition in healthy young adults" (Ilieva et al., 2013).

According to several other comprehensive reviews (de Jongh et al., 2008; Advokat, 2010; Repantis et al., 2010a, 2010b; Bidwell et al., 2011; Smith & Farah, 2011; Swanson et al., 2011; Advokat & Vinci, 2012; Langberg & Becker, 2012; Sharpe, 2014) of the research literature on the neuropsychological efficacy of ADHD medication among healthy people, mixed amphetamine salts formulations have actually proved to have very little or no significant nor lasting enhancing effects in cognitively healthy, non-ADHD individuals and, by the same token, to basically have no impact on the improvement of their academic achievements; as a matter of fact, various studies have demonstrated that even ADHD-diagnosed students do not actually experience improved academic performances beyond a general therapeutic amelioration in their poor capacity to concentrate, focus and calm down - which are the very symptoms of the cognitive

[40] For further insight, see Blank (2016): "[…] as de Jongh and colleagues (2008) note, there are a number of caveats in the development and use of neuroenhancers. First, according to the inverse U-function principle, enhancement is possible only as long as we do not already have an optimal level of arousal, vigilance or neurotransmitter concentration. Thus, an already optimally tuned brain can hardly be enhanced and, given that usually our brains already perform near the best of their ability, enhancement for most people seems limited (Quednow, 2010; Husain & Mehta, 2011; Sahakian & Morein-Zamir, 2007). To date, cognitive effects in well-rested healthy subjects have been small and hard to detect (Kumar, 2008). Interestingly, those who have the least ability in a particular area are likely to see the greatest drug-related improvement. In fact, on some tests of cognition, the smartest people actually showed performance reductions, thus stimulants had a levelling effect, allowing below-average performers to catch up to their peers, not dominate them (Szalavitz, 2009). […] Thus, individuals with a 'low memory span' might benefit from cognition-enhancing drugs, whereas 'high span subjects' might become 'overdosed.' At best, therefore, even if a technique proves to be an effective enhancer, it will not work for everyone."

deficit that ADHD medication is intended to treat, and for the sake of which it is prescribed to them (Quednow, 2010; Advokat & Scheithauer, 2013; Currie et al., 2014).

In the final analysis, then, the whole body of exhaustive reviews carried out so far on the scientific literature seem to have found no definite and incontrovertible empirical evidence in support of the oft-quoted claim that prescription psychostimulants have the power to boost cognition among the cognitively healthy, whether they be young or old. To quote Hall and Lucke (2010), there is to date "very weak evidence that putatively neuro-enhancing pharmaceuticals in fact enhance cognitive function", and this should suffice to debunk or at least reduce misleading claims about the alleged effectiveness of PCE in the betterment of human cognition.

However, in spite of the largely consistent body of evidence from neuropsychological tests finding very limited and overall unimpressive cognition-enhancing benefits of prescription psychostimulant medications in healthy individuals, these are nonetheless still persistently and widely used by healthy university student populations in particular when seeking to obtain better academic outcomes by means of the cognition-enhancing pharmaceutical shortcut allegedly provided by PCE. This contrast indeed stands out as a curious and apparently irrational phenomenon, which, with very few exceptions, has largely been neglected by the empirical literature on the topic to date.

In this respect, two seminal contributions were made in 2013, first by Vrecko and then by Ilieva and Farah respectively, who all suggested that the virtually unanimous evidence-based judgement of researchers on the general ineffectiveness of psychostimulants among healthy individuals could also be considered in a different light. Perhaps, the efficacy issue should be reformulated by also using the main reasons behind healthy individuals' (students, in this case) PCE use as an evaluation criterion – meaning that if, upon using prescription stimulants to achieve better academic outcomes, their expectations on the effects of PCE are met and if, thanks to PCE, they are very likely to accomplish the goal underlying their primary motive to use PCE, then PCE may actually be deemed effective, even in the absence of proper cognition-enhancing effects.

With regard to this, in 2013 Vrecko carried out a qualitative study on PCE use by interviewing a pool of 24 students enrolled in a U.S. elite university, in order to delve into respondents' experiences with the non-medical use of prescription stimulants. What he found is that the alteration induced in participants' emotional sphere by prescription stimulants intake was reported as a paramount reason for their engaging in PCE. In fact, the undergraduate respondents suggested that their overall improved emotional state (i.e. "feeling up" and the associated higher mental energy, "drivenness", "interestedness" and "enjoyment") was the most appreciable effect of PCE and what they perceived to be actually instrumental in order to get academic cognition-related tasks done quickly, efficiently and with top-level results. Vrecko (2013) then concluded that "emotional dynamics constitute a salient dimension of experience for university students who use stimulant-based medications as a means of improving their academic performance. […]

Participants' narratives reveal consistent links between stimulant use and altered emotional states; moreover, participants' accounts suggest that the emotional changes brought about by stimulant use are part of what makes stimulant drugs useful in relation to academic work."

Then, building upon updated scientific evidence on stimulants' capacity to improve motivation-related processes and behavioural responses in healthy research subjects, and taking the cue from the interview carried out by Vrecko (2013) showing that PCE users sought to have their academic performance enhanced mainly through the "motivational effects" of prescription stimulants, Ilieva and Farah reviewed relevant surveys, questionnaires, interviews and laboratory research and conducted a survey on their own to assess the hypothesis that PCE users may perceive prescription stimulants to be helpful in enhancing academic performances thanks to their "*non-cognitive*" effects. According to their findings, the participants "perceived stimulant effects on motivationally-related factors, especially "*energy*" and "*motivation*," and reported motivational effects to be at least as pronounced as cognitive effects, including the effects on "*attention*". These results, then, do suggest that participants perceived their motivation-related behaviours to have benefited substantially more from prescription psychostimulants than their cognitive functions did and, therefore, that such prescription pharmaceuticals may be used by healthy university students prominently for their motivational effects (e.g. improvement in energy and motivation) rather than, or in addition to, their proper cognitive effects – in spite of the widespread belief that they primarily and most significantly affect cognitive functions.

Therefore, notwithstanding the fact that this research only investigates enhancing effects of prescription stimulants as they were perceived by participants – and not as they were actually tested and demonstrated in laboratory settings –, it nonetheless proves fundamental in highlighting how it is also important to take into account experiential evaluations of PCE whilst assessing its efficacy in allowing enhancing users' ability to pursue and achieve the very aims behind their initial decision to engage in the use of prescription stimulants. As a matter of fact, the findings here strongly indicate that those university students using prescription psychostimulants for CE actually deemed PCE as both beneficial and effective, since they were unanimously satisfied by how they perceived their academic performances to have been enhanced mainly via the stimulating effects of PCE use on their motivation-related behaviours.

The results of these two qualitative analyses suggest that, overall, undergraduates may engage in PCE and deem it to effectively meet their expectations concerning the enhancement of academic performances mainly because of the relevant impact psychostimulants exert on users' emotions and feelings.

In fact, students often perceive the occurrence of such emotional alteration as "an important dimension of the drug effects that users perceive to enable improved academic performance": greater motivation is often as instrumental in achieving more successful results in the performance of cognition-related tasks as if an actual increase in cognition had taken place.

Such findings provide an alternative way of looking at the relation between the actual versus the perceived nature of the effects of prescription stimulants as used by healthy individuals with a view to enhance academic performances, shedding some light on the thorny issue of their efficacy as proper cognitive enhancers. To quote Vrecko (2013), "the conceptualization of nonmedical use of stimulants in terms of "cognitive enhancement" may fail to adequately capture the perspectives and experiences of individuals who use stimulant drugs as study aids."

To recap, in spite of the hype surrounding PCE in scientific and bioethical debates, and notwithstanding the fact that the use of prescription psychostimulants for CE purposes seems to be increasingly popular among the general public (especially among university and college students to enhance their academic achievements), the general consensus in the scientific literature so far is that no conclusive and unambiguous empirical evidence has been found yet for any relevant or appreciable cognition-enhancing effect of prescription stimulant medication on cognitively healthy individuals.
Moreover, even when studies have shown little or modest cognitive enhancement in healthy individuals, the positive effects have proved to concern only particular cognitive tasks, to be detectable only in a limited number of research subjects in specific dosages and, most importantly, not to be transferable to the performance of other non-trained cognitive tasks, nor replicable among individuals, nor able to be carried over from short-term laboratory studies to real-life settings of long-term use (de Jongh et al., 2008; Ragan et al., 2013; Farah et al., 2014; Maslen et al., 2014).

By all means, further empirical research on the cognition-enhancing effects of prescription stimulants is needed because, to date, the dearth of extensive and consistent empirical data[41] on the topic and the positive-reporting biases in the scientific domain[42] make it difficult to issue accurate claims of conclusive evidence for the effectiveness of PCE.

2.4. Health risks and potential adverse effects of PCE

The mirror side of the debate on cognitive effectiveness of prescription stimulants is represented by the discussion of the health risks and the potential adverse effects entailed by PCE among healthy individuals. In fact, the use of any marketed drug not only is meant to produce some appreciable, positive effects, but also necessarily comes with a certain potential for unintended risks to users' health.
In the case of CE and PCE in particular, safety concerns about the use of prescription stimulants to enhance cognition deserve special attention, insofar as both their positive effects and potential risks are bound to directly affect the brain, which is the most fundamental organ for human life (Greely et al.,

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[41] In this respect, two major problems are constituted by the lack of long-term clinical tests and by the usually small size of study pools. With regard to the former issue, Hyman (2011) claims that "to date, studies of stimulants in healthy people have been limited largely to single-dose laboratory experiments; longer-term clinical trials to investigate whether there is significant and lasting efficacy for cognitive enhancement have not been performed." As regards the latter problem, Blank (2016) states that "the small sample size of just several dozen subjects or fewer in most of the relevant studies and the likelihood of publication bias against null results" do indeed hinder the formulation of "definitive conclusions" about the efficacy of PCE.
[42] For further insight, see Blank (2016): "[…] there is a well-known bias across scientific disciplines for reporting positive effects: studies that show no effect are less likely to be published, and so the overall picture may be skewed towards showing success where it does not really exist (Ghorayshi, 2014)."

2008; Blank, 2016).
It is of paramount importance, then, to attempt to determine as much precisely as possible which is the risk-benefit ratio associated with the use of these prescription drugs, especially when used by cognitively healthy individuals for CE. In fact, the acceptable risk threshold of pharmaceutical drugs is usually much lower for "normal" people who are not diagnosed with any neuropsychiatric conditions and, therefore, do not need to engage in the use of such medications, but do that out of their own mere desire for enhancement "beyond what is necessary to sustain or restore good health" (Juengst, 1998). As Blank (2016) put it, "although there are potential adverse reactions to all therapeutic drugs, these injuries are usually outweighed by the relief afforded from the symptoms of the disease. However, when given to disease-free individuals, the trade-off between the harmful effects with the more uncertain benefits of enhancement is blurred". Then, in order for PCE to be acceptable on safety grounds for use among cognitively healthy people, its benefits should outweigh its potential risks to a considerable extent.

As far as safety clinical trials for the off-label use of prescription stimulants are concerned, things have not changed much since 2008, when Greely and colleagues claimed that "although regulations governing medicinal drugs ensure that they are safe and effective for their therapeutic indications, there is no equivalent vetting for unregulated 'off label' uses, including enhancement uses". However, it is also true that the steadily growing uptake of psychostimulants for CE purposes over the last two decades has meant that the use of these pharmaceutical drugs has been going on and has been contextually observed for quite some time now: therefore, as Hyman (2011) rightly points out, "long-term cohorts have been followed for a variety of reasons, making it unlikely that we are missing some truly awful long-term side effect".

On the whole, the empirical research literature has identified a wide range of significant health risks and severe side effects potentially connected to PCE – which should be enough to discourage this practice among the cognitively healthy, even more so because of the lack of solid scientific evidence in support of its general cognition-enhancing effectiveness (Franke et al., 2013).

First and foremost, clinical trials on the safety risks entailed by the non-medical use of prescription stimulants for CE by otherwise healthy individuals have produced plenty of evidence for high addiction potential and for PCE users' likelihood to develop abusive-compulsive patterns of prescription stimulant use, especially when these are taken in high doses and over long periods. The major, concrete risk for physical dependence was importantly highlighted by Kroutil and colleagues (2006) on the basis of a national survey, which they claimed it suggested that "almost one out of 20 non-medical users of prescription stimulants meet the criteria for dependence or abuse (Outram, 2010)".
Moreover, the abuse and addiction risks may have reinforcing effects and compound their behavioural consequences on PCE users by either encouraging them to also start assuming illicit drugs (e.g. cocaine, heroin, ecstasy etc.) or aggravating a pre-existing problem of illegal drugs abuse, giving rise to associated patterns of substance use (Sepúlveda et al., 2011). For instance, an early report on the diversion and abuse

of prescription drugs in the U.S. by the National Center on Addiction and Substance Abuse – CASA (2005) documented that "[prescription stimulants] abusers are 20 times more likely to use cocaine and heroin once the body builds a tolerance for [prescription stimulants]" (Varga, 2012). Evidence also exists for PCE users to be significantly more likely than non-users to engage in other risky behaviours, such as excessive alcohol consumption: according to Arria and DuPont (2010), studies have illustrated that PCE users tend to engage in regular binge-drinking or heavy drinking and take other illegal drugs more frequently than non-users do (Teter et al., 2003; Barrett et al., 2005; McCabe et al., 2005) and that they "are more likely to meet Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSMIV) criteria for dependence on alcohol and marijuana, skip class more frequently, and spend less time studying", as compared to students who do not use prescription stimulants for academic benefits (Arria et al., 2008).

Moving on to discuss the clinical evidence available to date for potential adverse effects of PCE, although the controlled use of prescription stimulant medications for their approved therapeutic indications has been extensively tested to be relatively safe, the misuse (i.e. the off-label or non-medical use) and abuse of any psychostimulant are potentially associated with unintended negative effects of different degrees of severity.

High-dose, short-term side effects of prescription psychostimulants in healthy individuals are mainly neuropsychiatric in nature and may be manifested behaviourally through sleep disturbances and worse sleep quality, appetite loss, anxiety, irritability, restlessness, dizziness, tics, drowsiness, fatigue, aggressive tendencies, panic attacks, aggressive episodes, over-focusing, or depressed mood; strictly somatic collateral adverse effects in the short term may include weight loss, headache, increased blood pressure and heart rate, palpitations and other cardiac complications, gastrointestinal irritation (CASA, 2005; Prudhomme-White et al., 2006; Quednow, 2010, Clegg-Kraynok et al., 2011).

Also, as far as PCE effects on cognitive functioning only are involved, some studies even hinted at the possibility that psychostimulants may negatively alter attentional control (Rogers et al., 1999), hinder working memory (Malenka et al., 2009) and "impair performance on tasks that require adaptation, flexibility and planning" (Advokat, 2010).

Upon prolonged, high-dose off-label use of prescription stimulants, long-term adverse effects may emerge. The most common ones include acute mood swings, hallucinations, psychotic, addictive and obsessive-compulsive behaviour (often because of sleep deprivation), paranoid episodes, depression, intense cravings, reduced cardiovascular circulation and heart failure, intoxication, comas, and even suicidal ideation – therefore, death is also a possible (although rare) unfortunate consequence of PCE abuse (CASA, 2005; Varga, 2012; Busardò et al., 2016; Bennett & Holloway, 2017; Carlier et al., 2019). Long-term PCE users may also witness an increase in magnitude of both short and long-term adverse effects. Another consequence of prolonged PCE use at high doses is the increase in drug tolerance, "resulting in heightened physiological dependency, which intensifies the impact of withdrawal symptoms when usage ceases" (Varga, 2012); in turn, withdrawal entails events such as excessively increased appetite, daily hypersomnolence, depressive symptoms, violent mood changes and psychophysical exhaustion (CASA, 2005).

All things considered, it appears that the evidence for definite and appreciable cognitive benefits of PCE is still too weak and therefore insufficient to decisively outweigh its potential health risks and harmful effects. Consequently, safety concerns for PCE among the cognitively healthy are, to date, still to be given serious consideration when striking a trade-off between PCE health pros and cons. For the time being then, it may be concluded that the uptake of PCE for use by healthy individuals may not be totally acceptable on safety grounds.

Chapter 3

Ethical and social implications of PCE in the context of academic competition

Over the last decade in particular, a great deal has been written about virtually anything related to CE in the neuroscience and bioethical literature: conceptual definitions, theoretical notions, empirical aspects and ethical issues have all been addressed by neuroscientists and academics alike - although to a different extent, level of detail and degree of conclusiveness.
As indicated by the previous chapters as well, the bulk of attention has indeed been drawn to PCE interventions in particular, since, to date, they represent virtually the only concretely viable as well as the most easily accessible opportunity for individuals wishing to enhance their mental capacities.
In the discourse over PCE, much attention has focused on the bioethical implications and concerns raised by the possibility that its uptake may keep on spreading in the near future, thanks to sustained advances in cognitive neuroscience, to the point of becoming a commonplace, lifestyle-enhancing practice across societies. In this regard, academic institutions are usually taken as a contextual backdrop in the vast majority of such debates - and in the present dissertation too - as universities and colleges are the social milieus where PCE use is currently reported to be most prevalent and where it can therefore be better assessed in practical terms, also as a basis for bioethical speculation about its future developments.

Yet, a quick glance at the sheer volume of bioethical discourse on PCE is enough to give the idea of how vast it really is and, at the same time, of how controversial the issue has progressively come to be construed by its observers since its very emergence as a prospective biomedical possibility for use by human beings. In fact, whilst a lively debate on PCE has indeed been spurred by the admittedly rapid progress in the fields of neurocognitive and pharmacological sciences (Saniotis, 2009; Cakic, 2009; Farah et al., 2014), the impression is that, in this case, the speculative discourse may be too far ahead of the state of the art with respect to the practical possibilities currently offered by PCE (Zohny, 2016). As a matter of fact, even after more than 15 years have elapsed since the non-medical use of prescription pharmaceutical drugs for cognition-enhancing purposes began to be attested in various educational and professional contexts, empirical evidence of reliable efficacy and long-term safety of PCE use in cognitively healthy individuals is still very limited, mixed (at best) and not at all conclusive. Therefore, one may wonder what has been fuelling the heated conjectural disputes on ethical issues concerning CE that have sprung, grown and widened over the last 10 years way beyond the very limited cognition-enhancing power of PCE.
More importantly, one may wonder why the bioethical debate still is so intense - and, under some respects, even increasingly so - and why radical positions are still being expressed on the topic by observers despite the fact that no breakthrough in PCE efficacy and safety has yet been made.

Most reasonably, such a keen and diversified interest in the bioethical implications of PCE use is likely to be aroused from at least three main determinants, which are all equally important:

1. The sheer novelty and the idea of innovation embodied by anything that is related to the mere (and often quite abstract) notion of "cognitive enhancement", due to the sustained progress in neuroscientific research;
2. The current dearth of definite certainties about the precise functioning of the human brain, due to the difficulties encountered in neuroscientific research because of the extreme complexity the organ itself;
3. The fact that PCE interventions affect the overall complex of human cognitive abilities, broadly intended as "intelligence" and usually regarded as both the ultimate distinguishing factor of the human species and its very essence, since they direct our emotions, thoughts, decisions and actions;

Time and again, whatever the specific role played by any of these determinants in stirring and shaping ever-new bioethical debates over PCE, the latter too often end by leaving an unsettling feeling of ambivalence in the observers. As Jotterand and Dubljević (2016) put it, "[…] the ambivalence that these new technologies provoke in us is the result of strong and conflicting feelings, of attraction and revulsion; this state is uncomfortable and sets the stage for mechanisms that reduce our dissonance by confabulation. Ambivalence causes us to accept weak arguments uncritically or to accept the replacement of arguments with slogans and rhetoric: "it is against nature," "it expresses a desire for mastery," "it is playing god," and so on, on the one hand, and "we already allow similar interventions" or "we each have a right to choose for ourselves," on the other."

In order to break free from this vacuous fickleness of opinion and to discern more clearly the relevant features of the ethical and social concerns that are truly worth debating in relation to CE in general and PCE in particular, the two authors suggest to "avoid focusing on the apparent novelty [of the technology…]. In discussing cognitive enhancements, we […] tend to attribute to existing interventions powers greatly beyond those they actually have or to bypass discussions of actual enhancements in favour of idealized and extremely powerful technologies. […] It may be that these discussions have set the tone for a polarized and unsophisticated debate because the focus has been on technologies at their most unfamiliar and therefore their most anxiety-provoking" (Jotterand & Dubljević, 2016). Therefore, when discussing PCE under an empirical perspective, the solution seems to be to focus only on currently-existing PCE interventions which are actually resorted to and not to inflate nor underestimate their potency; then, when addressing its bioethical aspects, one should also avoid radical positions on both extremes of the debate, unrealistic scenarios and exaggerated thought experiments in order to "deflate some of the hype in the associated literature, leading to a more realistic and sober assessment of these prospective technologies", to put it in the words of Zohny (2015).

Deeming this to be valuable not only as a piece of advice in general, but also as a guiding principle for the present dissertation to finally meander in the most seamless way possible through the maze of ethical dilemmas raised by PCE, this third and final chapter only casts light on some core ethical issues that have often been raised in realistic terms[43] and highlighted by critics and supporters alike as being especially pressing in current times, in that they may actually have concrete consequences in real-world settings if PCE were to become common practice across societies[44]. Actually, the most controversial ethical aspects of PCE use by healthy individuals - which also happen to be the most relevant ones, in the sense of having more concrete importance than other concerns in their bearing on the present period – are usually detected in the peculiar context of university and college examinations, where a significant number of students is reported to resort to PCE as it were a "smart aid" to successful academic performances.
Having the present dissertation itself kept its focus on PCE use among cognitively healthy undergraduates throughout this point, the following sections will too stick to this specific context and thereby provide a concise overview of the most compelling ethical and social concerns raised in the current bioethical literature with regard to the growing tendency of healthy university and college students to resort to PCE in circumstances of academic competition. Specifically, this final chapter will first address the likelihood for PCE to be regarded as downright cheating and the associated analogy that is often drawn between PCE within academia and doping in sports; then, it will move on to consider the risk of indirect and implicit coercion towards enhancement that may potentially be exerted by pervasive PCE use within academia on students otherwise unwilling to cognitively enhance themselves, who may then subconsciously persuade themselves into believing that only by so doing can they get to compete on a par with the enhanced ones in academic examinations.
Here, the scope of ethical assessment of PCE use within academia is openly narrowed down to these few and specific controversial aspects for two reasons:

1. Because the present dissertation is interested in the broader bioethical social consequences of PCE use among healthy student populations within academia, rather than in its mere individual moral implications for the single undergraduate;

[43] This means that the ethical issues addressed in the present chapter are those that have often been raised by observers in the context of bioethical debates framed to refer only to the PCE interventions that are currently resorted to - leaving aside bioethical speculation on the prospected ones which are still in an experimental or developing phase at present.
[44] Importantly, the critical discussion of these concerns gains its urgency from the acknowledgement of the increasingly strong demand for truly effective pharmacological means of CE, which will reasonably stimulate a quick market supply in the near future thanks to constant scientific research; therefore, the underlying assumption throughout the rest of the chapter is that this practice will increasingly take hold until it really becomes routine practice among students within educational institutions across civil societies. For instance, see Garasic & Lavazza (2016): "It should be pointed out that, despite their increasing use, there is still not robust evidence that methylphenidate and Modafinil provide effective cognitive enhancement. Yet, given the demand and the ongoing research, it is not unreasonable to assume that similar effective drugs will be available soon."

2. Because, as was illustrated in Chapter 2, the practice of PCE use among healthy undergraduates takes place in the context of tests and exams undertaken by all the students within colleges and universities, which can be most fittingly considered as being competitive-selective contexts[45].

Then, the necessary requirements for urgent and controversial bioethical concerns to be addressed in the present dissertation would be:

1. To be closely related to the essential moral issue of fairness (also intended more broadly as "justice"), which, in the overall bioethical debate on CE, is perhaps the single issue[46] that is truly demonstrated to impinge on the social fabric of civil society – as opposed, for instance, to other ethical concerns (e.g. authenticity, accountability, value of personal accomplishments, safety, etc.) which strictly deal with moral dynamics at the individual level (Kipke, 2013; Wagner, 2013);
2. To be points of ethical and moral contention typically identified in competitive-selective contexts, such as academic ones.

It clearly follows that the ethical and moral controversies surrounding cheating and implicit coercion are the best suited for discussion in this final chapter, since not only are they invested with great significance in the real-world situation of PCE use among healthy university and college students, but they also satisfy both the abovementioned criteria – in that they are framed as issues of fairness in academic competition[47].

Finally, it is important to stress that the ethical discourse included in the present chapter does not intend to take a precise stand on such specific ethical controversies, nor does it dare answer to the ultimate bioethical dilemmas surrounding PCE - and CE in general, of course - such as whether it is morally legitimate for otherwise healthy individuals to enhance their naturally-endowed capacities by way of, say,

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[45] For further insight into the relevance of competition in the socio-economic structure of society and the importance given to the requirement that it be fair, see Wagner (2013): "The competition-based allocation of work, income and opportunity is regarded as a normative foundation of modern societies. In the last two decades, competition has become a dominant mode of interaction in more and more spheres of life beyond economics. Competitions are regarded as legitimate modes of resource distribution, assuming everyone has the same opportunity to compete. This, of course, can never be the case. Level playing fields are always distorted by numerous inequalities that social life brings along. Nonetheless the question of whether cognitive enhancement has an impact on level playing fields and fairness in competition is an important issue in bioethical literature on cognitive enhancement. […] Both liberal and conservative ethicists agree that fair competition has an enormous normative impact on the legitimacy of social order. However, they offer different answers to the question of how to govern freedom and how to protect fairness in competition. Liberals and conservatives differ profoundly on the question of whether cognitive enhancement poses a threat to a fair, competitive society and whether the state should restrict the use of drugs or distribute drugs to preserve level playing fields.[…] Nonetheless, bioliberal and bioconservative positions seem to be in agreement regarding the significance of fair competition as a key source of the normative order of our society."

[46] The associated ethical questions of socio-economic inequality and distributive justice do also profoundly affect civil society as a whole in that they are strictly related to the broader issue of fairness: however, they are outside the scope of the bioethical discourse undertaken in the present dissertation, insofar as they are not strictly related to the phenomenon of PCE in academic competitive contexts. This line of reasoning follows from the common assumption that prescription stimulants used off-label are not expensive (and therefore equally economically accessible to anyone wishing to purchase them) and that students enrolled in a given university or college can be usually generalised as belonging to the same socio-economic group in society.

[47] For further insight, see Wagner (2013): "The focus on fairness that bioethicists deal with, whether they regard fairness as being undermined or not, is based on competition as a major mode of interaction [, on] a notion of society as competitive, in which fairness is the purpose of a certain degree of institutional intervention. In the context of cognitive enhancement, this intervention would be the regulation or deregulation of the use of certain drugs by schools, universities, employers or legislators with the goal to protect competition."

pharmacological means for the mere sake of self-betterment. On the other hand, the overview hereby provided merely intends to offer some thoughtful insights and inputs able to stir a more considered bioethical discussion on the social implications of PCE use within academia and let observers channel it in the most effective way possible.

3.1. Cheating

As has been expounded at length in the previous chapter, the conjunction between the academic literature on PCE and the popular media has more often than not resulted in reports suggesting that cognitively healthy university and college students in particular are increasingly engaging in the off-label use of prescription stimulants (i.e. mixed amphetamine salts, methylphenidate, modafinil etc.) to enhance academic performance. Although the use of "smart drugs" as enhancers of cognition has proved to have very limited efficacy to date, the widespread presumption that, in the future, pharmaceutical drugs will either be developed explicitly for the purpose of CE or that their off-label use for CE will anyways be rendered much more efficacious as compared to the current evidence thanks to advances in the biomedical sciences has nonetheless led many observers to predict that the prevalence of PCE use will increase further and become even more pervasive among undergraduates, perhaps to the point of becoming a trivial practice in the daily academic routine.

Such hypotheses have acted much like a detonator for the simmering debate over the ethics of otherwise healthy individuals (mis)using[48] prescription stimulants to enhance the performance of cognitive-related academic tasks. Perhaps quite predictably, the bulk of ethical controversy here has converged on the potential configuration of PCE use within academia as downright "cheating". In this regard, a number of skeptical bioethicists and critics among the general public (clearly including "not-enhanced" university students themselves) contend that the use of prescription psychostimulants for CE purposes by cognitively healthy students in the context of exams and admission tests may indeed qualify as a "cheating" practice. In fact, engaging in it would admittedly amount to artificially improving one's academic outcomes by supposedly altering the very cognitive[49] capacities which enable the performance of cognitive-related academic tasks and ultimately determine the quality of their results through an external pharmacological "shortcut", thereby violating the integrity of one's academic conduct and

[48] Quite obviously, in the event that pharmaceutical drugs are developed for the specific "label" purpose of enhancing cognition among healthy individuals, their use will then no longer be seen as non-medical or off-label, nor will it be possible to talk of "misuse". For further insight on this point, see the specific reference to Larriviere and colleagues (2009) in note 13 in section 1.2.1 of Chapter 1.

[49] Actually, PCE has so far proved to be slightly more effective with regard to the positive impact of psychostimulants on the emotional states of users rather than on their proper cognitive faculties. For further insight into this specific empirical aspect, see section 2.3 of Chapter 2 and Vrecko (2013): "The research presented here suggests that effects of stimulant drugs that help individuals improve academic performance are not as purely cognitive as often seems to be assumed. Accounts offered by healthy subjects suggest that stimulants are indeed perceived to enable augmented academic performance, for example, by improving abilities to work efficiently and productively on academic work—but they also suggest that changes in emotional states are a crucial factor to include within accounts of how and why such drugs work." Also, see Zohny (2015): "While the evidence for the efficacy and prevalence of these drugs as examples of PCE is limited, they may still be boosting performance either by inducing moods conducive to work or study, or by enhancing motivation itself".

altering the validity of the associated academic success. According to many, that would as well entail a fraudulent intent to outdo other "peer competitors" within the collegiate setting, according to the widespread assumption that regards academic contexts as being structurally competitive in nature.

However, there is no official, unambiguous or universally accepted definition of cheating in educational settings to date; rather, this particular instance of misconduct is usually outlined independently by each individual institution in its own academic code of conduct. Rather, as Dubljević and colleagues (2014) pointed out, "defining a certain practice as cheating can be viewed as a social process driven by group interests", meaning that virtually anything that is shaped by social processes – as the concept of cheating is also supposed to be - is bound to constantly evolve over time according to the relative pulling force exerted by different sets of societal shared interests. Much the same has been stressed by Savulescu (2006), who claims that even if there were proper rules against the use of PCE among the cognitively healthy insofar as that would amount to actual cheating, such rule would nonetheless retain a strongly arbitrary nature, because they are laid out by human beings.
In light of this, those who support PCE use – who are often referred to as "bioliberals"[50] and include scholars such as Dubljević, Savulescu and Harris - among healthy individuals strongly oppose "cheating" allegations in competitive contexts such as university examinations, arguing that cheating means "(1) breaking formal or informal social norms and (2) attempting to gain an unfair advantage" (Harris, 2011). They contend that since (1a) there currently exists no formal nor explicit prohibition on PCE use that has been adopted unanimously by academic institutions worldwide – not even by a majority of them – and (1b) there still seems to be no implicit social norm, across societies in the world, condemning[51] PCE, (2) the alleged "advantage" promised by the use of "smart drugs" should be regarded as available to everyone who may want to use them: it then stands to reason that such an advantage cannot be qualified as "unfair"[52]. Therefore, they argue that if there is no breach of formal or informal social norms, nor an

[50] For further insight, see Wagner (2013): "[…] Scholars' positions within the field of bioethics can be classified by the terms, liberal and conservative. There are two aspects that I want to emphasize with regard to that division: First, the distinction between liberal and conservative positions in bioethics is done in German- and English-language publications, although the sense of the term "liberal" differs significantly between Germany and the U.S. Within the German political sphere, the term "liberal" is associated with economic liberalism/laissez-faire, while in the U.S., it is associated with progressive or left-leaning cultural political attitudes. Additionally, the term "progressive" tends to imply a linear view of history and is, therefore, problematic since not all progressives favor, for example, all forms of technological progress. Second, I would like to point out that the liberal/conservative-distinction in bioethics is not in line with political camps as we know them. For example, Francis Fukuyama and Jürgen Habermas are both strongly opposed to enhancement biotechnology, but, at the same time, they hold completely opposite political positions."
[51] On the contrary, prescription stimulants are often deemed as virtually innocuous and helpful "study aids", perhaps on the basis of their being clinically tested for therapeutic use, which gives a false impression of safety to non-medical users.
[52] Rather, some proponents of PCE claim that it could even be regarded as potentially improving collective well-being by conferring society-wide advantages in relation to issues of injustice (in the sense of socio-economic inequality being allegedly increased by differential access to and availability of CE interventions). However, this aspect has been discussed at length elsewhere, and for a matter of focus it will not be delved into in the present work. For further insight, see Wagner (2013) citing Savulescu (2006): "[Savulescu] argues that the application of different theories of justice lead to the conclusion that enhancement increases justice rather than injustice. A libertarian theory of justice would not consider it unfair if the rich can buy enhancements and thus increase their opportunities "provided that their assets have been justly and legally acquired" (Savulescu 2006, 332). Utilitarian approaches also would require enhancement, given that enhancement is a good that increases well-being. Savulescu quotes Jeremy Bentham, who advocates the "greatest good to the greatest number" (Savulescu

attempt to gain an unfair advantage over one's peers, then, students using prescription psychostimulants for CE purposes are clearly not engaging in any cheating practice at all. In addition, those who uphold the moral legitimacy of PCE use by the cognitively healthy often tend to scale back the inflated enhancing powers which are often misleadingly attached to PCE, as if its use were able to deliver miraculous QI-enhancing effects. In fact, proponents of PCE just consider smart drugs to be an innovative, sound and worthwhile step further along the path which began to pe paved by the "conventional" enhancements everyone already takes advantage of in his life on a daily basis (e.g. good education, healthy sleeping and dietary habits and so on), without the drawback of being as highly expensive as a university degree is, for instance. Ultimately, according to its supporters, pursuing enhanced cognitive faculties through available means – be they prescription drugs or devices - on the part of healthy individuals is just a manifestation of the inherent aspiration the human species has for continuous evolution, self-betterment and progress[53] (Harris, 2011; Levy, 2007).

In response to these claims, critics of PCE use by cognitively healthy individuals predictably tend to express an opposite stance on the issue of cheating, but appealing to slightly different arguments (e.g. Selgelid, 2007). For instance, even observers sharing Dubljević's position (2012a) may hold that there is no need for formal rules to be in force first in order to consider the use of PCE by students as cheating: on the contrary, it is usually the case that new norms and laws are passed as a direct consequence of a new kind of misconduct or offence being identified; then, since the use of PCE is, in their view, widely frowned upon and very seldom perceived as morally acceptable at the societal level, this should indeed prompt new legislation banning it on the basis of its societal unfairness. This restrictive normative outcome is strongly endorsed in so-called "bioconservative" positions, such as the one expounded in *Beyond Therapy* by the Presidents' Council on Bioethics[54], which attaches intrinsic, almost metaphysical value to individual effort "as a normative source of our social order" (Wagner, 2013) and combines it with the interpretation of every socio-economic sphere as being intrinsically competitive in nature. According to bioconservatives, then, there is no need for official rules against cheating to be explicitly in

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2006, 332). Furthermore, an egalitarian approach in theories of justice, like John Rawls' concept of Justice as Fairness, would, according to Savulescu, require enhancement as well: "According to Rawls' Justice as Fairness, we should distribute enhancements so that the worst off in society are as well off as they can be" (Savulescu 2006, 332; Rawls 1971)." Also, see Garasic & Lavazza (2016): "In addition to this, it can be argued that cognitive performance enhancement is usually both an individual choice and a contribution to the wellbeing of society. The latter is obtained, for instance, through the enhancement of some professional performances, which could be an advantage for everyone. For example, surgeons could improve their practices and outcomes thanks to enhanced attention, working memory and self-control."

[53] For pertinent insight, see Dubljević and Ryan (2015) summing up similar arguments in support of PCE made by Harris (2011): "Harris posits an analogy with education and claims that using cognitive enhancement is comparable to seeking out the best schools to improving oneself or one's children. Furthermore, he notes that the costs of stimulant drugs are relatively low, compared to the fees associated with university education or specialized training. He and other proponents contend that we should use any means of improvement as long as they are effective and, by using examples such as aspirin, literacy, electricity, coffee, and computers, conclude that evolution and progress are synonymous with enhancement."

[54] The Presidents' Council on Bioethics was formed by George W. Bush in 2001 and was tasked with advising the President on bioethical concerns that may be raised in relation to developments in biomedical science. It was dissolved in 2001. Their book *Beyond Therapy: Biotechnology and the Pursuit of Happiness* (2003), is one of the most popular as well as conservative-leaning publication in the debate on CE (Wagner, 2013).

place in order to regard PCE as cheating, because resorting to the artificial aid provided by psychostimulants - regardless of the actual outcomes of their use - to achieve better results, especially in academic competition, would amount to be trampling on the intrinsic value and dignity of human endeavour and hard work, and would therefore be deontologically wrong and ultimately unfair in itself.

As far as the evidence from empirical research on the general public's perception of PCE use by university students is concerned, once again data are rather mixed. Several studies have indicated that the vast majority of the surveyed respondents would judge PCE use as morally inadmissible (Partridge et al., 2012; Dodge et al., 2012; Ragan et al., 2013; Dubljević et al., 2014). These findings are also corroborated by the available empirical data on the attitudes of university students themselves towards PCE, which again seems to be broadly regarded as unfair and therefore unacceptable, especially in the opinions of non-users[55] (Forlini & Racine, 2009, 2010; Scheske & Schnall, 2012; Bell et al., 2013; Bossaer et al., 2013; Brandt et al., 2014; Dubljević et al., 2014). Nonetheless, it must be noted that all such studies have proved both the general public and the student populations interviewed to include a small minority of participants - mainly comprising PCE users themselves - who deem the use of smart drugs to study longer and perform better as a fairly unproblematic and acceptable practice which does not give rise to any unfair advantage of sort. This attitudinal dissonance is most likely due to two factors in particular - namely, (1) a different perception of the risk-benefit ratio held, respectively, by PCE users and non-users, and (2) a different perception of the academic context as being either competitive or cooperative.
As far as the perceived balance between safety and efficacy of PCE is concerned, some studies (e.g. Brandt et al., 2014) have demonstrated that non-users tend to more frequently overestimate both the potency and the probability of serious health risks coming with PCE use as compared to users, while, on the other hand, users often display the tendency to underestimate potential harm associated with chronic use of PCE[56]. Since, overall, PCE users across societies only account for a small percentage of individuals so far (and are mainly found within academia and workplaces), it is then evident that smart drugs have a much higher chance to be seen by the general non-user population as offering an unfair advantage to those who use them, besides entailing potentially severe and therefore unacceptable safety risks.
On the other hand, different attitudes towards using prescription drugs for CE at colleges and universities

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[55] For instance, see Schelle and colleagues (2014): "[…] an online survey by Bossaer and colleagues (2013) demonstrated that 60% of the 372 student respondents agreed that PCE provides users with an unfair advantage over other students. An almost identical amount of just over half of the respondents (56%) believed that PCE use for study purposes could be seen as academic dishonesty. In a large-scale online survey, with respectively 5882 and 3486 participants in the first and second wave, (Dubljević et al., 2014) found that German students deem the use of PCE with the intention to increase study performance to be morally less acceptable than traditional forms of academic misconduct, such as cheating in exams, fabrication, or plagiarism."
Also, Brandt and colleagues (2014) report that "[…] when asked about whether stimulant use leads to an unfair advantage on exams, 50% of non-users and 45.7% of users indicated that they felt it does."
[56] For instance, see Brandt and colleagues (2014): "We found that non-users were more likely to report that non-medical prescription drug use is harmful to mental and physical health than users. Specifically, 83% of non-users reported that stimulants were harmful to mental health, compared to 51% of users who believed this. Consistent with this, non-users cited damage to mental and physical health as primary reasons they abstained from using the drugs."

may vary mainly depending on the degree of competitiveness that is thought to characterise academic contexts[57]. In fact, as has been explained at length in Chapter 2 and above, university education is usually viewed as entailing significant competition for access to job opportunities via better academic grades and, in such a scenario, colleagues are perceived as proper competitors: in that case, resorting to psychostimulants to try to even slightly improve academic performance could plausibly be disapproved of as an instance of trying to gain an unfair advantage over other peer competitors in a zero-sum game – therefore, as downright cheating – because the kind of moral analysis carried out in this circumstance attaches value to the positional advantage[58] resulting from better academic outcomes, as these would supposedly enhance people's employability and their opportunities in life.

However, there have been instances of ethical assessment of PCE use within academia where the moral focus has been drawn not merely to the individual final (supposedly better) result of enhanced students as compared to other non-enhanced ones, but, rather, to the value of the whole educational process whereby students, in their struggle to express their cognitive faculties through the accomplishment of academic tasks, have deemed it innocuous to resort to a pharmaceutical support in order to relieve themselves of the often burdensome weight of constant academic pressure, which usually constitutes a significant obstacle to the true enjoyment of achieving academic accomplishments and to the expression of students' true cognitive potential. According to this latter perspective, the academic context is not necessarily regarded as being absolutely dominated by a competition whereby the individual student needs to stand out over the others in order to reap good opportunities in life; then, achieving academic success may be seen as simply being part of a non-zero-sum game, where those who choose to enhance the quality of their efforts in the pursuit of good academic outcomes cannot be blamed for trying to reap unfair advantages over their peers, but instead can even contribute to the advancement in the aggregate level of knowledge and information[59] present in their educational institution of reference.

As will be mentioned in the following section, this picture may be regarded as being roughly consistent with the results of a study undertaken by Dodge and colleagues (2012) on the contrast between public the public opinion on the use of prescription stimulants to enhance cognitive performances in academic contexts and the unconditionally negative societal judgement of the use of doping substances to enhance athletic performance in sports. In fact, sporting contests traditionally epitomize the concept and value of

[57] For instance, also Dubljević and Ryan (2015) argue that "The fact that some students view cognitive enhancement as cheating and some do not could be related to the different interpretation of the character of university education – whether it is understood as being dominantly competitive (or a zero-sum game) or cooperative (and non-zero-sum)."

[58] Loewe (2016) further elaborates on this point by stating that "Cognitive abilities […] have an outcome worth in the marketplace. But the worth of cognitive faculties cannot be reduced to their market price: they are not only positional goods. Even if enhanced people would not achieve better market outcomes, it is evident that they would have access to more opportunities of enrichment in their lives, which can be productive in the process of developing, revising, and pursuing a rational life plan."

[59] For instance, see Loewe (2016): "The idea that improving the average of cognitive abilities doesn't implicate better market outcomes is based on the supposition that the overall market return is fixed and that the market interactions of individuals are a zero-sum game. But […] a knowledge economy with more people with enhanced cognitive abilities has better prospects for growth, and economic growth improves the outcomes of individuals. Furthermore, a better pool of cognitive capacities has positive social externalities beyond the economy (e.g., smarter solutions to social problems, new technologies, etc.)."

true competition and constitute the quintessential representation of the notion of zero-sum games, whereas the societal conceptualisation of academic contexts as categorically competitive still seems to be a bit unsettled at times. Thus, for the time being the moral comparison between doping in sports and PCE in academia is inevitably bound to make doping seem morally far worse, utterly unethical and especially deserving of severe penalties in the eyes of observers, who have so far proven not to feel the same way about PCE use.

3.1.1. The relationship between PCE within academia and doping in sports

As just mentioned, some parallelisms[60] may be and have indeed been drawn between the use of pharmacological substances for CE within academia and the use of illicit doping substances in athletic contexts. For instance, both circumstances feature the use of pharmacological agents and substances having legitimate medical uses for the treatment of various conditions[61] (e.g. ADHD, dementia, depression and narcolepsy) at dosage levels and/or via an administration route different from the therapeutic indications for use[62] and for a purpose other than prescribed - namely, for the sake of boosting one's "normal" performance, be it cognitive or physical, in the absence of any diagnosed medical condition; also, both circumstances have unsurprisingly sparked heated debate among observers over the moral implications of using performance-enhancing substances within educational and athletic settings alike (Petróczi & Aidman, 2008; Kipke, 2013; Petróczi, 2013; Zohny, 2015). On the other hand, however, there seem to be clearly visible differences between the use of prescription psychostimulants to enhance cognition and the use of doping substances to boost athletic performance: while in sports there is a clear-cut categorisation among doping substances and methods prohibited at all times, substances prohibited in-competition and substances forbidden only in particular sports[63], in educational settings there is still no explicit legal framework regulating PCE use – and neither has any institution been designated to this end yet. Still, it must be noted that, in this regard, some universities (e.g. Fresno State University[64] and Duke University[65]) have in recent years either tightened on-campus rules on the diagnosis of neuropsychiatric conditions and prescription of associated medications, or have begun to integrate their academic codes of conduct with principles defining the off-label use of prescription medication to improve academic performance as an act of academic dishonesty liable to disciplinary action. However, the adoption of

[60] However, the present section will not include a complete review of all the analogies existing between PCE within universities and doping substances in sports due to a lack of space and for a matter of focus.
[61] The vast majority of pharmaceutical drugs resorted to for CE purposes and some substances used for doping purposes were originally developed and are still widely prescribed for the treatment of a variety of neuropsychiatric illnesses and disorders. As far as pharmacological agents for CE are concerned, see section 1.2.1 of Chapter 1 for further insight. To take a look at the 2020 updated list of prohibited doping substances, visit https://www.wada-ama.org/en/content/what-is-prohibited?gclid=CjwKCAjwzIH7BRAbEiwAoDxxTt-_IWCrMTmrfuUep6oOC3o4zU-KwJpU_eTbU7Wqh3iQcZlJ7pSsXRoCED0QAvD_BwE
[62] This inappropriate use is often referred to as "non-medical" or "off-label". For an unambiguous definition of the terms "non-medical" or "off-label", see the one given by the National Institute of Drug Abuse (NIDA) and cited in note 13, Chapter 1.
[63] For a complete overview of doping substances, visit the website linked in note 15.
[64] See https://www.fresnostate.edu/studentaffairs/health/documents/ADHDPolicy_2020.pdf
[65] See https://hr.duke.edu/benefits/medical/pharmacy-benefits/covered-drugs

policies explicitly limiting or banning the use of cognition-enhancing drugs in specific contexts, such as universities and workplaces, is still discussed only as a matter of heated controversy in regulatory and public policy debates for the time being (e.g. Schermer, 2008; Dubljević, 2013).

Back to the comparison between the moral implications of PCE use and the ethical issues associated with doping, it is worth considering a study by Dodge and colleagues (2012), who reported how a consistent majority of the participants interviewed would morally differentiate between the use of "smart drugs" in academia and doping substances in athletic competitions, widely regarding the latter under a much more negative light than the former with respect to the moral principle of fairness in competitive contexts - as academic tests and sports competitions may equally be considered to be. Such results have been further corroborated by a great deal of anecdotal evidence for the tendency by the general public to display a more favourable attitude towards PCE as compared to doping, respectively considering the use of prescription stimulants for CE as an overall acceptable practice and the use of doping in sports as downright immoral and inadmissible. Importantly, this kind of studies has often emphasised how respondents' answers in this respect tend to be highly influenced by the presence of definite legal norms explicitly regulating which substances are admissible in sports and which ones are labelled as illegal doping, as compared to the lack of clear regulation on the off-label use of prescription stimulants used as PCE by university students. This normative deficiency in the PCE domain may indeed contribute to explain why observers still display a significant degree of uncertainty as to whether it should be equated with cheating and, therefore, as to why no moral consensus has been achieved yet in the societal attitude towards PCE among the cognitively healthy: in fact, the proper act of cheating usually requires breaching established (possibly in written form) rules or norms, and, to date, there still is no sign of whichever such written regulation addressing the use of PCE.

On the other hand, it is noteworthy that certain behaviours, even though they do not technically nor explicitly violate any code of conduct, integrity policy or sporting regulation, admittedly allow to obtain unfair advantages over other peers, and are therefore rather likely to be regarded as highly dubious (at best) or even as dishonest conduct by observers– much like what the concept of "gamesmanship" expresses in sports. Therefore, following an opposite line of reasoning as compared to the former one, it may be the case that it is society's specific moral evaluation of a given dubious behaviour to prompt its normative regulation - and not the other way around. In fact, an opposite explanation for this general misalignment in public ethical perception between PCE and doping may lie in the different societal processes of evolution of people's consensus on the ethical judgement of the use of enhancing substances in the two contexts. For instance, it is likely that the general public across societies has come to more or less implicitly agree on the inadmissibility of doping based on a negative moral emphasis put on the perceived intent of users to dishonestly enhance their performance through artificial means in order to unfairly outdo athletic competitors; on the other hand, the moral criteria to evaluate the use of PCE in academia may have disregarded the issues of academic competition - often displayed as eagerness for success over other peers at all costs - and shifted towards a more “co-operative” or “non-zero-sum” configuration of academic contexts, focusing mainly on the daily struggle experienced by undergraduates to cope with the inevitable stress associated with high academic workloads, fear of personal failure and growing societal pressures to be increasingly and unfailingly smart and to always do one’s best. This hypothesis serves to exemplify that the societal perception and evaluation of the non-medical use of pharmacological drugs for the purpose of enhancing one’s performance – be it physical or cognitive – may have serious consequences for the long-term emergence and establishment of stark ethical judgements of such behaviours and that may therefore play a crucial role in giving a boost to the creation of regulatory and normative frameworks in public policy.

3.2. Implicit coercion

In the ongoing debate on the relation between PCE use within academia and the issues of cheating and fairness in competition, many observers have also emphasised the need to address another potential problem, which is again strongly related to the overall impact of PCE on the mechanisms characterising a fair academic competition – namely, the problem of coercion. While the concerns voiced on cheating mainly refer to the potential of PCE use to distort fair competition, now the problem with coercion lies in the fact that the use of prescription psychostimulants on the part of healthy students to enhance their academic performances may unduly increase academic competition by raising the general level of standard cognitive performance: in turn, this would indirectly engender mechanisms of implicit coercion to use PCE on those who would not otherwise be willing to engage in such a practice (Farah et al., 2004; Greely et al., 2008; Hildt & Franke, 2013; Knafo & Venero, 2015; Dubljević, 2019).

Drawing on Kipke (2013), the argument of critics proceeds as follows. The notion of competition essentially entails a rivalry between two or more parties contending against each other in order to obtain a certain good (e.g. a scarce resource, a job position, a prize, profit, status etc.) through the use of certain abilities required by the specific nature of the given competition. The winning contestant then secures either the whole of such good to the loss of all the others (i.e. a zero-sum game) or the greatest share, leaving the other competing parties to secure for each of themselves the remaining share of the good in descending order of magnitude (i.e. non-zero-sum game). Thus, it stands to reason that every type of competition is necessarily characterised by the presence of a certain constant pressure to perform better than the other rivals in order to secure the desired good.

In the context of PCE use within academia, the specific point at issue is that the practice of resorting to prescription psychostimulants by a part of the healthy student population in order to enhance their academic outcomes may make it tougher for non-enhanced students to withstand academic competition with the enhanced ones, whose performances would allegedly be significantly better thanks to their PCE-increased cognitive abilities. This would excessively increase a given, already-existing level of generalised pressure to obtain high grades, which is naturally induced by the intrinsic presence of a healthy level of competition in academic contexts and is usually considered to be not only innocuous, but even benign and, furthermore, instrumental in the achievement of satisfactory academic results, in that it naturally impels students to put effort into their academic tasks so as to obtain the best possible outcome. It is then likely that non-enhanced as well may feel implicitly compelled to use smart drugs – perhaps, even against their rational wishes - just in order to stay "competitive" , to be effectively able to compete on a par with other colleagues and for fear of failure as compared to their peers. This perspective is increasingly popular among critical observers: for instance, Farah and colleagues (2004) rightly state that "merely competing against enhanced co-workers or students exerts an incentive to use neurocognitive enhancement"; Bublitz (2013) also claims that "very likely, a widespread use of enhancements will create pressures on persons preferring to abstain from using them. […] by subtly shifting ideas of mental normality, nonusers may be confronted with the social expectation to "take a pill". This position is reiterated by Kipke (2013), who argues that even "the mere suspicion that competitors are taking enhancers produces the pressure to do the same".

If this is the case, PCE use "is only an expression of the high level of this pressure to perform and […] it increases this pressure even more" (Kipke, 2013), much like a vicious circle where performance anxiety is dealt with through PCE use, which in turn increases competition and, consequently, the competitive pressure of those who still do not use PCE (either because they have not considered this possibility yet or because they do not genuinely feel like using smart drugs for moral or safety reasons), who eventually end up feeling almost coerced to use PCE themselves, perhaps even against their own convictions. Merkel (2007) has even advanced a thought-provoking (and perhaps slightly extreme) hypothesis, suggesting that this situation may turn into the "paradoxical perspective of some people expanding their freedom of action by restraining the freedom of will of equally numerous others".

Whatever the merits of this strong statement, it is safe to claim that, in the scenarios depicted above, universities and colleges would turn into contexts where unhealthy and implicitly coercive rivalry takes over for fair academic competition.

Therefore, building also on these concerns over the apparently realistic possibility of indirect coercion within academia due to PCE use, some scholars have suggested that the issue (along with the range of all the other key bioethical challenges posed by the use of PCE in situations of socio-economic competition, such as in certain professions) warrants more substantive efforts aimed at defining a normative framework to safeguard people's interests and common ethical judgements by possibly limiting or even banning the use of PCE, especially at colleges and universities: at the very least, this would amount to effectively try to preserve the just mechanisms of social competition or restore such justice when violated by the "unfair" and "coercive" practice of PCE use (Dubljević, 2012a,b). In fact, according to critics, generally speaking "the unfairness of the social practice of cognitive enhancement calls for the introduction of rules and/or justifies the implicit or explicit norms that are in place", and they also claim that "a similar position is intuitively shared by the majority of people " (Knafo & Venero, 2015).

However, it is at best dubious whether such a clear-cut and restrictive normative framework designed to eradicate the phenomenon of PCE use among healthy individuals and students would actually be preferable or even advisable.

In this respect, a seminal contribution by Farah and colleagues (2004) seems helpful in trying to solve this ethical dilemma by virtue of its shedding some light onto the other latent side of the moral coin. In fact, although the ethical issue of fairness in competition is undoubtedly concerned with the society as a whole, rather than with single individuals, and despite the fact that its preservation is therefore of greatest importance insofar as any individual member of society cannot help but being always directly or indirectly affected by distortions or violations of fairness in socio-economic matters, the intuition here is that its uncompromising protection may nonetheless entail a crucial moral drawback on the individual dimension.

The fundamental issue at stake here pertains to the key ethical principle of personal autonomy. Beauchamp and Childress (1979) explain what autonomy is and what it means for an individual to be autonomous in the following words: "Autonomy is a form of personal liberty of action where the individual determines his or her own course of action in accordance with a plan chosen by himself or herself. The autonomous person is one who not only deliberates about and chooses such plans but who is capable of acting on the basis of such deliberations, just as a truly independent government has autonomous control of its territories and policies." This oft-quoted definition emphasises a clear notion of self-governance as constituting the foundational core of personal autonomy, meaning that individuals are autonomous when they are able to think and contextually act as they prefer and have deliberately chosen to without being constrained, coerced or influenced in any way by any third party, neither physically nor psychologically. Furthermore, Beauchamp and Childress' definition carries an eminent philosophical onus in that it may also be intended as merging the complementary perspectives on autonomy expressed by Kant and Mill – respectively, autonomy intended as freedom of the will and as the typically liberal freedom of action in mutual respect of other individuals' own freedom. Even if this alone should suffice to express the absolute magnitude of autonomy as the most important moral principle in liberal societies, it is perhaps also worth reminding how autonomy is, more simply, one of the indispensable prerequisites for every person to live a meaningful life worthy of its name – a life whose legitimate and intrinsic personal freedom of will and liberty of action do not interfere with the respective freedom and liberty competing to every other individual.

Contextualising these moral and philosophical considerations about personal autonomy within the bioethical and normative discussion over PCE use by healthy undergraduates and its potential for implicit coercion on the non-enhanced, it is easy to see how rigid, severe normative approaches imposing very strict limitations or a straight ban on the use of PCE in order to prevent the deleterious effects on fair academic competition stemming from the indirect and/or implicit coercion potentially generated by widespread PCE use, may themselves be unduly coercive towards the personal autonomy which inalienably belongs to every single individual on earth. In light of that, some scholars have clearly voiced arguments against strict prohibition-oriented approaches and even against some mild attempts to disincentivise PCE use that have been suggested on the basis of the concern about coercion, on the basis that such restrictive normative approaches are contrary to the fundamental liberal principle that "the State should not interfere with its adult citizens' choices as long as they do not damage third parties" (Garasic & Lavazza, 2016), which is at the core of the politics of modern western civilisations, liberal societies and market economies: "In general, prohibiting the use of PCE per se would amount to a privation of freedom/autonomy and a reduction of the benefits that they could bring to the individual and society, which is not justified so far by the problems caused by cognitive enhancement" (Garasic & Lavazza, 2016).

For instance, Farah and colleagues (2004) reject such restrictive normative frameworks by claiming that "the straightforward legislative approach of outlawing or restricting the use of neurocognitive enhancement in the workplace or in school is itself also coercive. It denies people the freedom to practice a safe means of self-improvement, just to eliminate any negative consequences of the (freely taken) choice not to enhance". In Cakic's view (2009), in spite of the reasonable concerns voiced over the potential of PCE for implicit coercion, "to restrict the autonomy of all people for fear that it may influence the actions of some is untenable". Essentially, this alternative strand of opinion disputes that it is inadmissible to adopt this moral double standard when fighting PCE use by means of the complete sacrifice of personal autonomy in the name of societal fairness only. Their argument may be understood in the sense that the social fabric is not a superior, abstract entity, but it is rather composed of an enormous aggregate of single individuals who have moral rights as well as moral duties, which should be all taken into account as much as societal ones are in the assessment of ethical conflicts pitting individuals with society as a whole. According to these scholars, the ethical issues regarding society as a whole should not take incontrovertible precedence *a priori* over issues pertaining to the individual alone. However, for the sake of moral and practical common sense, neither should it invariably be the other way round: rather, the ethical and normative motto should be "*in medio stat virtus*". With regard to this, Garasic and Lavazza (2016) point out that "although on the one hand the unrestricted use of PCE preserves the principle of personal autonomy that (at least at the theoretical level) should be given priority in liberal societies, on the other hand, the consequences […] can lead to unfair outcomes or social situations that clash against some other principles dear to liberalism." As a solution, they suggest "[…] posing some limitations to personal autonomy related to the use of PCE through a restriction of the subject's privacy in competitive contexts. […] The legitimacy of introducing a duty of disclosure […] suggests a restriction of individual freedom/autonomy if the exercise of the latter puts in danger the freedom/autonomy of others, as it happens in the case of the concealed use of PCE."

To conclude, whatever the merits of both these different bioethical stances, it must be stressed that there currently exists only little empirical evidence (which is anecdotal for the most part) suggesting that the widespread use of prescription stimulants as an attempt to enhance academic performance gives rise to indirect or implicit coercion mechanisms in academic competition between the enhanced and the non-enhanced (Maher, 2008; De Santis et al., 2008). Thus, for the time being, the ethical debate specifically concerning PCE use and coercion in such competitive contexts is still mainly conducted by way of thought experiments, fictitious scenarios and near-future hypotheses based on present predictions. However, some studies have actually warned about the realistic possibility that, in the near future, this phenomenon may become a concrete, pervasive reality defined as "second stage enhancement"[66] (Khushf, 2005, 2008; ETAG, 2009). These concerns have been and are still raised on the basis of documented instances of both direct coercion in the military and indirect coercion in other economic settings (e.g. corporate agencies) and in cognitively demanding healthcare professions (Khushf, 2005, 2008; Appel, 2008; Academy of Medical Science et al., 2012). It is also worth noting that there have been a number of proposals to render PCE compulsory in some specific high-performance professional sectors providing essential public services, which therefore entail a great deal of responsibility towards the whole community on the part of the respective professionals (e.g. pilots, E.R. staff, surgeons, firemen etc.) and are usually both cognitively demanding and physically fatiguing (Santoni de Sio et al., 2014).

In light of this, it should then be easy to acknowledge the usefulness of attempts (such as the ones above) to frame inquiry into this point of ethical contention on the basis of this concrete cause for concern, even if, to date, the evidence of implicit coercion in academia because of widespread PCE use still appears to be very limited. At the very least, preventive ethical inquiry (which is nonetheless seemingly justified by these realistic worries) may prove helpful in providing people with the necessary tools to make informed moral choices in the event that such a coercive scenario actually materialises in the near future as biomedical research and neuroscientific knowledge progress further.

[66] Khushf (2008): "Stage 1 enhancements are discrete, medical enhancements; they involve a modest augmentation of some specific function or capacity, and have quantifiable harms and benefits that are amenable to conventional study designs. Examples of these enhancements include psychopharmaceuticals for enhanced cognitive function, cosmetic surgery, and sports doping. Stage 2 enhancements build upon stage 1, but involve more than a simple quantitative extension of stage 1 capacities. Stage 2 enhancement technologies are multifunctional; have an autocatalytic aspect that leads to accelerating development; and involve the convergence of multiple kinds of technology and technology platforms. These enhancements can involve radically new capacities that provide significant advantages to those who obtain them."

Conclusion

The aim of this dissertation has been to provide help and guidance in getting a deeper and firmer grasp of the different aspects pertaining to the practice of PCE use on the part of cognitively healthy university and college students, in order to shed light on the three main controversies characterising this mounting societal trend – namely, (1) its actual efficacy on healthy individuals, (2) the health risks it entails and the (3) potential ethical and social repercussions (and the associated regulatory considerations) of its widespread and eventually commonplace use in contexts of academic competition. This aim has been pursued by presenting the most comprehensive possible picture of this increasingly pervasive phenomenon by respectively taking stock of its theoretical premises, conceptual definitions, factual aspects and ethical-social implications in competitive academic settings.

With regard to this, the first chapter has kick-started this task by trying to dispel any lingering doubts regarding the precise meaning of the notion of "enhancement", which has been hereby defined as intrinsically different from the often associated notion of "therapy". The fundamental shared feature making their distinction rather blurry at times is that both concepts entail some sort of physiological improvement in human beings. However, while "therapy" provides such improvement by means of curing, palliating or rehabilitating patients from medical conditions typical of a defective state of health which should therefore be restored to "normality", "enhancement" is simply aimed at inducing improvements which go beyond a "normal" state of health. In fact, even though any improvement whatsoever may generically be considered as an enhancement, for the sake of clarity it is necessary to highlight the fact that a proper enhancement does not entail the features of prevention, rehabilitation from or mitigation of diseases, disorders or impairments in an attempt to remedy to disadvantaged health conditions of patients and restore "normality", but it simply implies some sort of identifiable and measurable improvement in individuals who already enjoy good health. Then, this concept has been explored and further specified in its practical application to human cognitive faculties in order to define the ongoing endeavour to enhance cognitive abilities in otherwise cognitively healthy individuals by the expression "cognitive enhancement" (CE). More specifically, the two currently existing and viable approaches to CE have been reviewed as being either pharmacological or fundamentally technological in nature – categorised, respectively, under the labels Pharmacological Cognitive Enhancement (PCE) and Non-Pharmacological Cognitive Enhancement (NPCE). However, for the outlined purposes of the present dissertation, the bulk of attention has been drawn to the former category, by means of a detailed overview of the various pharmacological psychostimulant substances used by university students for neuro-cognitive enhancement purposes.

Building on this thorough conceptual groundwork, the second chapter has delved into the empirical aspects of PCE use within academia by cognitively healthy students - namely, its prevalence rates and social relevance, the self-reported reasons and the deeper underlying causes behind such practice, its effectiveness and the risks it entails. This assessment has hopefully proved useful in providing the empirical basis upon which the first two urgent points of contention concerning the actual efficacy and health risks of PCE in the absence of any diagnosed neuropsychiatric conditions can be cleared a bit. To this purpose, the present work has tried to suggest that the pharmaceutical drugs or "smart pills" which are, at present, most widely resorted to off-label by healthy individuals for the purpose of enhancing cognitive faculties do not actually live up to the extremely high hype they have been attracting so far.

In fact, plenty of clinical research findings seem to converge on the stance that oft-quoted claims about their cognition-enhancing powers may definitely be overinflated. The available empirical evidence for reliable effectiveness of PCE in the improvement of cognitive abilities such as memory, learning, attention and concentration in otherwise healthy individuals is still extremely slim, inconsistent and not at all conclusive: in fact, even when research studies have shown some modest improvement in the cognitive abilities of healthy individuals, the positive effects have been detected to concern only the performance of specific cognitive tasks, only in a limited number of research subjects in specific dosages and, most importantly, not to be transferable to the performance of other non-trained cognitive-related tasks, nor replicable among individuals, nor able to be carried over from laboratory studies to real-life settings. Therefore, notwithstanding the nearly-miraculous "brain boosting" benefits apparently promised by popular media claims on PCE use in cognitively healthy subjects, the consensus in the scientific literature so far is that no conclusive and unambiguous clinical evidence has been found yet for any relevant enhancing effect of prescription psychostimulants on the cognitive abilities of otherwise healthy individuals. On the other hand, it should be made clear that the fact that the popularity of "smart drugs" use seems to even be on the rise among the general public (especially among university and college students to enhance their academic achievements) in spite of their overall cognition-enhancing inefficacy may be due to the clinically proved, positive effects of prescription stimulants on healthy individuals' emotional faculties (such as motivation, arousal, enthusiasm, interestedness, enjoyment of tasks etc.) and on physical tiredness and sleepiness: since these factors are clearly involved nearly as much as cognitive faculties are in the achievement of successful academic performances of cognitive-related tasks, users may deem their improvement as appreciable and effective enough for the purposes of academic efficiency and excellence in order to consider PCE drugs "effective" - when in fact they are most likely not, with regard to their claimed primary purpose.

In light of this comprehensive review of available empirical findings on the actual cognitive effectiveness of PCE, the dissertation has then proceeded to assess the health risks and potential side effects associated with its use on the part of healthy individuals, in order to evaluate whether its verified benefits outweigh its potential risks – and, if yes, to what extent. Once again, what has emerged in this regard from clinical data is, for the time being, rather disappointing on safety grounds as well. In fact, safety clinical trials conducted on the off-label use of prescription stimulants have identified a wide range of significant health risks and severe side effects potentially connected to PCE in healthy individuals, including abuse and addiction risks, toxicity, potential cardiac events and serious behavioural alterations. However, cognitively healthy individuals should, in theory, be only willing to accept a much lower risk threshold for pharmaceutical drugs use, since they willingly choose to use them in the absence of a defective state of health, therefore outside the scope of medicine and irrespective of the purpose for which they were developed in the first place - as compared to those who are actually diagnosed with neuropsychiatric conditions and, therefore, do need to engage in the use of such medications in order to restore their good health or mitigate impairing symptoms. That being said, PCE use would then seem not to be acceptable on safety grounds among cognitively healthy people (let alone young undergraduates whose brains and internal organs are not even fully developed yet), as the potential health risks entailed by PCE use are, for the time being, not in the slightest outweighed by established benefits to cognition – rather, it definitely appears to be the other way round. All things considered, the present work then makes the point that even if the kind of health risks and side harmful effects potentially caused by PCE should alone be enough to discourage this practice among the cognitively healthy, the additional combination with the lack of sound scientific evidence for appreciable cognition-enhancing effectiveness should act, in principle, as the strongest disincentive towards the non-medical use of prescription stimulants for CE purposes.

Moving on to address the last of the three major areas of debate associated with PCE use among healthy university and college students, the dissertation has provided a concise overview of the most compelling ethical and social concerns raised in the current bioethical literature with regard to this growing tendency in competitive academic contexts, especially in the likely prospect of this practice becoming increasingly pervasive, up to the point of it being commonplace in the near future. The ethical assessment of this phenomenon has focused on issues of fairness in academic competition, because competition itself is, in the most general sense, one of the most fundamental features in any socio-economic sphere across liberal societies. The present work has discussed two issues of fairness in academic competition in particular – namely, the possibility of PCE use to be regarded as "cheating" (along with the associated, plausible parallels that have often been drawn between PCE within academia and doping in sports), and the risk of indirect and implicit coercion potentially exerted by an ubiquitous tendency to resort to PCE within academia on students otherwise unwilling to enhance themselves, who may then turn to consider engaging in this practice as well in the belief that this may be the only effective way to "stay competitive" on a par with their enhanced peers in the context of academic examinations and competitions. The moral evaluation of PCE use within academia has explicitly been limited to these few controversial aspects because the bioethical focus of the present dissertation is strictly on the social consequences of PCE use among healthy undergraduates - in which the moral issue of fairness (central in the notions of cheating and coercion) is perhaps the only one playing a concrete role, among all others - and because these are points of ethical contention almost exclusively associated to competitive-selective contexts, such as the academic ones (e.g. tests and exams undertaken by large student populations) where PCE is most resorted to by healthy undergraduates.

With regard to these two significant moral controversies pertaining to the relation between PCE use by healthy undergraduates and the broader issue of fairness in academic competition, the dissertation has examined the ethical stances of both "bioliberals" and "bioconservatives", suggesting that none of these two factions can be claimed to be right in an absolute sense, but that, on the other hand, the most reasonable ethical, social and regulatory positions lie in a middle ground between them. In fact, while it is true that PCE use by the cognitively healthy may potentially come to be configured as cheating in tests and exams and as prompting indirect and implicit coercion on non-enhanced students (as bioconservatives claim, ethically speaking), the most responsible policy stance on the issue seems not to entail downright ban and prohibition (and not even strict limitation), as the latter would in turn not only infringe other equally fundamental values (e.g. personal autonomy, as bioliberals point out on normative grounds) in the liberal political framework adopted as a general outlook of reference in the chapter, but would also prove useless in the eradication of the primary determinant of this phenomenon – i.e., the unhealthy dynamics of competition currently holding unbridled sway in global liberal market economies.

Basically, the idea emerging from the ethical discussion undertaken in the third chapter is that these are controversies indeed worth discussing, as they are invested with great significance in real-world, ordinary circumstances involving individuals dealing with a very peculiar tool whose overall features are still unclear under many respects and from which serious implications for the broader community may stem.

To conclude, I sincerely hope that, notwithstanding their possible limitations, the conceptual, empirical and ethical analyses hereby provided have been able to offer some thoughtful and perhaps novel insights and inputs such as to generate new, different ways of structuring the bioethical discussion on the factual advantages and risks of PCE use within academia and over its broader social implications, with a view to encouraging even more innovative assessments of the phenomenon - even by those who lack expertise in the field.

Bibliographic references

Academy of Medical Sciences, British Academy, Royal Academy of Engineering and Royal Society. (2012). *Human enhancement and the future of work*. ISBN: 978-1-903401-35-4 Available at: https://acmedsci.ac.uk/file-download/35266-135228646747.pdf

Advokat, C. (2010). What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neuroscience & Biobehavioral Reviews*, *34(8)*, 1256–1266. https://doi.org/10.1016/j.neubiorev.2010.03.006

Advokat, C., Guidry, D., & Martino, L. (2008). Licit and Illicit Use of Medications for Attention-Deficit Hyperactivity Disorder in Undergraduate College Students. *Journal of American College Health*, *56(6)*, 601-606. https://doi.org/10.3200/jach.56.6.601-606

Advokat, C., & Scheithauer, M. (2013). Attention-deficit hyperactivity disorder (ADHD) stimulant medications as cognitive enhancers. *Frontiers in Neurosci*ence, *7,* 82. https://doi.org/10.3389/fnins.2013.00082

Advokat, C., & Vinci, C. (2012). "Do stimulant medications for attention deficit/hyperactivity disorder (ADHD) enhance cognition?". In: J. Norvilitis (ed.), *Current Directions in ADHD and Its Treatment*. Rijeka: InTech, pp. 125-156. ISBN: 978-953-307-868-7. conclusion

Aldred, E.M. (2009). The Nervous System. In: E.M. Aldred & C. Buck (eds.), *Pharmacology: A Handbook for Complementary Healthcare Professionals*. Churchill Livingstone, pp. 235-246. https://doi.org/10.1016/B978-0-443-06898-0.00031-1

Appel, J.M. (2008). When the boss turns pusher: a proposal for employee protections in the age of cosmetic neurology. *Journal of Medical Ethics, 34*, 616 - 618. https://doi.org/ 10.1136/jme.2007.022723

Arria, A.M., & DuPont, R.L. (2010). Nonmedical prescription stimulant use among college students: why we need to do something and what we need to do. *Journal of Addictive Diseases*, *29(4)*, 417–426. https://doi.org/10.1080/10550887.2010.509273

Arria, A., O'Grady, K.E., Caldeira, K.M., Vincent, K.B., & Wish, E.D. (2008). Nonmedical Use of Prescription Stimulants and Analgesics: Associations with Social and Academic Behaviors among College Students. *Journal of Drug Issues*, *38(4)*, 1045-1060. https://doi.org/10.1177/002204260803800406

Babcock, Q., & Byrne, T. (2000). Student Perceptions of Methylphenidate Abuse at a Public Liberal Arts College. *Journal Of American College Health*, *49(3)*, 143-145. https://doi.org/10.1080/07448480009596296

Ball, N., & Wolbring, G. (2014). Cognitive Enhancement: Perceptions Among Parents of Children with Disabilities. *Neuroethics, 7(3)*, 345-364. https://doi.org/10.1007/s12152-014-9201-8.

Balloon, J.S., & Feifel, D. (2006) A systematic review of modafinil: Potential clinical uses and mechanisms of action. *The Journal of Clinical Psychiatry*, *67(4)*, 554-66. https://doi.org/10.4088/jcp.v67n0406.

Banjo, O.C., Nadler, R., & Reiner, P.B. (2010) Physician attitudes towards pharmacological cognitive enhancement: safety concerns are paramount. *PloS One, 5(12)*, e14322. https://doi.org/10.1371/journal.pone.0014322.

Barrett, S., Darredeau, C., Bordy, L., & Pihl, R. (2005). Characteristics of Methylphenidate Misuse in a University Student Sample. *The Canadian Journal of Psychiatry*, *50(8)*, 457-461. https://doi.org/10.1177/070674370505000805

Bavarian, N., Flay, B.R., Ketcham, P.L., & Smit, E. (2013). Illicit use of prescription stimulants in a college student sample: a theory-guided analysis. *Drug and Alcohol Dependence, 132(3)*, 665-673. https://doi.org/10.1016/j.drugalcdep.2013.04.024

Beauchamp, T. & Childress, J. (1979). *Principles of biomedical ethics*. New York: Oxford University Press, pp. 56-57. ISBN: 9780190640873

Been, G., Ngo, T.T., Miller, S.M., & Fitzgerald, P.B. (2007). The use of tDCS and CVS as methods of non-invasive brain stimulation. *Brain research reviews*, *56(2)*, 346–361. https://doi.org/10.1016/j.brainresrev.2007.08.001

Bell, S.K., Lucke, J.C., & Hall, W.D. (2012). Lessons for enhancement from the history of cocaine and amphetamine use. *American Journal of Bioethics Neuroscience, 3(2)*, 24–29. https://doi.org/10.1080/21507740.2012.663056

Bell, S.K., Partridge, B., Lucke, J.C., & Hall, W.D. (2013). Australian university students' attitudes towards the acceptability and regulation of pharmaceuticals to improve academic performance. *Neuroethics, 6*, 197–205. https://doi.org/10.1007/s12152-012-9153-9

Bennett, T., & Holloway, K. (2017). Motives for illicit prescription drug use among university students: A systematic review and meta-analysis. *International Journal of Drug Policy, 44*, 12-22. https://doi.org/10.1016/j.drugpo.2017.02.012

Ben-Menachem, E. (2001). Vagus nerve stimulation, side effects, and long-term safety. *Journal of Clinical Neurophysiology: official publication of the American Electroencephalographic Society*, *18*(5), 415–418. https://doi.org/10.1097/00004691-200109000-00005

Benson, K., Flory, K., Humphreys, K.L., & Lee, S.S. (2015). Misuse of Stimulant Medication Among College Students: A Comprehensive Review and Meta-analysis. *Clinical Child and Family Psychology Review*, *18*(1), 50–76. https://doi.org/10.1007/s10567-014-0177-z

Bergström, L.S., & Lynöe, N. (2008). Enhancing concentration, mood and memory in healthy individuals: an empirical study of attitudes among general practitioners and the general population. *Scandinavian Journal of Public Health*, *36(5)*, 532-537. https://doi.org/10.1177/1403494807087558

Bidwell, L.C., McClernon, F.J., & Kollins, S.H. (2011). Cognitive enhancers for the treatment of ADHD. *Pharmacology, Biochemistry and Behavior, 99(2),* 262–274. https://doi.org/10.1016/j.pbb.2011.05.002

Bishop, J.H. (2003). *Nerd harassment and grade inflation: Are college admissions policies partly responsible?* Available at: https://files.eric.ed.gov/fulltext/ED481756.pdf

Blank, R.H. (2016). *Cognitive Enhancement: Social and Public Policy Issues.* Basingstoke: Palgrave Macmillan. https://doi.org/10.1057/9781137572486.0001

Blank, R.H. (2016). Regulating Cognitive Enhancement Technologies: Policy Options and Problems. In: F. Jotterand & V. Dubljević (eds.), *Cognitive Enhancement: Ethical and Policy Implications in International Perspectives*. Oxford: Oxford University Press, pp. 239-258. ISBN 9780199396825.

Borst, S.E., Goswami, D.T., Lowenthal, D. & Newell, D. (2007) Autonomic Nervous System. In: J.E. Birren (ed.), *Encyclopedia of Gerontology (Second Edition)*. Elsevier, pp. 129-135. https://doi.org/10.1016/B0-12-370870-2/00019-6

Bossaer, J.B., Gray, J.A., Miller, S.E., Enck, G., Gaddipati, V.C., & Enck R.E. (2013). The use and misuse of prescription stimulants as “cognitive enhancers” by students at one academic health sciences center. *Academic Medicine, 88(7)*, 967–971. https://doi.org/10.1097/Acm.0b013e318294fc7b

Bostrom, N., & Sandberg, A. (2009). Cognitive Enhancement: Methods, Ethics, Regulatory Challenges. *Science and Engineering Ethics*, *15(3)*, 311–341. https://doi.org/10.1007/s11948-009-9142-5

Brandt, S.A., Taverna, E.C., & Hallock, R.M. (2014). A survey of nonmedical use of tranquilizers, stimulants, and pain relievers among college students: Patterns of use among users and factors related to abstinence in non-users. *Drug and Alcohol Dependence, 143*, 272-276. https://doi.org/10.1016/j.drugalcdep.2014.07.034

Brooks, D. (2001). The organization kid. *The Atlantic Monthly, 287(4),* 40-54. Available at: http://fryett.org/files/Brooks_OrganizationalKid.pdf

Brühl, A.B., d'Angelo, C., & Sahakian, B.J. (2019). Neuroethical issues in cognitive enhancement: Modafinil as the example of a workplace drug? *Brain and Neuroscience Advances, 3*, 1–8. https://doi.org/10.1177/2398212818816018

Brukamp, K. (2013). Better Brains or Bitter Brains? The Ethics of Neuroenhancement. In: E. Hildt & A.G. Franke (eds.), *Cognitive Enhancement: An Interdisciplinary Perspective*. Dordrecht: Springer, pp. 99-112. https://doi.org/10.1007/978-94-007-6253-4

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., & Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation, 5(3)*, 175–195. https://doi.org/10.1016/j.brs.2011.03.002

Bublitz, J.C. (2013). My mind is mine!? Cognitive liberty as a legal concept. In: E. Hildt & A.G. Franke (eds.), *Cognitive Enhancement: An Interdisciplinary Perspective.* Dordrecht: Springer, pp. 233-264. https://doi.org/10.1007/978-94-007-6253-4

Busardò, F.P., Kyriakou, C., Cipolloni, L., Zaami, S., & Frati, P. (2016). From Clinical Application to Cognitive Enhancement: The Example of Methylphenidate. *Current Neuropharmacology*, *14(1)*, 17–27. https://doi.org/10.2174/1570159x13666150407225902

Busch, K.W., & Busch, M.A. (2006). *Chiral analysis.* Elsevier Science. https://doi.org/10.1016/B978-0-444-51669-5.X5000-5

Bylund, D.B., & Bylund, K.C. (2014). Norepinephrine. In: M.J. Aminoff & R.B. Daroff (eds.), *Encyclopedia of the Neurological Sciences (Second Edition).* Academic Press, pp. 614-616. https://doi.org/10.1016/B978-0-12-385157-4.00047-6

Cakic, V. (2009). Smart drugs for cognitive enhancement: ethical and pragmatic considerations in the era of cosmetic neurology. *Journal of medical ethics*, *35(10)*, 611–615. https://doi.org/10.1136/jme.2009.030882

Caplan, J.P., Epstein, L.A., Quinn, D.K., Stevens, J.R., & Stern, T.A. (2007). Neuropsychiatric effects of prescription drug abuse. *Neuropsychology Review, 17(3)*, 363–380. https://doi.org/10.1007/s11065-007-9037-7

Carlier, J., Giorgetti, R., Varì, M.R., Pirani, F., Ricci, G., & Busardò, F.P. (2019) Use of cognitive enhancers: methylphenidate and analogs. *European Review for Medical and Pharmacological Sciences, 23*, 3–15. https://doi.org/10.26355/eurrev_201901_16741

Castaldi, S., Gelati, U., Orizio, G., Hartung, U., Moreno-Londono, A.M., Nobile, M., & Schulz, P.J. (2012). Use of Cognitive Enhancement Medication Among Northern Italian University Students. *Journal of Addiction Medicine, 6(2)*, 112–117. https://doi.org/10.1097/adm.0b013e3182479584

Catterall, W.A. (2009). Neuromodulation of Sodium Channels. In: In: L.R. Squire (ed.), *Encyclopedia of Neuroscience*. Academic Press, pp. 513-519. https://doi.org/10.1016/B978-008045046-9.00683-5

Chatterjee, A. (2007). Cosmetic neurology and cosmetic surgery: Parallels, predictions, and challenges. *Cambridge Quarterly of Healthcare Ethics, 16,* 129–137. https://doi.org/10.1017/S0963180107070156

Chi, R.P., Fregni, F., & Snyder, A.W. (2010). Visual memory improved by non-invasive brain stimulation. *Brain research*, *1353*, 168–175. https://doi.org/10.1016/j.brainres.2010.07.062

Chronicle of Higher Education. (2005). Admissions today: 6 experts speak out. *Chronicle of Higher Education*, *51*, B15. ISSN: 0009-5982, 1931-1362

Clark, V.P., Coffman, B.A., Mayer, A.R., Weisend, M.P., Lane, T.D., Calhoun, V.D., Raybourn, E.M., Garcia, C.M., & Wassermann, E.M. (2012). TDCS guided using fMRI significantly accelerates learning to identify concealed objects. *NeuroImage*, *59(1)*, 117–128. https://doi.org/10.1016/j.neuroimage.2010.11.036

Clark, K.B., Naritoku, D.K., Smith, D.C., Browning, R.A., & Jensen, R.A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience*, *2(1)*, 94–98. https://doi.org/10.1038/4600

Clark, V.P., & Parasuraman, R. (2014). Neuroenhancement: enhancing brain and mind in health and in disease. *NeuroImage*, *85 Pt 3*, 889–894. https://doi.org/10.1016/j.neuroimage.2013.08.071

Clegg-Kraynok, M.M., McBean, A.L., & Montgomery-Downs, H.E. (2011). Sleep quality and characteristics of college students who use prescription psychostimulants nonmedically. *Sleep Medicine*, *12(6)*, 598–602. https://doi.org/10.1016/j.sleep.2011.01.012

Coenen, C. (2008). Converging technologies: The status of the debate and political activities. TAB background paper no. 016. Berlin: Office of Technology Assessment at the German Bundestag.

Coffman, B.A., Clark, V.P., & Parasuraman, R. (2014). Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*, *85 Pt 3*, 895–908. https://doi.org/10.1016/j.neuroimage.2013.07.083

Cohen Kadosh, R., Levy, N., O'Shea, J., Shea, N., & Savulescu, J. (2012). The neuroethics of non-invasive brain stimulation. *Current Biology: CB*, *22(4)*, R108–R111. https://doi.org/10.1016/j.cub.2012.01.013

Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current biology: CB*, *20(22)*, 2016–2020. https://doi.org/10.1016/j.cub.2010.10.007

Conrad, B. (2008). The Role of Dopamine as a Neurotransmitter in the Human Brain. *Enzo Science Center.* Available at: https://www.enzolifesciences.com/science-center/technotes/2018/november/the-role-of-dopamine-as-a-neurotransmitter-in-the-human-brain/

Conrad, P., & Horwitz, A. (2013). Marketing of neuropsychiatric illness and enhancement. In: A. Chatterjee & M.J. Farah (eds.), *Neuroethics in Practice: Medicine, Mind, and Society*. New York: Oxford University Press, pp. 46–56. https://doi.org/10.1093/acprof:oso/9780195389784.001.0001

Coveney, C., Gabe, J., & Williams, S. (2011). The sociology of cognitive enhancement: Medicalisation and beyond. *Health Sociology Review, 20(4)*, 381–93. https://doi.org/10.5172/hesr.2011.20.4.381

Currie, J., Stabile, M., & Jones, L. (2014). Do stimulant medications improve educational and behavioral outcomes for children with ADHD? *Journal of Health Economics, 37*, 58–69. https://doi.org/10.3386/w19105

Dayan, E., Censor, N., Buch, E.R., Sandrini, M., & Cohen, L.G. (2013). Noninvasive brain stimulation: from physiology to network dynamics and back. *Nature Neuroscience, 16 (7),* 838–844. https://doi.org/10.1038/nn.3422

Daly, B.P., Eichen, D.M., Bailer, B., Brown, R.T., & Buchanan, C.L. (2012). Central Nervous System. In: V.S. Ramachandran (ed.), *Encyclopedia of Human Behavior (Second Edition)*. Academic Press, pp.454-459. https://doi.org/10.1016/B978-0-12-375000-6.00084-7

de Jongh, R., Bolt, I., Schermer, M., & Olivier, B. (2008). Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. *Neuroscience & Biobehavioral Reviews, 32(4),* 760–776. https://doi.org/10.1016/j.neubiorev.2007.12.001

DeSantis, A.D., Webb, E.M., & Noar, S.M. (2008). Illicit use of prescription ADHD medications on a college campus: a multimethodological approach. *Journal of American College Health, 57(3)*, 315–324. https://doi.org/10.3200/JACH.57.3.315-324

Dell'Osso, B., Dobrea, C., Cremaschi, L., Arici, C., & Altamura, A.C. (2014). Wake-promoting pharmacotherapy for psychiatric disorders. *Current Psychiatry Reports, 16(12),* 524. https://doi.org/10.1007/s11920-014-0524-2

Dennhardt, A.A., & Murphy, J.G. (2013). Prevention and treatment of college student drug use: A review of the literature. *Addictive behaviors*, *38(10)*, 2607–2618. https://doi.org/10.1016/j.addbeh.2013.06.006

Dietz, P., Soyka, M., & Franke, A.G. (2016). Pharmacological Neuroenhancement in the Field of Economics—Poll Results from an Online Survey. *Frontiers in Psychology*, *7*, 520. https://doi.org/10.3389/fpsyg.2016.00520

Dietz, P., Striegel, H., Franke, A.G., Lieb, K., Simon, P., & Ulrich, R. (2013). Randomized Response Estimates for the 12-Month Prevalence of Cognitive-Enhancing Drug Use in University Students. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *33(1)*, 44–50. https://doi.org/10.1002/phar.1166

Dodge, T., Williams, K.J., Marzell, M., & Turrisi, R. (2012). Judging cheaters: Is substance misuse viewed similarly in the athletic and academic domains? *Psychology of Addictive Behaviors, 26(3)*, 678-682. https://doi.org/10.1037/a0027872

Dresler, M., & Konrad, B. (2013). Mnemonic expertise during wakefulness and sleep. *Behavioral and Brain Sciences, 36(6)*, 616-617. https://doi.org/10.1017/S0140525X13001301

Dresler, M., Sandberg, A., Ohla, K., Bublitz, C., Trenado, C., Mroczko-Wąsowicz, A., Kühn, S., & Repantis, D. (2013). Non-pharmacological cognitive enhancement. *Neuropharmacology*, *64*, 529–543. https://doi.org/10.1016/j.neuropharm.2012.07.002

Drazdowski, T.K. (2016). A systematic review of the motivations for the non-medical use of prescription drugs in young adults. *Drug and Alcohol Dependence, 162*, 3-25. https://doi.org/10.1016/j.drugalcdep.2016.01.011

Drug Enforcement Agency. (2002). *Yearly Aggregate Production Quotas (1990– 2000)*. Washington, DC: Office of Public Affairs, Drug Enforcement Administration.

Dubljević, V. (2012a). Principles of justice as the basis for public policy on psychopharmacological cognitive enhancement. *Law, Innovation and Technology, 4(1),* 67–83. https://doi.org/10.5235/175799612800650617.

Dubljević, V. (2012b). Toward a legitimate public policy on cognition enhancement drugs. *American Journal of Bioethics Neuroscience*, *3(3),* 29–33. https://doi.org/10.1080/21507740.2012.700681

Dubljević, V. (2013). Prohibition or Coffee Shops: Regulation of Amphetamine and Methylphenidate for Enhancement Use by Healthy Adults. *American Journal of Bioethics, 13(7)*, 23–33. https://doi.org/10.1080/15265161.2013.794875

Dubljević, V. (2014). Neurostimulation Devices for Cognitive Enhancement: Toward a Comprehensive Regulatory Framework. *Neuroethics*, *8*, 115–126. https://doi.org/10.1007/s12152-014-9225-0

Dubljević, V. (2019). *Neuroethics, Justice and Autonomy: Public Reason in the Cognitive Enhancement Debate.* Cham, Switzerland: Springer Nature. of Ethics, Law and Technology ISBN 978-3-030-13642-0 https://doi.org/10.1007/978-3-030-13643-7

Dubljević, V., & Ryan, C. (2015). Cognitive enhancement with methylphenidate and modafinil: Conceptual advances and societal implications. *Neuroscience and Neuroeconomics*, *4*, 25-33. https://doi.org/10.2147/nan.s61925

Dubljević V., Sattler, S., & Racine, É. (2014). Cognitive enhancement and academic misconduct: a study exploring their frequency and relationship. *Ethics & Behavior, 24(5)*, 408-420. https://doi.org/10.1080/10508422.2013.869747

Dubljević, V., Venero, C., & Knafo, S. (2015). What Is Cognitive Enhancement? In: S. Knafo & C. Venero (eds.), *Cognitive Enhancement. Pharmacologic, Environmental and Genetic Factors.* Academic Press, pp. 1-9.

Dworkin, J. (2005). Risk taking as developmentally appropriate experimentation for college students. *Journal of Adolescent Research*, *20(2)*, 219–240. https://doi.org/10.1177/0743558404273073

Elsworth, J.D., & Roth, R.H. (2009). Dopamine. In: L.R. Squire (ed.), *Encyclopedia of Neuroscience*. Academic Press, pp. 539-547. https://doi.org/10.1016/B978-008045046-9.00683-5

Emanuel, R.M., Frellsen, S.L., Kashima, K.J., Sanguino, S.M., Sierles, F.S., & Lazarus, C.J. (2013). Cognitive Enhancement Drug Use Among Future Physicians: Findings from a Multi-Institutional Census of Medical Students. *Journal of General Internal Medicine*, *28*(8), 1028–1034. https://doi.org/10.1007/s11606-012-2249-4

European Technology Assessment Group (ETAG) on behalf of the Science and Technology Options Assessment – STOA. (2009). *Human Enhancement Study*. Brussels: European Parliament. Available at: https://www.europarl.europa.eu/RegData/etudes/etudes/join/2009/417483/IPOL-JOIN_ET(2009)417483_EN.pdf

Farah, M.J., Illes, J., Cook-Deegan, R., Gardner, H., Kandel, E., King, P., Parens, E., Sahakian, B.J., & Wolpe, P.R. (2004). Neurocognitive enhancement: what can we do and what should we do? *Nature Reviews Neuroscience*, *5*(5), 421–425. https://doi.org/10.1038/nrn1390

Farah, M.J., Smith, M.E., Ilieva, I., & Hamilton, R.H. (2014). Cognitive enhancement. *Wiley Interdisciplinary Review of Cognitive Science, 5(1),* 95–103. https://doi.org/10.1002/wcs.1250

Farrell, E. (2006). College searches gone wild: An unprecendented surge in applications catches admissions off-guard. *The Chronicle of Higher Education*, *52(30)*, A39. ISSN: 0009-5982, 1931-1362

Foresight Program (2005). *Drugs Futures 2025?* United Kingdom: Government Office for Science. Available at: https://www.gov.uk/government/publications/drugs-futures-2025

Forlini, C., & Racine, É. (2009). Autonomy and Coercion in Academic "Cognitive Enhancement" Using Methylphenidate: Perspectives of Key Stakeholders. *Neuroethics, 2(3)*, 163-177. https://doi.org/10.1007/s12152-009-9043-y

Forlini, C., & Racine, É. (2010). Stakeholder perspectives and reactions to “academic” cognitive enhancement: unsuspected meaning of ambivalence and analogies. *Public Understanding of Science, 21(5),* 606-625. https://doi.org/10.1177/0963662510385062.

Forlini, C., Hall, W., Maxwell, B., Outram, S.M., Reiner, Repantis, P.B.D., Schermer, M., & Racine, É. (2013). Navigating the enhancement landscape: Ethical issues in research on cognitive enhancers for healthy individuals. *EMBO Reports, 14(2)*, 123–28. https://doi.org/10.1038/embor.2012.225

Fox, D. (2011). Brain buzz. *Nature*, *472(7342),* 156. ISSN: 0028-0836, 1476-4687. Available at: https://ubneuro-ccohan.webapps.buffalo.edu/readings/TranscranialDCS.pdf

Franke, A.G., & Lieb, K. (2010). Pharmakologisches Neuroenhancement und "Hirndoping" : Chancen und Risiken [Pharmacological neuroenhancement and brain doping : Chances and risks]. *Bundesgesundheitsblatt – Gesundheitsforschung - Gesundheitsschutz*, *53*(8), 853–859. https://doi.org/10.1007/s00103-010-1105-0

Franke, A.G., Bonertz, C., Christmann, M., Huss, M., Fellgiebel, A., Hildt, E., & Lieb, K. (2011). Non-medical use of prescription stimulants and illicit use of stimulants for cognitive enhancement in pupils and students in Germany. *Pharmacopsychiatry, 44(2)*, 60-66. https://doi.org/10.1055/s-0030-1268417

Franke, A.G., Bagusat, C., Dietz, P., Hoffmann, I., Simon, P., Ulrich, R., & Lieb, K. (2013). Use of illicit and prescription drugs for cognitive or mood enhancement among surgeons. *BMC Medicine*, *11*(1), 102. https://doi.org/10.1186/1741-7015-11-102

Franke, A.G., Bagusat, C., Rust, S., Engel, A., & Lieb, K. (2014). Substances used and prevalence rates of pharmacological cognitive enhancement among healthy subjects. *European Archives of Psychiatry and Clinical Neurosciences, 264(1),* 83-90. https://doi.org/10.1007/s00406-014-0537-1

Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S. P., Silva, M.T., Paulus, W., & Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental brain research*, *166(1)*, 23–30. https://doi.org/10.1007/s00221-005-2334-6

Gallucci, A. (2013). Pill popping problems: The non-medical use of stimulant medications in an undergraduate sample. *Drugs: Education, Prevention and Policy, 5(3)*, 181-188. https://doi.org/10.3109/09687637.2013.848840

Gagnon, G., Schneider, C., Grondin, S., & Blanchet, S. (2010). Enhancement of episodic memory in young and healthy adults: a paired-pulse TMS study on encoding and retrieval performance. *Neuroscience Letters, 488(2)*, 138-142. https://doi.org/10.1016/j.neulet.2010.11.016.

Garasic, M.D., & Lavazza, A. (2015). Performance enhancement in the workplace: why and when healthy individuals should disclose their reliance on pharmaceutical cognitive enhancers. *Frontiers in Systems Neuroscience, 9.* https://doi.org/10.3389/fnsys.2015.00013

Garasic, M.D., & Lavazza, A. (2016). Moral and social reasons to acknowledge the use of cognitive enhancers in competitive-selective contexts. *BMC Med Ethics, 17*, 18. https://doi.org/10.1186/s12910-016-0102-8

Gerrard, P., & Malcolm, R. (2007). Mechanisms of modafinil: A review of current research. *Neuropsychiatric disease and treatment*, *3(3)*, 349–364. PMCID: PMC2654794. PMID: 19300566

Ghandour, L.A., El Sayed, D.S., Martins, S.S. (2012). Prevalence and patterns of commonly abused psychoactive prescription drugs in a sample of university students from Lebanon: An opportunity for cross-cultural comparisons. *Drug and Alcohol Dependence, 121(1–2),* 110-117. https://doi.org/10.1016/j.drugalcdep.2011.08.021

Ghorayshi, A. (2014). Brain games exploit anxieties about memory loss for profit-scientists. *The Guardian.* Available at: https://www.theguardian.com/science/2014/oct/23/brain-games-memory-loss-open-letter

Greely, H., Sahakian, B.J., Harris, J., Kessler, R.C., Gazzaniga, M., Campbell, P., & Farah, M.J. (2008). Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature*, *456*, 702-705. https://doi.org/10.1038/456702a

Giurgea, C., & Salama, M. (1977). Nootropic drugs. *Progress in Neuro-psychopharmacology, 1(3-4)*, 235-247. https://doi.org/10.1016/0364-7722(77)90046-7

Groves, D. A., & Brown, V. J. (2005). Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neuroscience and Biobehavioral Reviews*, *29*(3), 493–500. https://doi.org/10.1016/j.neubiorev.2005.01.004

Hall, K.M., Irwin, M.M., Bowman, K.A., Frankenberger, W., & Jewett, D.C. (2005). Illicit Use of Prescribed Stimulant Medication Among College Students. *Journal of American College Health*, *53*(4), 167–174. https://doi.org/10.3200/jach.53.4.167-174

Hall, W.D., & Lucke, J.C. (2010). The enhancement use of neuropharmaceuticals: more scepticism and caution needed. *Addiction*, *105(12)*, 2041-3. https://doi.org/10.1111/j.1360-0443.2010.03211.x.

Hamani, C., McAndrews, M.P., Cohn, M., et al. (2008). Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Annals of Neurology, 63(1)*, 119-123. https://doi.org/10.1002/ana.21295

Hamilton, R., Messing, S., & Chatterjee, A. (2011). Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation. *Neurology*, *76(2)*, 187–193. https://doi.org/10.1212/WNL.0b013e318205d50d

Harris, J. (2011). Chemical cognitive enhancement: Is it unfair, unjust, discriminatory, or cheating for healthy adults to use smart drugs. In: J. Illes & B.J. Sahakian (eds.), *Oxford handbook of Neuroethics*. Oxford: Oxford University Press, pp. 265–272. https://doi.org/10.1093/oxfordhb/9780199570706.001.0001

Harvey, P.D., & Keefe, R.S.E. (2015). Methods for delivering and evaluating the efficacy of cognitive enhancement. Cognitive Enhancement. *Handbook of Experimental Pharmacology, 228*, 5–25. https://doi.org/10.1007/978-3-319-16522-6_1

Hashemian, S.M., & Farhadi, T. (2020). A review on modafinil: the characteristics, function, and use in critical care. *Journal of drug assessment*, *9(1)*, 82–86. https://doi.org/10.1080/21556660.2020.1745209

Heal, D.J., & Pierce, D.M. (2006). Methylphenidate and its isomers: their role in the treatment of attention-deficit hyperactivity disorder using a transdermal delivery system. *CNS Drugs*, *20(9)*, 713–38. https://doi.org/10.2165/00023210-200620090-00002

Hildt, E., & Franke, A.G. (2013). *Cognitive Enhancement: An Interdisciplinary Perspective*. Dordrecht: Springer. https://doi.org/10.1007/978-94-007-6253-4

Howe, N., & Strauss, W. (2000). *Millennials rising: The next great generation*. New York, NY: Vintage Books. ISBN: 9780375707193

Hsieh, E. (2015). On the horizon: A magnetic zap that strengthens memory. *Scientific American Mind 26(3)*, 15. https://doi.org/10.1038/scientificamericanmind0515-15a

Husain, M., & Mehta, M.A. (2011). Cognitive enhancement by drugs in health and disease. *Trends in Cognitive Sciences, 15(1)*, 28–36. https://doi.org/10.1016/j.tics.2010.11.002

Hyman, S.E. (2011). Cognitive Enhancement: Promises and Perils. *Neuron, 69(4)*, 595-598. https://doi.org/10.1016/j.neuron.2011.02.012

Ilieva, I.P., Boland, J. & Farah, M.J. (2013). Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology, 64*, 496–505. https://doi.org/10.1016/j.neuropharm.2012.07.021

Ilieva, I.P., & Farah, M.J. (2013). Enhancement stimulants: perceived motivational and cognitive advantages. *Frontiers in Neuroscience, 7,* 198. https://doi.org/10.3389/fnins.2013.00198

Ilieva, I.P., Hook, C.J., & Farah, M.J. (2015). Prescription Stimulants' Effects on Healthy Inhibitory Control, Working Memory, and Episodic Memory: A Meta-analysis. *Journal of Cognitive Neuroscience, 27(6)*, 1069–1089. https://doi.org/10.1162/jocn_a_00776

Ishizuka, T., Murakami, M., & Yamatodani, A. (2008). Involvement of central histaminergic systems in modafinil-induced but not methylphenidate-induced increases in locomotor activity in rats. *European Journal of Pharmacology, 578 (2–3)*, 209–15. https://doi.org/10.1016/j.ejphar.2007.09.009.

Iuculano, T., & Cohen Kadosh, R. (2013). The Mental Cost of Cognitive Enhancement. *Journal of Neuroscience, 33(10)*, 4482-4486. https://doi.org/10.1523/JNEUROSCI.4927-12.2013

Iversen, L. (2006). Neurotransmitter transporters and their impact on the development of psychopharmacology. *British Journal of Pharmacology, 147(1)*, 82–88. https://doi.org/10.1038/sj.bjp.0706428. PMC 1760736. PMID 16402124.

Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E.M. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology*, *64(5)*, 872–875. https://doi.org/10.1212/01.WNL.0000152986.07469.E9

Javadi, A.H., Cheng, P., & Walsh, V. (2012). Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. *Brain stimulation*, *5(4)*, 468–474. https://doi.org/10.1016/j.brs.2011.08.003

Javadi, A.H., & Walsh, V. (2012). Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. *Brain stimulation*, *5(3)*, 231–241. https://doi.org/10.1016/j.brs.2011.06.007

Jotterand, F., & Dubljević, V. (2016). *Cognitive Enhancement: Ethical and Policy Implications in International Perspectives*. Oxford: Oxford University Press. ISBN 9780199396825.

Juengst, E.T. (1998). What does enhancement mean? In: E. Parens (ed.), *Enhancing Human Traits: Ethical and Social Implications*. Washington, DC: Georgetown University Press, pp. 29-47. ISBN: 9780878407804 (0878407804)

Kadison, R., & Digeronimo, T. (2004). *College of the Roverwhelmed: The campus mental health crisis and what to do about it.* San Francisco, CA: Jossey-Bass. ISBN: 978-0-787-98114-3

Karoum, F., Chrapusta, S. J., Brinjak, R., Hitri, A., & Wyatt, R. J. (1994). Regional effects of amphetamine, cocaine, nomifensine and GBR 12909 on the dynamics of dopamine release and metabolism in the rat brain. *British Journal of Pharmacology, 113(4)*, 1391–1399. https://doi.org/10.1111/j.1476-5381.1994.tb17152.x

Knechtel, L., Thienel, R., & Schall, U. (2013). Transcranial direct current stimulation: Neurophysiology and clinical applications. *Neuropsychiatry, 3(1)*, 89-96. https://doi.org/10.2217/npy.12.78

Khushf, G. (2005). The use of emergent technologies for enhancing human performance: are we prepared to address the ethical and policy issues? *Public Policy and Practice, 4(2)*, 1–17. Available at: https://www.academia.edu/592339/The_Use_of_Emergent_Technologies_for_Enhancing_Human_Performance_Are_We_Prepared_to_Address_the_Ethical_and_Policy_Issues

Khushf, G. (2008). Stage Two Enhancements. In: F. Jotterand (ed), *Emerging Conceptual, Ethical and Policy Issues in Bionanotechnology. Philosophy and Medicine, vol 101*. Dordrecht: Springer, pp. 201-218. https://doi.org/10.1007/978-1-4020-8649-6_12

Kincses, T.Z., Antal, A., Nitsche, M.A., Bártfai, O., Paulus, W. (2004). Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia, 42(1)*, 113-117. https://doi.org/ 10.1016/s0028-3932(03)00124-6.

Kipke, R. (2013). What Is Cognitive Enhancement and Is It Justified to Point Out This Kind of Enhancement Within the Ethical Discussion? In: E. Hildt & A.G. Franke (eds.), *Cognitive Enhancement: An Interdisciplinary Perspective.* Dordrecht: Springer, pp. 145-157. https://doi.org/10.1007/978-94-007-6253-4

Knafo, S., & Venero, C. (2015). *Cognitive Enhancement: Pharmacologic, Environmental and Genetic Factors*. New York: Academic Press.

Kohn, A. (2003). How not to get into college. *Independent School, 62(2)*, 12–22. Available at: https://www.alfiekohn.org/article/get-college/

Kolker, R. (2013). *The Real Limitless Drug isn't just for Lifehackers Anymore*. New York: New York Magazine. Available online at: http://nymag.com/news/intelligencer/modafinil-2013-4/

Krahl, S. E., Clark, K. B., Smith, D. C., & Browning, R. A. (1998). Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*, *39*(7), 709–714. https://doi.org/10.1111/j.1528-1157.1998.tb01155.x

Kroutil, L.A., Van Brunt, D.L., Herman-Stahl, M.A., Heller, D.C., Bray, R.M., & Penne, M. A. (2006). Nonmedical use of prescription stimulants in the United States. *Drug and alcohol dependence, 84(2)*, 135–143. https://doi.org/10.1016/j.drugalcdep.2005.12.011

Kuhn, J., Gründler, T.O., Lenartz, D., Sturm, V., Klosterkötter, J., & Huff, W. (2010). Deep brain stimulation for psychiatric disorders. *Deutsches Arzteblatt international*, *107*(7), 105–113. https://doi.org/10.3238/arztebl.2010.0105

Kumar, R. (2008). Approved and investigational uses of modafinil: An evidence-based review. *Drugs, 68(13)*, 1803–1839. https://doi.org/10.2165/00003495-200868130-00003

Labig, C.E., Zantow, K., & Peterson, T.O. (2005). Factors Affecting Students' Medicine-Taking Habits. *Journal of American College Health*, *54*(3), 177–183. https://doi.org/10.3200/jach.54.3.177-184

Lanese, N. (2009). Fight or Flight: The Sympathetic Nervous System. *Live Science*. Available at : https://www.livescience.com/65446-sympathetic-nervous-system.html#:~:text=The%20sympathetic%20nervous%20system%20directs,extra%20blood%20to%20the%20muscles.

Langberg, J.M., & Becker, S.P. (2012). Does Long-Term Medication Use Improve the Academic Outcomes of Youth with Attention-Deficit/Hyperactivity Disorder? *Clinical Child and Family Psychology Review*, *15*(3), 215–233. https://doi.org/10.1007/s10567-012-0117-8

Lange, K.W., Reichl, S., Lange, K.M., Tucha, L., & Tucha, O. (2010). The history of attention deficit hyperactivity disorder. *ADHD Attention Deficit and Hyperactivity Disorders*. *2(4)*, 241–255. https://doi.org/10.1007/s12402-010-0045-8

Larriviere, D., Williams, M.A., Rizzo, M., Bonnie, R.J., & AAN Ethics, Law and Humanities Committee (2009). Responding to requests from adult patients for neuroenhancements: guidance of the Ethics, Law and Humanities Committee. *Neurology*, *73*(17), 1406–1412. https://doi.org/10.1212/WNL.0b013e3181beecfe

Law, D.W. (2007). Exhaustion in University Students and the Effect of Coursework Involvement. *Journal of American College Health*, *55*(4), 239–245. https://doi.org/10.3200/jach.55.4.239-245

Levy, N. (2007). *Neuroethics: Challenges for the 21st Century*. Cambridge, UK: Cambridge University Press. https://doi.org/10.1017/CBO9780511811890

Loewe, D. (2016). Cognitive Enhancement and the Leveling of the Playing Field. The Case of Latin America. In: F. Jotterand & V. Dubljević (eds), *Cognitive Enhancement: Ethical and Policy Implications in International Perspectives*. Oxford: Oxford University Press. ISBN 9780199396825.

Luber, B., & Lisanby, S.H. (2014). Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *NeuroImage*, *85 Pt 3*(0 3), 961–970. https://doi.org/10.1016/j.neuroimage.2013.06.007

Luthar, S.S., & Becker, B.E. (2002). Privileged but Pressured? A Study of Affluent Youth. *Child Development*, *73*(5), 1593–1610. https://doi.org/10.1111/1467-8624.00492

Maher, B. (2008). Poll results: look who's doping. *Nature, 452(7188)*, 674–675. https://doi.org/10.1038/452674a

Maier, L.J., Liechti, M.E., Herzig, F., & Schaub, M.P. (2013). To dope or not to dope: neuroenhancement with prescription drugs and drugs of abuse among Swiss university students. *PLoSONE, 8*, e77967. https://doi.org/10.1371/journal.pone.0077967

Maier, L.J., & Schaub, M.P. (2015). The use of prescription drugs and drugs of abuse for neuroenhancement in Europe: Not widespread but a reality *European Psychologist*, *20*(3), 155–166. https://doi.org/10.1027/1016-9040/a000228

Malenka, R.C., Nestler, E.J., & Hyman, S.E. (2009). "Chapter 13: Higher Cognitive Function and Behavioral Control". In A. Sydor & R.Y. Brown (eds.), *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (2nd ed.)*. New York: McGraw-Hill Medical, p. 318.

Mallia, L., & Lucidi, F. (2016). *Dopare il corpo, dopare la mente… Il fenomeno del Neuro-Enhancement nei contesti educativi*. Roma: Roma Tre-Press. ISBN: 978-88-97524-88-5 Available at : http://romatrepress.uniroma3.it/repository/76/pdf/29ce572e-6551-45ad-bdb4-a613abe97026.pdf

Marshall, L., Mölle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *24(44),* 9985–9992. https://doi.org/10.1523/JNEUROSCI.2725-04.2004

Maslen, H., Douglas, T., Cohen Kadosh, R., Levy, N., & Savulescu, J. (2014a). The regulation of cognitive enhancement devices: extending the medical model. *Journal of law and the biosciences*, *1*(1), 68–93. https://doi.org/10.1093/jlb/lst003

Maslen, H., Douglas, T., Cohen Kadosh, R., Levy, N., & Savulescu, J. (2015). The regulation of cognitive enhancement devices: refining Maslen et al.'s model. *Journal of law and the biosciences*, *2(3)*, 754–767. https://doi.org/10.1093/jlb/lsv029

Maslen, H., Faulmüller, N., & Savulescu, J. (2014b). Pharmacological cognitive enhancement – how future neuroscientific research could advance ethical debate. *Frontiers in Systems Neuroscience, 8*, 107. https://doi.org/10.3389/fnsys.2014.00107

Mayo Clinic (2014). *Risks of deep brain stimulation*. Available at: http://www.mayoclinic.org/tests-procedures/deep-brain-stimulation/basics/risks/PRC-20019122/.

McCabe, S.E., Knight, J.R., Teter, C.J., & Wechsler, H. (2005). Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. *Addiction*, *100(1)*, 96–106. https://doi.org/10.1111/j.1360-0443.2005.00944.x

McCabe, S.E., Teter, C.J., & Boyd, C. (2006). Medical use, illicit use, and diversion of abusable prescription drugs. *Journal of American College Health, 54(5)*, 269–278. https://doi.org/10.3200/JACH.54.5.269-278

Mendelsohn, D., Lipsman, N., & Bernstein, M. (2010). Neurosurgeons' perspectives on psychosurgery and neuroenhancement: A qualitative study at one center. *Journal of Neurosurgery, 113(6)*, 1212-1218. https://doi.org/10.3171/2010.5.JNS091896

Merkel, R. (2007). Treatment – prevention – enhancement: normative foundations and limits. In: R. Merkel, G. Boer, J. Fegert, T. Galert, D. Hartmann, B. Nuttin & S. Rosahl (eds.), *Intervening in the brain – changing psyche and society*. Berlin: Springer, pp 285–378. https://doi.org/10.1007/978-3-540-46477-8

Moore, D.R., Burgard, D.A., Larson, R.G., & Ferm, M. (2014). Psychostimulant use among college students during periods of high and low stress: an interdisciplinary approach utilizing both self-report and unobtrusive chemical sample data. *Addictive behaviors*, *39*(5), 987–993. https://doi.org/10.1016/j.addbeh.2014.01.021

Nagel, S.K. (2010). Too much of a good thing? Enhancement and the burden of self-determination. *Neuroethics, 3(2)*, 109–119. https://doi.org/ 10.1007/s12152-010-9072-6

National Center on Addiction and Substance Abuse - CASA. (2005*). Under the counter: The diversion and abuse of controlled prescription drugs in the U.S*. Available at: http://www.casacolumbia.org/absolutenm/articlefiles/380- under_the_counter_-_diversion.pdf

National Institute of Drug Abuse – NIDA. (2014). Prescription and Over-the-Counter Medications. National Institute of Drug Abuse. Available at: http://www.drugabuse.gov/publications/drugfacts/prescription-overcounter-medications

Nelson, J.T., McKinley, R.A., Golob, E.J., Warm, J.S., & Parasuraman, R. (2014). Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *NeuroImage*, *85 Pt 3*, 909–917. https://doi.org/10.1016/j.neuroimage.2012.11.061

Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W., & Tergau, F. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of physiology*, *568(Pt 1)*, 291–303. https://doi.org/10.1113/jphysiol.2005.092429

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain stimulation*, *1(3)*, 206–223. https://doi.org/10.1016/j.brs.2008.06.004

Ohn, S.H., Park, C.I., Yoo, W.K., Ko, M.H., Choi, K.P., Kim, G.M., Lee, Y.T., & Kim, Y.H. (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *Neuroreport, 19(1)*, 43–47. https://doi.org/10.1097/WNR.0b013e3282f2adfd

Ott, R. & Biller-Andorno, N. (2014). Neuroenhancement among Swiss students – a comparison of users and non-users. *Pharmacopsychiatry, 47(1)*, 22–28. https://doi.org/10.1055/s-0033-1358682

Outram, S.M. (2010). The use of methylphenidate among students: The future of enhancement? *Journal of Medical Ethics, 36(4)*, 198–202. https://doi.org/ 10.1136/jme.2009.034421

Pacholczyk, A. (2011). DBS makes you feel good! Why some of the ethical objections to the use of DBS for neuropsychiatric disorders and enhancement are not convincing. *Frontiers in Integrative Neuroscience, 5*. https://doi.org/10.3389/fnint.2011.000014.

Partridge, B.J., Lucke, J.C, & Hall, W.D. (2012). A comparison of attitudes toward cognitive enhancement and legalized doping in sport in a community sample of Australian adults. *American Journal of Bioethics Primary Research, 3(4),* 81–86. https://doi.org/10.1080/21507716.2012.720639

Petersen, M.A., Enghoff, O., & Demant, J. (2018). The uncertainties of enhancement: A mixed-methods study on the use of substances for cognitive enhancement and it's unintended consequences. *Performance Enhancement & Health, 6(3-4)*, 111-120. https://doi.org/10.1016/j.peh.2018.09.001

Petróczi, A. (2013). The doping mindset—Part I: Implications of the Functional Use Theory on mental representations of doping. *Performance Enhancement & Health, 2(4)*, 153-163. https://doi.org/10.1016/j.peh.2014.06.001

Petróczi, A., & Aidman, E. (2008). Psychological drivers in doping: The life-cycle model of performance enhancement. *Substance Abuse Treatment, Prevention, and Policy, 3,* 7. https://doi.org/10.1186/1747 597X-3-7

Pitsch, W. (2016). Minimizing response bias: an application of the randomized response technique. In: V. Barkoukis, L. Lazuras & H. Tsorbatzoudis (eds.), *The Psychology of Doping in Sport*. Abingdon: Routledge, pp. 111-125. ISBN:978-1-1138-79347-7.

Ponnet, K., Wouters, E., Walrave, M., Heirman, W., & Van Hal, G. (2015). Predicting students' intention to use stimulants for academic performance enhancement. *Substance use & misuse, 50(3)*, 275–282. https://doi.org/10.3109/10826084.2014.952446

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain research bulletin*, *72(4-6)*, 208–214. https://doi.org/10.1016/j.brainresbull.2007.01.004

Prudhomme-White, B., Becker-Blease, K.A., & Grace-Bishop, K. (2006). Stimulant Medication Use, Misuse and Abuse in an Undergraduate and Graduate Student Sample*. Journal of American College Health, 54(5)*, 261-268. https://doi.org/10.3200/JACH.54.5.261-268

Quednow, B.B. (2010). Ethics of neuroenhancement: A phantom debate. *BioSocieties, 5(1)*, 153–56. Available at: https://www.researchgate.net/profile/Boris_Quednow/publication/43014563_Ethics_of_Neuroenhancement_A_Phantom_Debate/links/0912f50a0f418c8654000000/Ethics-of-Neuroenhancement-A-Phantom-Debate.pdf

Quintero, G., Peterson, J., & Young, B. (2006). An exploratory study of socio-cultural factors contributing to prescription drug misuse among college students. *Journal of Drug Issues, 36(4)*, 903–932. https://doi.org/10.1177%2F002204260603600407

Rabiner, D.L., Anastopoulos, A.D., Costello, E.J., Hoyle, R.H., McCabe, S.E., & Swartzwelder, H.S. (2009). Motives and perceived consequences of nonmedical ADHD medication use by college students: are students treating themselves for attention problems? *Journal of attention disorders*, *13*(3), 259–270. https://doi.org/10.1177/1087054708320399

Racchi, M., Mazzucchelli, M., Porrello, E., Lanni, C., & Govoni, S. (2004). Acetylcholinesterase inhibitors: novel activities of old molecules. *Pharmacological research*, *50(4)*, 441–451. https://doi.org/10.1016/j.phrs.2003.12.027

Ragan, C.I., Bard, I., & Singh, I. (2013). What should we do about student use of cognitive enhancers? An analysis of current evidence. *Neuropharmacology*, *64*, 588–595. https://doi.org/10.1016/j.neuropharm.2012.06.016

Rawls, J. (1971) *A Theory of Justice*. Cambridge, Mass.: The Belknap Press of Harvard University Press. https://doi.org/10.2307/j.ctvjf9z6v ISBN: 9780674880146

Repantis, D. (2013). Psychopharmacological neuroenhancement: Evidence on safety and efficacy. In: E. Hildt & A.G. Franke (eds.), *Cognitive Enhancement: An Interdisciplinary Perspective.* Dordrecht: Springer, pp. 29–38. https://doi.org/10.1007/978-94-007-6253-4

Repantis, D., Laisney, O., & Heuser, I. (2010a). Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research, 61(6)*, 473–81. https://doi.org/10.1016/j.phrs.2010.02.009

Repantis, D., Schlattmann, P., Laisney, O., & Heuser, I. (2010b). Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research, 62(3)*, 187–206. https://doi.org/10.1016/j.phrs.2010.04.002

Rogers, R.D., Blackshaw, A.J., Middleton, H.C., Matthews, K., Hawtin, K., Crowley, C., Hopwood, A., Wallace, C., Deakin, J.F., Sahakian, B.J., & Robbins, T.W. (1999). Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. *Psychopharmacology, 146(4)*, 482-491. https://doi.org/10.1007/pl00005494

Ross. M.M., Arria, A.M., Brown, J.P., Mullins, C.D., Schiffman, J., Simoni-Wastila, L., dosReis, S. (2018). College students' perceived benefit-to-risk tradeoffs for nonmedical use of prescription stimulants: Implications for intervention designs. *Addictive Behaviors, 79*, 45-51. https://doi.org/10.1016/j.addbeh.2017.12.002

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *120(12)*, 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

Sahakian, B.J., & Morein-Zamir, S. (2007). Professor's little helper. *Nature, 450(7173)*, 1157–1159. https://doi.org/10.1038/4501157a

Saniotis, A. (2009). Present and future developments in cognitive enhancement technologies. *Journal of Future Studies, 14(1),* 27 – 38. ISSN: 1027-6084. Available at: https://jfsdigital.org/wp-content/uploads/2014/01/141-A02.pdf

Santoni de Sio, F., Faulmüller, N., & Vincent, N. A. (2014). How cognitive enhancement can change our duties. *Frontiers in Systems Neuroscience*, *8*, 131. https://doi.org/10.3389/fnsys.2014.00131

Sattler, S., Mehlkop, G., Graeff, P., & Sauer, C. (2014). Evaluating the drivers of and obstacles to the willingness to use cognitive enhancement drugs: the influence of drug characteristics, social environment, and personal characteristics. Subst. *Substance Abuse Treatment, Prevention, and Policy, 9*, 8. https://doi.org/10.3109/10826084.2012.751426

Sattler, S., & Wiegel, C. (2013). Test anxiety and cognitive enhancement: the influence of students' worries on their use of performance-enhancing drugs. *Substance Use & Misuse, 48(3)*, 220-232. https://doi.org/10.3109/10826084.2012.751426

Savulescu, J. (2006). Justice, Fairness, and Enhancement. *Annals of the New York Academy of Sciences.*, *1093(1)*, 321–338. https://doi.org/10.1196/annals.1382.021

Sax, L. (2003). Our incoming students: What are they like? *About Campus, 8(3)*, 15-20. https://doi.org/10.1177/108648220300800305

Schanker, B.D. (2011). Neuroenhancement in a medicated generation: Overlooked uses of cognitive stimulants. *American Journal of Bioethics Neuroscience, 2(4)*, 28–30. http://dx.doi.org/10.1080/21507740.2011.

Schelle, K.I.J., Faulmüller, N., Caviola, L., & Hewstone, M. (2014). Attitudes toward pharmacological cognitive enhancement - a review. *Frontiers in Systems Neuroscience, 8,* 53. https://doi.org/10.3389/fnsys.2014.00053.

Schelle, K.I.J., Olthof, B.M.J., Reintjes, W., Bundt, C., Gusman-Vermeer, J., & van Mil, A.C.C.M. (2015). A survey of substance use for cognitive enhancement by university students in the Netherlands. *Frontiers in Systems Neuroscience, 9*, 10. https://doi.org/10.3389/fnsys.2015.00010

Schermer, M. (2008). On the argument that enhancement is "cheating". *Journal of Medical Ethics, 34(2),* 85-88. https://doi.org/10.1136/jme.2006.019646

Schermer, M., Bolt, I., de Jongh, R., & Olivier, B. (2009). The Future of Psychopharmacological Enhancements: Expectations and Policies. *Neuroethics*, *2*, 75–87. https://doi.org/10.1007/s12152-009-9032-1

Scheske, C., & Schnall, S. (2012). The ethics of 'smart drugs': moral judgments about healthy people's use of cognitive-enhancing drugs. *Basic and Applied Social Psychology, 34(6)*, 508–515. https://doi.org/10.1080/01973533.2012.711692

Selgelid, M.J. (2007). An argument against arguments for enhancement. *Studies in Ethics, Law, and Technology, 1(1)*. https://doi.org/10.2202/1941-6008.1008

Sepúlveda, M.J., Roa, J., & Muñoz, M. (2011). Estudio cuantitativo del consumo de drogas y factores sociodemográficos asociados en estudiantes de una universidad tradicional chilena. *Revista medica de Chile, 139(7)*, 856-863. https://doi.org/10.4067/S0034-98872011000700005

Sharpe, K. (2014). Medication: The smart-pill oversell. Evidence is mounting that medication for ADHD doesn't make a lasting difference to schoolwork or achievement. *Nature, 506(7847)*, 146–148. https://doi.org/10.1038/506146a

Singh, I. (2005). Will the 'real boy' please behave: Dosing dilemmas for parents of boys with ADHD. *American Journal of Bioethics 5(3)*, 34–47. https://doi.org/ 10.1080/15265160590945129

Singh, I. (2008). Beyond polemics: science and ethics of ADHD. *Nature Reviews Neuroscience, 9(12)*, 957-964. https://doi.org/10.1038/nrn2514

Smith, M.A., Riby, L.M., van Eekelen, J.A.M, & Foster, J.K. (2011). Glucose enhancement of human memory: A comprehensive research review of the glucose memory facilitation effect. *Neuroscience and Biobehavioral Reviews, 35(3)*, 770–783. https://doi.org/1016/j.neubiorev.2010.09.008.

Smith, M.E., & Farah, M.J. (2011). Are prescription stimulants smart pills? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin, 137(5)*, 717-741. https://doi.org/10.1037/a0023825.

Sonkusare, S.K., Kaul, C.L., & Ramarao, P. (2005). Dementia of Alzheimer's disease and other neurodegenerative disorders-memantine, a new hope. *Pharmacological Research, 51(1)*, 1–17. https://doi.org/10.1016/j.phrs.2004.05.005

Spencer, T.J., Brown, A., Seidman, L.J., Valera, E.M., Makris, N., Lomedico, A., Faraone, S.V., & Biederman, J. (2013). Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies. *The Journal of Clinical Psychiatry*, *74(9)*, 902–17. https://doi.org/10.4088/JCP.12r08287

Spencer, R.C., Devilbiss, D.M., & Berridge, C.W. (2015). The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex. *Biological Psychiatry*, *77(11)*, 940–950. https://doi.org/10.1016/j.biopsych.2014.09.013

Stagg, CJ., Best, J. G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M., & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, *29(16)*, 5202–5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009

Stagg, C.J., & Nitsche, M.A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist: a review journal bringing neurobiology, neurology and psychiatry*, *17(1)*, 37–53. https://doi.org/10.1177/1073858410386614

Stahl, S.M. (2017). "Modafinil". In: S.M. Stahl (ed.), *Prescriber's Guide: Stahl's Essential Psychopharmacology* (6th ed.). Cambridge, UK: Cambridge University Press, pp. 491–495. ISBN 9781108228749

Stella, F., Radanovic, M., Canineu, P.R., de Paula, V.J., & Forlenza, O.V. (2015). Anti-dementia medications: current prescriptions in clinical practice and new agents in progress. *Therapeutic advances in drug safety*, *6(4),* 151–165. https://doi.org/10.1177/2042098615592116

Stoeber, J., & Hotham, S. (2016). Perfectionism and attitudes toward cognitive enhancers (“smart drugs”). *Personality and Individual Differences, 88,* 170-174. https://doi.org/10.1016/j.paid.2015.09.011

Sulzer, D., Sonders, M.S., Poulsen, N.W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: a review. *Progress in neurobiology*, *75*(6), 406–433. https://doi.org/10.1016/j.pneurobio.2005.04.003

Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., & Fried, I. (2012). Memory enhancement and deep-brain stimulation of the entorhinal area. *The New England journal of medicine, 366(6)*, 502–510. https://doi.org/10.1056/NEJMoa1107212

Suthana, N., & Fried, I. (2014). Deep brain stimulation for enhancement of learning and memory. *NeuroImage*, *85 Pt 3*(0 3), 996–1002. https://doi.org/10.1016/j.neuroimage.2013.07.066

Swanson, J., Baler, R.D., & Volkow, N.D. (2011). Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology, 36(1)*, 207–226. https://doi.org/10.1038/npp.2010.160

Szalavitz, M. (2009). Popping smart pills: The case for cognitive enhancement. Available at: http://content.time.com/time/health/article/0,8599,1869435,00.html

Talbot, M. (2009). Brain gain: The underworld of ‘neuroenhancing’ drugs. *The New Yorker*, *4*, 32–43. https://www.newyorker.com/magazine/2009/04/27/brain-gain

Taya, F., Sun, Y., Babiloni, F., Thakor, N., & Bezerianos, A. (2015). Brain enhancement through cognitive training: A new insight from brain connectome. *Frontiers in Systems Neuroscience*, *9*, 44. https://doi.org/10.3389/fnsys.2015.00044.

Taylor, L., Pogrebin, M., & Dodge, M. (2002). Advanced placement-advanced pressures: Academic dishonesty among elite high school students. *Educational Studies, 33(4)*, 403–421. ISSN: 0013-1946, 1532-6993

Teo, F., Hoy, K.E., Daskalakis, Z.J., & Fitzgerald, P.B. (2011). Investigating the Role of Current Strength in tDCS Modulation of Working Memory Performance in Healthy Controls. *Frontiers in psychiatry*, *2*, 45. https://doi.org/10.3389/fpsyt.2011.00045

Teter, C.J., McCabe, S.E., Boyd, C.J., Guthrie, S.K. (2003). Illicit methylphenidate use in an undergraduate student sample: Prevalence and risk factors. *Pharmacotherapy*, *23*(5), 609–617. https://doi.org/10.1592/phco.23.5.609.34187

Teter, C.J., McCabe, S.E., Cranford, J.A., Boyd, C.J., & Guthrie, S.K. (2005). Prevalence and Motives for Illicit Use of Prescription Stimulants in an Undergraduate Student Sample. *Journal of American College Health, 53(6)*, 253-262. https://doi.org/10.3200/JACH.53.6.253-262

The President’s Council on Bioethics (U.S.) (2003). *Beyond therapy: biotechnology and the pursuit of happiness.* Available at: https://biotech.law.lsu.edu/research/pbc/reports/beyondtherapy/beyond_therapy_final_report_pcbe.pdf

Tomažič, T., & Čelofiga, A.K. (2019). Ethical aspects of the abuse of pharmaceutical enhancements by healthy people in the context of improving cognitive functions. *Philosophy, ethics, and humanities in medicine: PEHM, 14(1)*, 7. https://doi.org/10.1186/s13010-019-0076-5

Turner, D.C., & Sahakian, B.J. (2008). Neuroethics of cognitive enhancement. In: L. Zonneveld, H. Dijstelbloem & D. Ringoir (eds.), *Reshaping the Human Condition: Exploring Human Enhancement*. The Hague: Rathenau Institute, pp. 37-51. Available at: https://old.parliament.uk/documents/post/poste15.pdf

Varga, M. D. (2012). Adderall abuse on college campuses: a comprehensive literature review. *Journal of Evidence-Based Social Work, 9(3)*, 293–313. https://doi.org/10.1080/15433714.2010.525402

Vrecko, S. (2013). Just how cognitive is “cognitive enhancement”? On the significance of emotions in university students’ experiences with study drugs. *American Journal of Bioethics Neuroscience, 4(1)*, 4-12. https://doi.org/10.1080/21507740.2012.740141

Wagner, G. (2013). Leveling the Playing Field: Fairness in the Cognitive Enhancement Debate. In: E. Hildt & A.G. Franke (eds.), *Cognitive Enhancement: An Interdisciplinary Perspective.* Dordrecht: Springer, pp. 217-231. https://doi.org/10.1007/978-94-007-6253-4

Wallace, L.J. (2012). Effects of amphetamine on subcellular distribution of dopamine and DOPAC. *Synapse, 66(7)*, 592–607. https://doi.org/10.1002/syn.21546

Wang, J.X., Rogers, L.M., Gross, E.Z., Ryals, A.J., Dokucu, M.E., Brandstatt, K.L., Hermiller, M.S., & Voss, J.L. (2014). Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science, 345(6200)*, 1054–1057. https://doi.org/10.1126/science.1252900

Warwick, K. (2008) Cybernetic Enhancements. In: L Zonneveld, H. Dijstelbloem & D. Ringoir (eds.), *Reshaping the Human Condition: Exploring Human Enhancement*. The Hague: Rathenau Institute, pp. 123–131. Available at: https://old.parliament.uk/documents/post/poste15.pdf

Wilens, T.E., Adler, L.A., Adams, J., Sgambati, S., Rotrosen, J., Sawtelle, R., Utzinger, L., & Fusillo, S. (2008). Misuse and diversion of stimulants prescribed for ADHD: A systematic review of the literature.

Journal of the American Academy of Child and Adolescent Psychiatry, 47(1), 21–31. https://doi.org/10.1097/chi.0b013e31815a56f1

White, B.P., Becker–Blease, K.A., & Grace–Bishop, K. (2006). Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *Journal of American College Health, 54(5)*, 261–268. https://doi.org/10.3200/JACH.54.5.261-268.

Wolff, W., & Brand, R. (2013). Subjective stressors in school and their relation to neuroenhancement: a behavioral perspective on students' everyday life "doping". *Substance Abuse Treatment, Prevention, and Policy, 8*, 23. https://doi.org/10.1186/1747-597X-8-23

Wolff, W., Brand, R., Baumgarten, F., Lösel, J., & Ziegler, M. (2014). Modeling students' instrumental (mis-)use of substances to enhance cognitive performance: Neuroenhancement in the light of job demands-resources theory. *BioPsychoSocialMedicine, 8(1)*, 12. https://doi.org/10.1186/1751-0759-8-12

Wolff, W., Sandouqa, Y., & Brand, R. (2016). Using the simple sample count to estimate the frequency of prescription drug neuroenhancement in a sample of Jordan employees. *International Journal of Drug Policy*, *31*, 51–55. https://doi.org/10.1016/j.drugpo.2015.12.014

Zohny, H. (2015). The Myth of Cognitive Enhancement Drugs. *Neuroethics, 8(3)*, 257-269. https://doi.org/10.1007/s12152-015-9232-9

Abstract

La presente tesi ha come oggetto di studio un fenomeno relativamente recente che, da circa venti anni a questa parte, ha progressivamente preso piede in particolar modo nelle università e nei college di vari paesi (specialmente negli Stati Uniti e, in misura minore, in Europa) e ha contestualmente suscitato un sempre maggiore interesse non solo in dibattiti multidisciplinari condotti in ambienti accademici, ma anche in ambiti di confronto più informali che vedono la partecipazione di membri non esperti del grande pubblico.

Il fenomeno in questione consiste nella apparentemente crescente diffusione, specialmente tra gli studenti universitari (stando perlomeno ai risultati di un vasto corpo di studi sociologici), dell'uso improprio di farmaci psicostimolanti soggetti a prescrizione medica allo scopo di potenziare le proprie capacità cognitive oltre il loro "normale" livello e sortire dunque migliori risultati in ambito accademico.

Tale uso è definito improprio poiché i soggetti tipicamente coinvolti in questa pratica non presentano patologie neuropsichiatriche o deficit cognitivi di sorta che si intenda curare o cui si intenda rimediare, in armonia con gli scopi primari delle terapie per mezzo di farmaci soggetti a prescrizione: viene a mancare, dunque, la condizione necessaria all'ottenimento di una prescrizione medica che giustificherebbe il ricorso a medicinali ad essa soggetti (come, ad esempio , i sali di amfetamina, il metilfenidato e il modafinil). In tal senso, l'uso (in generale) di medicinali in assenza di scopi propriamente terapeutici da parte di consumatori "sani" è anche definito come uso "off-label" - ossia, per indicazioni altre da quelle per le quali il farmaco in questione è stato autorizzato sul mercato farmaceutico.

Applicando questa definizione all'oggetto di indagine della presente tesi, si può configurare come "off-label" anche la suddetta pratica, sempre più socialmente pervasiva, concernente l'assunzione di psicostimolanti da prescrizione da parte di studenti universitari cognitivamente sani con l'obiettivo di migliorare le proprie performance accademiche. Numerosi report indicano come, specialmente negli Stati Uniti e - in maniera meno evidente ma comunque significativa - nei paesi Europei, studenti universitari in tutto e per tutto sani si stiano rivolgendo in misura sempre maggiore, almeno da una decina di anni a questa parte, a farmaci psicostimolanti (ribattezzati, per l'occasione, "smart drugs" o "nootropics") che erano stati originariamente sviluppati e autorizzati nei rispettivi mercati farmaceutici nazionali per il trattamento terapeutico dei sintomi legati a vari disturbi neuropsichiatrici e malattie neurodegenerative (come ad esempio i l'Alzheimer e i sintomi da morbo di Parkinson, il disturbo da deficit di attenzione e iperattività, la narcolessia etc.) nella speranza che l'effetto psicostimolante di questi ultimi si riveli efficace anche sulle facoltà cognitive di soggetti sani, in modo da migliorare qualitativamente e quantitativamente rispettivamente lo svolgimento e l'esito di attività strettamente dipendenti dalle abilità cognitive dell'individuo (memoria, facoltà di apprendimento, concentrazione ecc.), come lo studio e il sostenimento di test ed esami in ambito accademico. Probabilmente, tutto ciò non costituisce nemmeno una novità poi tanto sorprendente o scandalosa, dato che, col passare del tempo, gli studenti universitari sono notoriamente esposti in misura crescente ai danni causati da uno stress accademico sempre più

intenso e alle dinamiche di una competizione universitaria sempre più accanita, la cui vittoria incrementa le opportunità di entrare con successo nel mercato del lavoro ormai pienamente globalizzato e di assicurarsi un posto di lavoro remunerativo e soddisfacente - naturalmente, assieme ai benefici e privilegi socio-economici che ne conseguono nell'economia di mercato liberate, anch'essa globalizzata a tutti gli effetti e sempre più attenta al valore delle competenze e delle skills dell'individuo. Dunque, non c'è da meravigliarsi se questo sentirsi costantemente pungolati e spronati (per non dire costretti) ad ottenere infallibilmente risultati accademici eccellenti e, conseguentemente, ad ottenere un vantaggio sui propri colleghi, arrivi, a un certo punto, a costituire un terreno fertile per l'uso improprio (e, in alcuni casi, l'abuso) di farmaci psicostimolanti, non per la cura di problemi neuro-cognitivi, ma semplicemente nel tentativo di migliorare le proprie abilità cognitive oltre gli standard della normalità. Tale pratica viene comunemente riassunta nella letteratura accademica internazionale dall'espressione "Pharmacological Cognitive Enhancement" (abbreviata in PCE) - letteralmente, "miglioramento cognitivo farmacologico" – e riflette il tentativo di questi studenti di vedere realizzati i semi-miracolosi effetti di "doping del cervello" spesso vagheggiati dai più entusiasti, nella speranza di alleggerire il peso quotidiano costituito nella routine universitaria dagli spesso gravosi impegni accademici e di innalzare il livello della loro performance cognitiva "standard". Tuttavia, nonostante i primi cenni di questo fenomeno tra gli studenti universitari abbiano fatto la loro comparsa ormai quasi venti anni fa, tale pratica è ancora contraddistinta da molti aspetti controversi di natura sia empirica sia etico-morale.
In particolare, tre sono le principali aree di controversia che, nonostante il loro essere percepite e presentate nella letteratura neuroscientifica e bioetica come estremamente urgenti nella realtà del PCE tra gli studenti universitari, al momento sembrano ancora essere avvolte – almeno parzialmente – da un fitto velo di dubbio e incertezza:

1. La vera efficacia come "doping del cervello" dei farmaci psicostimolanti soggetti a prescrizione medica utilizzati da soggetti sani non per ripristinare un buono stato di salute neuropsichiatrica ma per presunti scopi di potenziamento cognitivo. Le "smart drugs" e i "nootropics" sono dunque in grado di apportare benefici cognitivi tangibili in individui senza alcun deficit neuropsichiatrico? In tal senso, questo agognato miglioramento delle facoltà intellettive finalizzato a ottenere risultati accademici impeccabile rappresenta una possibilità concreta per gli studenti che utilizzano tali psicostimolanti, oppure si tratta dell'ennesima chimera, di un miraggio alimentato da valutazioni eccessivamente ottimistiche dell'effettivo potere "potenziante" delle "smart drugs"?
2. I rischi per la salute e gli effetti collaterali potenzialmente derivanti dall'uso off-label di psicostimolanti da parte di soggetti in salute. Quali sono dunque i rischi che gli studenti alle prese con farmaci da PCE dovrebbero conoscere per prepararsi eventualmente ad affrontarli? Inoltre, in termini di analisi rischi-benefici, quanti sono i potenziali rischi del PCE a paragone con i benefici promessi, al fine di valutare se tale pratica sia accettabile o conveniente per tentare di potenziare il proprio intelletto?

3. <u>Implicazioni e ripercussioni etico-sociali di una diffusione estremamente pervasiva del PCE nei contesti accademici.</u> Nella prospettiva realistica che, nel futuro prossimo, l'assunzione off-label di farmaci psicostimolanti da parte diventi sempre più popolare nelle università e nei college, quali sarebbero i principali risvolti etici (e le relative considerazioni normative) nei confronti della comunità studentesca?

La presente tesi mira precisamente a cercare di fornire basi concettuali, empiriche ed etico-morali sufficientemente vaste, approfondite e coerenti da rendere possibile il servirsene per tentare di fare chiarezza su questi punti controversi del fenomeno dilagante del PCE nelle università. Questo scopo viene perseguito mediante il tentativo di rappresentare nel modo più chiaro ed esaustivo possibile le varie sfaccettature teoretiche, fattuali e bioetiche del fenomeno così come esso viene solitamente a configurarsi nei contesti di competizione accademica. Tuttavia, essa non si prefigge lo scopo di fornire risposte definitive o prese di posizione assolute, giacché, nonostante la ormai ventennale diffusione di questa pratica, i veloci sviluppi raggiunti nel campo delle scienze neuro-cognitive e le progressive evoluzioni del dibattito bioetico sul PCE, è ancora prematuro tentare di fare affermazioni – di qualsiasi natura esse siano – con troppa certezza su una realtà che, tutto sommato, non fa ancora preso piede al punto da radicarsi propriamente come parte della comune esperienza di vita delle società civili nel mondo e che, alla luce di ciò, è ancora caratterizzata da tante zone d'ombra.

Per cominciare, il primo capitolo tenta, in prima istanza, di fugare i dubbi – molto diffusi tra esperti e non - concernenti il preciso significato del concetto di "miglioramento", che viene qui distinto nettamente da quello di "terapia" col quale spesso viene confuso a causa del fatto che entrambe le nozioni condividono l'aspetto di miglioramento fisiologico nell'essere umano. Tuttavia, una terapia apporta tale miglioramento in virtù del fatto che essa curi o tenti di riabilitare i pazienti da sintomi di patologie necessariamente contemplate in un cattivo stato di salute, che deve quindi essere ripristinato alla "normalità; d'altro canto, si può parlare di un vero e proprio "miglioramento" (forse ancor meglio definito dal termine "potenziamento") se il punto di partenza è già una condizione complessiva di buona salute, che viene portata a livelli oltre lo standard del "normale". Nel capitolo, questo concetto di miglioramento viene ulteriormente specificato e applicato agli sforzi concreti di miglioramento cognitivo dell'essere umano "sano", per i quali le neuroscienze proseguono a ritmo sostenuto la ricerca. Nello specifico, vengono esaminati quelli che, per il momento, costituiscono gli unici due metodi fattualmente praticabili allo scopo di tentare di potenziare l'intelletto umano, classificati nelle due rispettive categorie di "Pharmacological Cognitive Enhancement" (PCE) e "Non-Pharmacological Cognitive Enhancement (NPCE)" – "miglioramento cognitivo non-farmacologico". Tuttavia, ai fini della dissertazione, l'attenzione viene posta soprattutto sulla categoria del PCE, che viene esaminata mediante una esposizione dettagliata delle sostanze psicostimolanti attualmente usate dagli studenti universitari per scopi di potenziamento cognitivo.

Sulla base di questa discussione condotta su toni prevalentemente teoretici e concettuali, il secondo capitolo rivolge il suo sguardo critico agli aspetti prettamente empirici del fenomeno dell'assunzione di farmaci da PCE nelle università: ossia, il suo tasso di prevalenza e di rilevanza all'interno della società, le motivazioni esplicitamente addotte dagli studenti stessi per l'uso di "smart drugs" e le più profonde cause prime che si celano dietro di esse, l'efficacia di tali farmaci secondo i test clinici e, infine, i rischi e gli effetti collaterali potenzialmente associati al loro uso da parte di soggetti sani. Questa analisi empirica mira in particolare a fare chiarezza sulle prime due urgenti controversie sul PCE menzionate in precedenza – vale a dire, gli effettivi benefici e i potenziali rischi apportati dagli psicostimolanti in individui cognitivamente sani. Viene dunque presentata un'ampia discussione dei dati emersi da test clinici, i quali suggeriscono che le "smart pills" attualmente più utilizzate dagli studenti universitari non reggono affatto il confronto col clamore e le grandi aspettative suscitate dal massiccio battage pubblicitario nei media classici e online, dai riscontri aneddotici e dal passa-parola tra gli studenti stessi. Infatti, il vasto numero di studi scientifici condotti sull'efficacia cognitiva dei farmaci da PCE non sembra sortire alcuna prova affidabile, univoca e coerente circa il miglioramento effettivo di abilità come la memoria, la capacità di apprendimento, l'attenzione e la concentrazione in soggetti neuropsichiatricamente sani. Anzi, anche quando test clinici hanno mostrato un qualche modesto miglioramento di sorta, gli effetti positivi sono stati rilevati solamente riguardo la performance di specifiche attività cerebrali, solamente in dosi specifiche e in un numero limitato di soggetti sperimentali e, soprattutto, non è stato possibile replicare tali miglioramenti in diversi individui né trasferirli dal laboratorio clinico in contesti di vita reale. Si dà tuttavia credito al fatto che, nonostante questa generale inefficacia cognitiva delle "smart drugs" in individui cognitivamente sani, la loro popolarità sia comunque alta tra gli studenti universitari (se non ulteriormente in crescita) per la ragione che, come è stato comprovato da test di laboratorio, i farmaci psicostimolanti sono attualmente in grado di determinare effetti positivi nella sfera emotiva, migliorando aspetti come la motivazione, l'entusiasmo, l'eccitazione e l'interesse. Questi ultimi rappresentano fattori chiaramente coinvolti tanto quanto delle buone abilità cognitive nel miglioramento del rendimento accademico, ed ecco perché molti studenti che utilizzano psicostimolanti off-label allo scopo di potenziare le loro performance universitarie li ritengono comunque molto efficaci – anche se, relativamente al loro scopo primario, sono scientificamente provati come largamente inefficaci.
Alla luce di questa disamina esaustiva sugli effettivi benefici del PCE, la dissertazione procede verso la valutazione dei rischi e dei potenziali effetti collaterali del PCE. Ancora una volta, ciò che emerge dai dati clinici non fa ben sperare: infatti, test condotti sulla sicurezza dell'uso off-label di questi psicostimolanti hanno evidenziato numerosi rischi per la salute (come il rischio di abuso, di dipendenza e di assuefazione) e una certa probabilità di effetti indesiderati potenzialmente anche molto gravi, tra i quali figurano insonnia, depressione, ansia, sbalzi di umore acuti, sviluppo di comportamenti ossessivo-compulsivi ed

eventi cardiaci. In virtù di ciò, considerando sia che la soglia di rischio accettabile da parte di individui sani dovrebbe essere considerevolmente bassa, se paragonata a quella accettabile da parte di pazienti neuropsichiatrici in forte bisogno di cure, sia che tali rischi ed effetti indesiderati non sono controbilanciati da un maggior numero di benefici comprovati, l'assunzione di psicostimolanti per scopi di miglioramento cognitivo in individui che godono di buona salute sembrerebbe non essere totalmente accettabile da una mera prospettiva di sicurezza medica.

Infine, il terzo e ultimo capitolo passa alla discussione dell'ultimo dei tre capi di controversia evidenziati in relazione a una eventuale diffusione molto pervasiva del PCE nelle università, offrendo una rassegna concisa ma esauriente delle preoccupazioni di carattere etico-morale avvertite come le più urgenti dalla letteratura bioetica contemporanea in contesti di competizione accademica. Queste preoccupazioni sono formulate e inquadrate nell'ambito più ampio della questione etica relativa al requisito di giustizia nella competizione - che in questo caso è strettamente accademica, ma, in senso generale, costituisce una delle caratteristiche fondamentali di ogni sfera socioeconomica nelle società di matrice liberale. A tal proposito, il lavoro qui presente discute specificamente due questioni di giustizia nella competizione academica: in primis, la possibilità che l'utilizzo di farmaci da PCE nelle università sia considerato alla stregua di un atto fraudolento, di un vero e proprio imbroglio in sede di esami di valutazione – così come viene considerato il doping nello sport – e, in secondo luogo, il rischio di coercizione indiretta e implicita verso l'uso di psicostimolanti per il miglioramento della performance accademica potenzialmente esercitata su studenti che, in altre circostanze, non sarebbero affatto disposti ad assumere tali farmaci, ma che, in contesti fortemente competitivi dove la diffusione del PCE è pressoché capillare tra i colleghi concorrenti, possono comprensibilmente sentirsi forzati o perfino autoconvincersi ad assumere farmaci da PCE, ritenendo che solo in questo modo possano essi stessi rimanere effettivamente competitivi in sede di test ed esami selettivi.

La valutazione morale del PCE in contesti universitari competitivi viene limitata a queste due sole specifiche aree di dibattito perché il focus etico della presente dissertazione è posto strettamente sui principali risvolti sociali (e sulle relative considerazioni normative) del PCE nei confronti del corpo studentesco generale – nei quali risvolti la questione morale della giustizia (centrale nei concetti di imbroglio e coercizione) è forse l'unica a giocare un ruolo concreto – e perché questi sono due punti di controversia che emergono quasi esclusivamente in contesti competitivo-selettivi, come lo sono le circostanze accademiche nelle quali test ed esami sono sostenuti da numeri molto elevati di studenti ai fini di una selezione finale più limitata.

Per quanto riguarda la relazione tra il PCE nelle università e la questione della giustizia nella competizione accademica, la dissertazione riporta ed esamina le posizioni etiche sia dei cosiddetti "bioliberali" sia dei "bioconservatori", suggerendo tuttavia che le prospettive etiche, sociali e normative più ragionevoli risiedano nel mezzo tra questi due estremi. Infatti, se è pur vero che l'utilizzo di "smart drugs" da parte di studenti senza particolari problemi cognitivi potrebbe essere configurato dai più come un vero e proprio imbroglio e come una pratica che, se diffusa su larga scala nelle università, potrebbe dare adito a meccanismi di coercizione implicita e indiretta nei confronti di coloro che non sarebbero altrimenti disposti ad assumere psicostimolanti (come suggeriscono i bioconservatori), d'altronde la posizione normativa più responsabile in merito non dovrebbe comportare un divieto o una proibizione assoluta (e, probabilmente, nemmeno una limitazione molto restrittiva), giacché tali misure andrebbero a ledere a loro volta altri valori ugualmente fondamentali (ad esempio l'autonomia personale, come evidenziato dai bioliberali) nel framework liberale adottato come prospettiva politica di riferimento nel capitolo, e si rivelerebbero comunque inutili nel tentativo di estirpare le radici profonde di questo fenomeno, le quali risiedono nelle dinamiche spesso malsane che caratterizzano lo strapotere rivestito dalla competizione nelle società contemporanee e nelle economie globali di mercato.

In ultima analisi, una delle idee principali che il terzo capitolo e il presente lavoro in sé intendono esprimere è che tutte quelle di cui sopra sono controversie che vale davvero la pena affrontare nell'immediato sotto tutti i punti di vista – teorici, empirici, etici e normativi -, poiché hanno una effettiva e urgente importanza in circostanze riguardanti concretamente la vita vera di intere comunità - come quella studentesca, nel caso specifico. La speranza, più in generale, è che questa tesi possa offrire una sorta di modello di valutazione del fenomeno in esame dotato di una varietà di spunti di riflessione validi abbastanza da stimolare nuovi modi di concepire ulteriori discussioni bioetiche sull'argomento da differenti e/o nuove angolazioni, anche da parte di chi non è esperto nel settore.