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THE PHILOSOPHY OF HUMAN COGNITIVE PHARMACOLOGICAL ENHANCEMENT: THE GENESIS OF PHARMACOMETAPHYSICS

Abstract: Today's technological progress allows for precise and effective human enhancement, based on technological devices, and based on pharmacological means – via biologically active compounds. This then raises a multitude of philosophical, legal, ethical and biomedical questions. The breakthrough in psychopharmacology and biotechnology came in the middle of the 20th century, and since then, thousands of active compounds have been synthesized and successfully applied in clinical practice. The article focuses on philosophical aspects (including ethical, biomedical and genetic) of contemporary human cognitive neuroenhancement based on neuro-psychopharmacological (i.e. psychotropic and nootropic) agents in the era of cognitive science.

Keywords: human enhancement; pharmacometaphysics; neuropsychopharmacology; philosophy; biomedical ethics; cognitive science; nootropic drugs; genetics.

***Петър Димков* – Философия на човешкия когнитивен фармакологичен инхенсмънт: Възникване на фармакометафизиката**

Резюме: Постиженията в науката днес позволяват прецизен и ефективен човешки инхенсмънт, както по технологичен път, така и фармакологично, чрез биологично активни вещества. Това развитие повдига редица философски, правни, етични и биомедицински въпроси. Пробивът на психофармакологията и биотехнологията бе направен в средата на миналия век, като досега са синтезирани хиляди активни вещества, които успешно се прилагат в клиничната практика. Настоящата статия разглежда философските аспекти, вкл. етически, биомедицински и генетични, на съвременния човешки когнитивен невроинхенсмънт, постигнат чрез невропсихофармакологични – т.е. психотропни и ноотропни – агенти в ерата на когнитивната наука.

There is evidence that man has used various methods including ingestion of psychoactive compounds for mind expansion, healing purposes and enhancement in general since ancient times. Cognitive neuroenhancement is increasingly sought nowadays. Today the topic of human enhancement, particularly of the narrow area of pharmaceutical cognitive enhancement (PCE), is in the spotlight of attention (Pustovrh & Mali 2013). In the literature, arguments for and against cognitive enhancement can be found. Pharmaceutical or pharmacological enhancement is one of the means for enhancement. Bostrom & Sandberg thus carefully distinguish the difference between therapeutic manipulation and enhancement: in the first case of therapeutic manipulation, there is a defect or deficiency, whereas enhancement is related solely to improvement. However, in practice, proving this distinction mostly failed as the distinction between health as normality and illness as abnormality is not a clear-cut one (ibid.). Pharmaceutical cognitive enhancement should not be regarded as a therapeutic manipulation, such as

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an amelioration of particular symptoms *per se*, e. g. negative symptoms in schizophrenia, but rather it represents a personal choice for exogenous improvement of one's cognitive capacities above the norm. Two classes of pharmaceutical compounds are used for such purposes, namely psychostimulants and nootropic drugs (nootropics). Their effects and pharmacodynamical profiles differ. The article depicts in the form of a review the state of the art of pharmaceutical cognitive neuroenhancement today. From a philosophical perspective I discuss the future of such enhancements as this is an issue touching upon the old question of the pace and direction of evolution. Provided are insights from the fruitful intersection of genetics and philosophy. In the end, it is hypothesized that a foundation of a specialized interdisciplinary project to deal with the debate of pharmaceutical cognitive neuroenhancement would be beneficial as the debate belongs to no man's land at the present moment. Such an interdisciplinary field of knowledge can be united under the umbrella term *pharmacometaphysics*, whereas man can be thought of as *homo pharmacos*. Pharmacometaphysics will thus comprise the intersection of genetics, pharmacology, law and philosophy.

Definition of Pharmacological Cognitive Enhancement

Man is vitally dependent on his performance for survival and social status. Work performance in humans depends on variables such as health, age, genetic predisposition, vulnerability of the organism, et cetera. Performance can be increased or decreased (improved or aggravated) in many ways, for example, via specific behavioural techniques, nutritional enhancement, training of attention, working memory and cognitive control, cognitive and behavioural psychotherapy, emotional regulation strategies, work therapy, meditation practice, strategies for environmental adaptation and most recently via neuroenhancement methods. The latter include methods such as sufficient sleep, adequate nutrition, physical exercise, the use of mnemonic techniques and brain training (Brukamp 2013: 102). In this way, man can "model" and adjust his performance according to his needs and desires.

Let us first start with the broader definition of cognitive enhancement. The definition of cognitive enhancement is far from clear today. There are authors who accentuate the sophisticated and complicated character of cognitive enhancement. For example, Hauskeller (2013: 118) argues that "[…] generally speaking, what counts as cognitive enhancement is highly context-dependent. It depends on what someone wants or what the goal is". Various terms for enhancement can be found in the literature: "Pharmacological ''Neuroenhancement'', ''Cosmetic Neurology'', ''Academic Performance Enhancement'', ''Academic doping'', ''cognitive enhancement'' (CE) or even ''Brain Doping''" (Franke et al. 2014: 1).

Due to its complex status, the debate on cognitive enhancement requires some philosophical elucidation as the problem is wider than the scope of both psychiatry and law. In the current article I present the state of the art of pharmaceutical cognitive neuroenhancement. I define this state of the art as one reflecting the need of founding the new discipline of pharmacometaphysics, dealing with the debate on pharmaceutical cognitive enhancement. Here an elucidation of the concept of pharmaceutical cognitive enhancement will be provided as it is found and used in con-

temporary literature. The situation is further complicated due to the lack of a unified theory of the mind-body complex. The "hard problem" of consciousness – known also as the psycho-physiological problem in philosophy – has not been solved.

The following quote illustrates why and how pharmaceutical neuroenhancement works: "[…] there is yet no existing brain-machine interface based on exchange of electrical (electromagnetic) signals that would improve human cognitive abilities above and beyond what a natural brain can do […] We do not have yet a theory correctly approximating physical substrate of higher cognitive processes. *Brain did not evolve by adding defined units for more complex functions, it improved its performance by physiological modulation enabled by biochemical alterations of neuroactive substances […] what the brain needs is continuous input of the new information (i.e., learning)*" (Saniotis et al. 2014: 3; emphasis added). Generally speaking, "Pharmacological neuroenhancement is used to refer to the misuse of prescription drugs, other illicit drugs, or alcohol for the purpose of enhancing cognition, mood, or prosocial behaviour in academic or work-related contexts" (Maier & Schaub 2015: 2). There are narrower definitions of the term as well. Hauskeller (2013: 142), for example, defines pharmaceutical cognitive enhancement as a process in which "[…] drugs enhance cognitive functions by modulating only parts of the neural network that correspond to the cognitive functions, while behavioural training enhances cognitive functions by modulating a larger neural network within which the target neural network is only a part […] There are synergistic effects because drugs and behavioural training modulate different parts of neural networks independently". Interestingly, recently a conception was postulated stating that attention can be equated with working memory or rather working memory is a form of attention (Fuster 2008: 349). Thus it is not surprising that both behavioural techniques and intake of pharmacological agents for cognitive enhancement target enhancement of attentional and working memory functioning. There are, however, reasons other than cognitive enhancement that inspire people to take enhancers, e.g. increase of energy, wakefulness and motivation, induction of euphoria, decrease of appetite, recreational and performance enhancement (Smith & Farah 2011; Upadhyaya et al. 2010).

Pharmacological Enhancement of Cognition in Humans

One can distinguish between two main classes of pharmaceutical drugs that can be used for cognitive enhancement, namely nootropic drugs and psychostimulant drugs. The general pharmacological principle states that drugs are used for controlling excessive or deficient neurotransmitter levels with high success rates, but in healthy individuals, it is postulated, they do not exert any positive effects. Some authors even speak of negative effects in healthy individuals after administration of psychostimulants, such as impaired cognition and reduced creativity (Mohamed 2014).

With respect to the abovementioned potential pharmacological possibilities for enhancement, the focus of research is on the class of unrelated chemical compounds of nootropics such as the prototype compounds of piracetam (Nootropil) and related racetams (aniracetam, oxiracetam, pramiracetam, phenylpiracetam) (Gualtieri et al. 2002). In particular, "Most traditional and modern nootropics ac-

tivate an excitatory neurotransmitter or suppress the action of its inhibitory counterpart; [thus] *a nootropic agent is a substance that may alter, nourish or augment cognitive performance, predominantly through the stimulation or inhibition of certain neurotransmitters*" (Saniotis et al. 2014: 4; my emphasis). The interest in pharmaceutical cognitive enhancement is on the encoding mechanisms in synapses (Bostrom & Sandberg 2009: 317; Saniotis et al. 2014: 2; Regan 2015). Of special interest is also neuroplasticity, which is thought to be the main target of therapeutic manipulation as well as of neuroenhancement. In general it is accepted that pure nootropics do not have any motivational or affective effects. For cognitive enhancement people used over-the-counter drugs such as caffeine, prescription medicines such as methylphenidate and illicit drugs such as amphetamine (Franke et al. 2014). The main underlying mechanism of the class of nootropic compounds is a direct or an indirect enhancement of brain metabolism and homeostasis, a potentiation of the action of various neurotransmitters, hormones and neuromodulators, neurons, glial cells and blood circulation. In short, the brain is brought up to a higher level of functioning. One can manipulate, for example, the biological substrate, underlying mnemonic processes, on several levels.

Furthermore, it should be noted that synthetic biologically active chemical compounds, such as the ones psychopharmacology utilizes, can possess far more robust or comparable effects such as high receptor affinity and high selectivity in comparison with naturally occurring biologically active chemical compounds. There are other biologically active substances such as galantamine (Nivalin), which represents an isolated extract from the plants *Galanthus caucasicus* and *Galanthus woronowii*, known to be a potent nootropic compound, comparable to the substance Huperzine A, an alkaloid found in the plant *Huperzia serrata*. These two nootropics are with potencies, comparable to synthetic compounds such as donepezil. They all act as acetylcholinesterase inhibitors (AChE inhibitors). Many natural compounds nowadays can be synthesized artificially or extracted.

Psychostimulants, another class of unrelated chemical compounds, are considered prototypic cognitive enhancers. Psychostimulants such as amphetamine (Adderall), methamphetamine (Desoxyn), methylphenidate (a DRI – dopamine reuptake inhibitor) and modafinil (an analeptic drug) are rather referred to as motivation enhancing drugs or performance enhancers rather than pure nootropic or creativity enhancing agents (Hauskeller 2013: 117; Zohny 2015). There is some evidence that stimulants enhance learning, whereas the evidence of enhancement of working memory and cognitive control is rather mixed (Smith & Farah 2011). Improvements of performance and functionality can occur on any level of cognition: "Cognition can be defined as the processes an organism uses to organize information. This includes acquiring information (perception), selecting (attention), representing (understanding) and retaining (memory) information, and using it to guide behaviour (reasoning and coordination of motor outputs). Interventions to improve cognitive function may be directed at any one of these core faculties" (Bostrom & Sandberg 2009: 312). Perhaps long-term effects are based on structural (morphological) changes in synapses. Overall, however, psychostimulants have

complex pharmacodynamical profiles, therapeutic effects as well as side effects and due to this fact they are under the control of special laws and are prescribed solely by specialists (neurologists, psychiatrists). Nonetheless, there is strong evidence that nowadays they are misused and abused (Wilens et al. 2007: 28). Methods for cognitive enhancement act as "amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems", so that the performance of a subsystem of cognition is improved (Bostrom & Sandberg 2009: 311). Psychostimulants are said to improve the following cognitive domains: concentration, attention, wakefulness and memory (Pustovrh & Mali 2013). Psychostimulants stimulate the exocytosis of noradrenaline and dopamine (Franke & Leib 2013: 19). These drugs possess positive as well as negative effects: "[…] Methylphenidate [for example] improves memory, and modafinil increases wakefulness, both under normal conditions and after sleep deprivation, but the latter also potentially induces unsubstantiated overconfidence in one's own abilities" (Brukamp 2013: 104).

Non-pharmacological human enhancement methods include transcranial direct-current stimulation (tDCS), transcranial magnetic stimulation (TMS) (Sahakian et al. 2015: 8–9) and genetic means (Hauskeller 2013: 117). Neuroimaging methods (fMRI, EEG, spectroscopy in MRI) along with psychometric methods (behavioural psychology) in general can be used to assess objectively the status of one's cognitive capacities.

Examples of other pharmaceutical cognitive enhancers are enumerated in Table 1 below. (Ташев 1971: 217–218; Темков & Киров 1976: 102–106; Йорданов 1982; Петков 1985: 196–227, 1998: 160–198; Георгиев & Овчаров 1985; Овчаров и сътр. 1987: 194–195; Schneider et al. 1994; Feldman et al. 1997; Lanza & Makovec 1997; Szatmári, & Whitehouse 2003; Mehlman 2004; Morris et al. 2004; Stipa et al. 2005; Писева и сътр. 2005: 331–332; Nathan 2006; Slutsky et al. 2010; Kelley et al. 2012: 688; Harvey & Bowie 2012; Saletu et al. 2014; Fond 2015; Venero 2015; Warthon-Medina et al. 2015; Zhang et al. 2016; For detailed review, see: Knafo & Esteban 2015 & Nelson et al. 2015).

Table 1. List of pharmaceutical cognitive enhancers

Centrophenoxin and pyrithioxin, caffeine, theophylline and ginseng, glutamatergic drugs (ampakines, memantine, D-cycloserine), vasodilators (alpha-1-blockers such as nicergoline, beta-blockers such as propranolol, PDE inhibitors such as vinpocetine), alpha-2-blockers such as guanfacine, amino acids (L-Theanine, tryptophan, tyrosine, phenylalanine, glycine), NMDA-Glycine site modulators, N-methyl-d-aspartate (NMDA) receptor agonists (glycine, D-serine), GABA, GABAergic drugs and L-Glutamine, vitamin B_6 (pyridoxine), niacin (B_3) and Vitamin C, Ginkgo biloba, Zn^{2+} and Mg^{2+}, direct and indirect cholinergic agonists such as galantamine (Nivalin), nicotine and phosphatidylcholine, serotoninergic agents (releasing agents (fenfluramine), 5-HTP, 5-HT_{1A} agonists/antagonists, 5-HT_{2A} agonists/antagonists, 5-HT_3 antagonists, 5-HT_6 antagonists, SSRIs and SNRIs – see: Dimkov 2018), dopaminergic agents (L-DOPA, D_2-agonists, the MAO-B inhibitor selegiline), glucocorticoids and histaminergic agents (modafinil).

Recent Discussions in the Human Neuroenhancement Debate

Today there are numerous positions and arguments in the debate of human neuroenhancement (Gualtieri et al. 2002; Bostrom & Sandberg 2009; Hyman 2011; Ilieva & Farah 2013; Franke & Leib 2013; Brukamp 2013; Dubljević 2013; Hauskeller 2013; Lynch et al. 2013; Pustovrh&Mali 2013; Partridge 2013; Wolff et al. 2014; Maier & Schaub 2015; Zohny 2015; Sahakian et al. 2015; Schelle et al. 2015; Dimkov et al. 2015; For more on enhancement of creativity, see: Plucker et al. 2011 and Dimkov 2016, 2018). Critics attack the methodology of human enhancement with the argument that any intervention into the natural flow of evolution is disastrous (Pustovrh & Mali 2013). On the other hand, as already noted, there is an increasing number of persons who use cognitive enhancers. One part of the users is constituted of patients who, according to the *self-medication hypothesis of substance use in neuropsychiatric disorders*, self-medicate themselves to ameliorate existing cognitive deficits and impairments (see: Maier et al. 2015: 222), for example the negative and pseudonegative symptoms in schizophrenia and depression. In this case, however, it is not always clear whether it is a question of misdiagnosed conditions such as ADHD, and, therefore, should not be considered a misuse but rather a self-treatment. This type of substance use should be regarded rather as therapeutic manipulation and not as pure pharmaceutical cognitive enhancement. The other part is composed healthy individuals who, for one reason or another, such as improved work performance, use pharmaceutical cognitive enhancers. There are numerous theories and hypotheses concerning the off-label users of enhancers. According to Hyman (2011), for example, enhancers are coming out of neuropsychiatry as "off label use" (see: Sahakian et al. 2015: 1–8), only after they have been approved for clinical application, so attention is carefully directed to the aspects of safety of such manipulations. With respect to the more nutritional methods for enhancement, Hyman carefully notes that they are in fact not particularly effective. Maier et al. (2015) and Zohny (2015) direct attention to the affective and motivation effects of pharmaceutical cognitive enhancement and argue that such effects should be considered as well when we speak of such substances and their pharmacodynamical profiles. Interestingly, Herman-Stahletal et al. (2007), for example, assume that cognitive enhancement is to be found in universities and schools, i. e. in cognitively demanding places, which is not surprising at all. Indeed, recently the *syndrome of work burnout* has come into focus as well (Raycheva et al. 2012; Zaharieva et al. 2014). Certainly, college students are more likely to use cognitive enhancers (psychostimulants) than nonstudents of the same age (Smith & Farah 2011). Moreover, there is evidence that users of prescription stimulants for attention deficit hyperactivity disorder report impaired study habits, decreased motivation and attentional problems (Ilieva & Farah 2015), which further confirms the self-medication hypothesis. In this line of reasoning, the alternative theory named *Job Demands-Resources Theory* postulates that neuroenhancement is to be found in persons with mental health issues and persons facing high work and occupational demands (Wolff et al. 2014). Moreover, Schelle et al. (2015: 2) report that recently the focus seems to have shifted "from prevalence of substance use for cogni-

tive enhancement toward broader topics, such as the motives behind the use, differences between users and non-users, or theoretically grounded accounts of why certain students choose to use drugs for cognitive enhancement while others do not". Administration of cognitive enhancers is to be found in more stressed individuals, who are more likely to engage in the use of multiple substances, either legal or illicit (ibid.: 7). As far as the magnitude of the use of enhancers is concerned results are rather mixed. For example, Schelle et al. report that only 1.6-1.7% of all people do use cognitive enhancers (pharmaceutical cognitive enhancement) in the Netherlands in comparison with 4.6-16% in Europe, 8.5-12.3% in America for individuals between 12-25 years of age (prescription stimulants) (Smith & Farah 2011) and 5-35% in total in college students (Dresler & Repantis 2015: 274). In Switzerland, around 4% of students and employees do use neuroenhancers (Maier et al. 2016). According to Boyd & McCabe (2008) no clear reason for the use of psychostimulants or prescription medication is to be found (see the Job Demands-Resources Theory in: Wolff et al. 2014). Finally, physicians themselves seem to be unaware of this wide-spread misuse of psychostimulants (Clemow & Walker 2014: 760). For a review on the subject, see the paper of Partridge (2013).

Philosophy and Genetics: Insights from an Interdisciplinary Collaboration

Pharmaceutical cognitive enhancers enhance mnemonic functions or cognition in humans, including the capacity for creativity. Creativity engages all mnemonic functions. The psychopharmacology of creativity in terms of enhancement via psychedelic compounds is discussed elsewhere (Dimkov 2018). In particular, Dimkov hypothesizes that it is not a massive hyperdopaminergic state in the mesolimbic system but rather a moderate glutamatergic state in the prefrontal cortex that is required for the emergence of creativity. Enhancement of creativity and mnemonic functions undoubtedly has a huge impact on the normative question of the future of human evolution. Is cognitive enhancement advantageous or disadvantageous, ethical or unethical, moral or unmoral? In the case of human pharmaceutical cognitive neuroenhancement, the stimulation of creativity with psychedelic compounds and the "boost" of cognitive capacities with stimulants and nootropics are both sought today. Scientific evidence at best remains inconclusive. This means that, albeit artificial, any pharmacological interference into the genetically set physiological regulatory mechanisms will induce phenotypic and perhaps genotypic changes in human biology, particularly in synapses; such changes can be short-lasting or long-lasting. On the one hand, anti-enhancement supporters and enhancement critics stand against any artificial interference in natural evolutionary processes (see: Zohny 2015).

On the other hand, a contradictory view is offered by the *argument of liberty*, namely that *everyone is free to use and benefit from neuroenhancement in one form or another* (Brukamp 2013: 109). Zohny (2015: 266), for example, claims that the "evidence for cognitive enhancing drugs boosting cognition amongst healthy users is, at best, inconsistent", drawing attention to the fact that perhaps cognitive enhancement in normal individuals would not work at all. Nonetheless, the misuse of psychostimulants for enhancement and the use of cognitive en-

hancers, as noted, are rising, eloquently explained by the argument of liberty – everyone is free to manipulate his brain chemistry seeking enhancement.

The general question is thus one of the pace and direction of human evolution. As conscious agents we can interfere into this evolutionary process, we can mould ourselves, our future. From general physiology it is known that evolution proceeds via dialectical jumps. At the base of every physiological regulation lie regulatory mechanisms functioning with feedback connections, which have genetically set values that can be subsequently subjected to changes by environmental influences to allow evolutionary jumps to appear (Векилов и сътр. 1982; Кардашева & Куприянов 1974; Начев и сътр. 1987). For example, the neuroendocrine regulation of the brain is very similar to that in other animals, although quantitatively there could be some differences insofar as the degree of myelination in particular species is different (Previc, cited in: Saniotis et al. 2014: 2). From the point of view of biology itself, it does not matter whether the induced evolutionary change is endogenous or exogenous. In fact, all pharmacological interventions are apodictically exogenous inducers of evolutionary changes. Thus, the following question arises: Are such interventions ethically correct or they are rather wrong?

If one can enhance himself or herself pharmacologically, and this depends on access and money only, then the equality among men seems to be violated; see the *concept of distributive justice* (Brukamp 2013: 109). For example, some authors speak of issues with "authenticity, good life, the role of medicine, enhancers as cheating or diminishing personal accomplishments, ethical and pragmatic implications in academia" (Zohny 2015: 257–262), of issues with "maintenance of, or search for, authenticity, truth, originality, personality, and identity as a human being" (Brukamp 2013: 106). Such constructions are social constructs, which determinate what is normal and what is not, that is, what is culturally valid and what is alien. If this is excluded and put aside, then the road of the future human enhancement, in the case of pharmacological enhancement, is clear. Specifically, Shelley-Egan et al. (2017: 5) emphasize three ethical issues with pharmaceutical cognitive enhancement, namely: fairness and personal achievement, distributive justice and coercion. They explicitly accentuate the need for adequate governance of human cognitive enhancement. At present, results are at best moderate, with available drugs sometimes having side effects (e.g. addiction and personality changes with psychostimulant use), low potency and lack of selectivity. Nonetheless, the future of cognitive pharmaceutical neuroenhancement belongs to the discovery of new, purer drugs with fewer side effects and better selectivity, potency, affinity and efficacy. In a sense, therefore, the future is one of human enhancement. Indeed, "from the ongoing debate on human enhancement is about *ourselves today rather than about the future of the human nature* […] *enhancement is an open process without telos* […] *enhancement has no intrinsic limits or measures but opens up infinite possibilities* […] a future is thus not something separate from the present, but a specific part of each present" (Grunwald 2013: 202, 203, 206, 211; emphases added). Unfortunately, such enhancements viewed

as a cultural phenomenon are a recent appearance and the long-term effects, e.g. genetic mutations, are not known.

To elucidate further the situation around pharmaceutical cognitive neuroenhancement I provide some insights from the intersection of genetics and philosophy. In general, evolution can be defined as "a process of successful transformation of the genetic structure of populations" (Тончева 1984: 35; my translation). Mutations caused by physical, chemical and biological factors along with the process of natural selection play main roles in the process of evolution. Mutations as a molecular process usually are represented by recessive genes. Moreover, mutations are random processes. Natural selection as stochastic process controls the selection of adaptive mutations and their integration in the phenotype and the genotype: directly affecting the phenotype and indirectly the genotype (ibid.: 39). Such adaptive mutations, be they micro- or macro-mutations, are the building blocks of every evolutionary process. Additionally, the possibility for recombination allows for the emergence of a variety of new genotypes. There are also genetic victims, i.e. deleted mutative genes. Mutations occur either due to a gradual accumulation or due to a process of dialectic jump. Each gene can mutate endless times and the phenotype under environmental influences determines the forms and scope of the reactions of the individual (Крачунова 1984: 59, 63). The genetic code furnishes only basic programs – programs for self-organization at all levels of matter – for development to the organism; other additional influences are coming from the external, exogenous environment (Ведъонов 1969: 43–46, 49; Кремлянский 1969: 55–57, 59, 61, 63–67; Веденов & Кремлянский 1970: 37–39; Кардашева & Куприянов 1974: 161–163). According to Кардашева & Куприянов (1974: 163–166) the unfolding of life, that is ontogenesis, is related to the accumulation of various "errors" or signal "noise" during the maintenance of the homeostatic equilibrium leading to ageing and death. However, the species remains "eternal" (ibid.: 167). Maintenance of homeostasis is devoted to regulatory mechanisms functioning with feedback connections (ibid.: 168-172; see: Начев и сътр. 1987). Such regulatory mechanisms producing deviations in the long run are subjected to a gradual decline. To what extent can such regulatory mechanisms be subjected to improvement via enhancement? This touches upon the issues of the "limit" of cognition in humans and the notion of normality. According to Тягуненко (1970: 61–63, 66–69) heredity transformations can be classified into mutations with a chance of 10^{-8} and heredity changes or recombination, relations of autonomy and integrity, et cetera. Mutations are viewed as spontaneous transformations, independent of or dependent on external environment, which are genetically stable. Mutations change genetic information and they are inheritable.

Cognition in humans and its underlying neurobiological substrate, the brain, have a limit, which is genetically set. It can be changed during ontogenesis under the influence of exogenous or extra-genetic factors. Normality comprises the "limit" of cognition, whereas enhancement can push and extend this limit forward. Otherwise the cognitive evolutionary potential may remain unrealized. If,

on the other hand, it refers to improvement, it is rather a treatment of a medical condition, i. e therapeutic manipulation. Some authors (e.g. Zohny 2015: 267) speak of the fear of enhancing the brain with pharmaceutical cognitive enhancers rather enhancing the psyche. Thus we speak of cognitive enhancement in the spectrum of normality with respect to the limit value of cognition or just the limit of cognition. In particular, however, the issue is revealed as being one of a transposition of the phenotypic genetic material to the phylogenetic DNA storage: To what extent does the life of the individual determine what number of his genes (mutations) will be transmitted to next generations? Biochemical and submolecular anthropology (anthropochemistry) has to answer such questions (Цветков & Кардашев 1974: 150, 153). Can human neuroenhancement have genetic consequences, which can subsequently be transmitted genetically to the next generation? In summary, potential problematic issues around human cognitive enhancement are the following ones (Shelley-Egan et al., 2017: 13): drug side effects, dealing with pressures (e.g. work and academic pressures), alterations in self-perception, and potential societal effects of enhancement in work and education.

The Genesis of Pharmacometaphysics

Stress is an inevitable phenomenon in life and each organism reacts uniquely to stressful stimuli. With respect to coping with stress related to cognitive performance, people use different strategies. One group is composed of methods to combat stress naturally, e.g. with sports, healthy diet, meditation, good sleep and work hygiene. Another group comprises strategies for combating stress artificially with psychotropic and nootropic drugs. As far as enhancement is concerned, a misperception about the usage of enhancers as an adequate stress coping strategy has emerged in the media, which is troublesome (Maier et al. 2015). Moreover, "pharmacological neuroenhancement is regarded as an external, artificial measure that merely serves as a means of self-deception" (Brukamp 2013: 107). From this it follows that at least at the present moment pharmacological neuroenhancement is viewed by some authors as a method of cheating and thus as a false method. On the one hand, if such methods for enhancement are not effective, it does not matter if they are used or not. On the other hand, if they are effective, but produce side-effects, it is important how and why they are used. In reality, however, such individuals are not being supervised at all and self-administrate pharmaceutical cognitive enhancers. The latter induce known and unknown effects, desirable and undesirable. What is important is not so much the ontogenetic modification of the phenotype, but rather the modification of the genotype with respect to the genes to be transmitted to the next generation. As far as the subject of the question is a normative one, it belongs to the field of philosophy. As far as its object is empirical, it belongs to science. There are positive and negative views in the debate of human enhancement in both fields. In this line of reasoning, Brukamp, for example, writes: "Arguments, both those in support of and those opposed to neuroenhancement, relate to various disciplines. From a medical standpoint, several perspectives justify a critical stance, be it because of *med-*

ical risks, deficits in evidence-based medicine, or challenges to health care systems. Considering society as a whole, sceptic arguments also stem from anthropology, sociology, and classical ethics and they touch on the concepts of *human nature, virtues, purposes, liberty, and justice*. In conclusion, neuroenhancement should be discouraged at present" (ibid.: 110; emphases added). Such a position symbolizes passivity and cautiousness.

Science is blind without philosophy and philosophy falls prey to illusions without science. Pharmaceutical cognitive neuroenhancement is a real-life phenomenon, which deserves appropriate attention as negative and long-term effects are currently not well known. Neuroenhancement is a normative question, which has to be philosophically elucidated. As pointed by Grunwald (2013), attention is directed to the present state of affairs, but I nonetheless emphasize the need of elucidation of the future effects of present-day enhancement. In a sense, therefore, the need for an emergence of a new discipline is strongly felt, a discipline working jointly with genetics and pharmacology, which will actively research and elucidate further the topic of pharmaceutical cognitive neuroenhancement. Experience has proven that the merging of scientific disciplines into interdisciplinary projects is fruitful as is the case with cognitive science. The interdisciplinary spirit allows for better interpenetration and interaction among different disciplines; it is a sign of progress in science. This new discipline can be termed *pharmacometaphysics*. Pharmacometaphysics thus will be concerned with the evolutionary progress of humanity where pharmaceutical neuroenhancement is implicated. Man is a creature of pharmacological self-experimentation. Man is thus revealed as *homo pharmacos*, a creature he was from the very beginning of his existence (see: the idea of *enhancement society* in Grunwald 2013). Consider for example coffee intake today or the use of psychedelic compounds in ancient tribes and ceremonies. To be precise, the use of such substances and the emergence of consciousness seem to be related as "[…] many authors support the co-evolution of early hominins with the use of nootropic substances and the attainment of altered states of consciousness" (Saniotis et al. 2014: 4). Such uses, however, were not systematic and for sure not scientific in the strict sense of the word. It should be noted, furthermore, that "the limits of pharmacologically aided human cognition should not exceed the capacities of the brain. The human brain is a complex organ, thus pushing its performance beyond its adaptive capacity using pharmacological products could lead to failure" (ibid.: 5). Such statements reflect wisdom and practicality. It is true that pharmaceutical enhancement contains its own risks, it is not a panacea; there are side effects and information on such drugs is usually not consistent enough. When used properly, however, pharmaceutical cognitive enhancement can bring numerous advantages and help uncover undiscovered territories of knowledge and cognition. This further supports that more research is needed.

The 20th century was the century of enhancement of creativity (see: Dimkov 2018). The early experiments with psychotomimetic compounds such as LSD-25 exposed *homo pharmacos* to the general public and provided modern scientific

evidence that creativity can be enhanced pharmaceutically. Today in the 21st century we are witnessing a second wave justifying the need of founding the discipline of pharmacometaphysics. Both justify that, at least in theory, cognition can be enhanced pharmaceutically with success via the methodology of science and the elucidation of philosophy. With the help of science and with the guidance of philosophy the normative question of pharmaceutical cognitive neuroenhancement can be further developed and systematized. An active interdisciplinary project such as the one of pharmacometaphysics will move us one step further in our evolution: "[…] we have to desire and hope that the more man intervenes rationally in his environment and creates for himself a better life environment and the more man finds more and more humane and effective ways of perfection of his heredity, evil and darkness will retreat more in the face of good and light" (Астауров, cited in: Еврев 1984: 58; my translation).

Conclusion

For millennia man has used biologically active compounds to induce both psychological and somatic changes, to change the dynamics of the mind-brain complex. Thus man can be defined par excellence as homo pharmacos. Biologically active compounds de facto represent tools for manipulation. For example, in the twentieth century psychotomimetic drugs such as LSD-25 were used to potentiate both the process and the trait of creativity. Today we are witnessing a new but connected wave of drug use, namely the wave of human neuroenhancement in general and the one of human cognitive pharmaceutical enhancement in particular. Cognitive enhancers include the pharmaceutical classes of nootropic drugs and psychostimulants, which potentiate different aspects of cognition. At present both the effectiveness of such enhancements and their potential side effects remain largely unknown. This allows one to unite the history of drug use for enhancement purposes with modern scientific research and philosophy to postulate the establishment of the discipline of pharmacometaphysics. Such a discipline will bring focus and direction to the debate of human pharmaceutical cognitive neuroenhancement by formulating clear and specific goals, research questions and approaches. The discipline will include genetics, pharmacology, law and philosophy.

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