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Neuroenhancement: status quo and perspectives

Abstract Neuroenhancement is a pharmacological attempt to increase cognitive performance in healthy humans. Strategies to improve learning and memory aim at plasticity pathways in the brain; phosphodiesterase inhibitors such as rolipram and NMDA-modulating drugs like donepezil and D-cycloserine have been tested in clinical trials. Modafinil and methylphenidate are used to increase attention and vigilance. Other fields of intense research include mood, social interaction and sexual performance. So far, all clinical trials of neuroenhancing drugs have either failed or demonstrated only very limited efficacy. However, the high demand for neuroenhancement and the intense research efforts might come up with more efficacious drugs in the near future implying the need for an extended ethical discussion in society.

Key words neuroenhancement · plasticity · learning · cognition · modafinil

Introduction

The working and leisure environment of many people in developed countries is changing dramatically. Confronted with exponentially increasing computer performance, fluid intelligence is gaining against crystallized intelligence. Whereas crystallized intelligence is based on broad knowledge and experience, fluid intelligence is the ability to find meaning in confusion and solve new problems. It is the ability to draw inferences and understand the relationships of various concepts, independent of acquired knowledge. Fluid intelligence peaks in young adulthood and then steadily declines [4]. This has increased the demand for pharmacological enhancement of brain performance.

It has become common practice to modify the human "hardware". The body is shaped and built up or is changed by surgery. Technical devices aim to compensate for major disabilities. The deaf learn to hear by cochlear implants, brain–machine interfaces control artificial extremities just by the power of the will [11]. The selection and modification of genes will allow to prevent or to heal major illnesses. But is it possible to update the "brain computer", to increase the capabilities of the human software?

Two psychiatric disorders illustrate how broad the limits of human performance are. "Savants" are subjects with special abilities as a feature of their autistic disorder. Savants demonstrate that circumscript parts of the fluid intelligence can be increased excessively. The savant syndrome is commonly explained as an inability to sort incoming information by relevance which normally prevents information overload in order to allow fast and intuitive reactions. Savants process and store any information within a certain field irrespective of their relevance. This impairs, however, other aspects of their cognitive performance so that the average IQ of autistic savants is around 70.

Kim Peek has been the role model for the film character "Rain Man". He knows the contents of 12,000 books by heart and he is able to store the contents of a book page within 10 s, scanning each page by one eye individually. Moreover, he has superior calculating abilities (http://www.wisconsinmedicalsociety.org/savant). Other savants can remember every detail of their life, including every single meal or rain shower. Stephen Wiltshire, a

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British artist with autism born in 1974, is able to draw highly detailed panoramic views of cities after short round flights (http://www.stephenwiltshire.co.uk).

Another psychiatric disorder demonstrates the plasticity of brain performance. Bipolar disorder is characterized by the episodic recurrence of manic and depressive episodes. In mania, the intellectual pace of a patient is highly increased; he has racing thoughts and is sometimes highly creative. Mood is euphoric and sexuality is lived out excessively. A short time span later, the same patient might no longer be able to solve even the most simple cognitive tasks and his cognition is deteriorated up to pseudodementia within depression. The patient has major difficulties to store new information, thinking is slow and the language production is decreased. Libido is reduced to a minimum.

Autism with savant syndrome and bipolar disorder demonstrate that the cognitive and social performance of humans can be modified by neurobiological factors within broad limits. Is it possible to improve this performance by pharmacological interventions? In the following sections, we will describe pharmacological methods to improve learning and memory, attention, mood, communicative skills and sexual performance in healthy humans.

Learning and memory

The human brain is a plastic organ which can adapt to changing environmental conditions. Until some years ago, it has been a dogma in neurobiology that neurons develop early and cannot be replaced in adults. This view has been changed by the demonstration of adult neurogenesis in rodents, primates and humans. In the adult brain, new neurons are generated and integrated into neuronal networks. However, neurogenesis is limited to a distinct part of the brain, namely the dentate gyrus of the hippocampus, and could not be detected in cortical regions [7].

Beneath this form of structural plasticity, there are other forms of functional plasticity. As early as 1949, Canadian psychologist Donald Hebb postulated that "when an axon of cell A excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased." [10]. These theoretical predictions were experimentally confirmed in 1973 when Bliss and Lomo described long-term synaptic potentiation (LTP) [3]. In LTP, repeated activation of a synaptic pathway leads to a persistent increase in synaptic transmission (Fig. 1). In its counterpart, long-term depression (LTD), transmission is persistently decreased [5, 13, 14].

Long-term synaptic plasticity is an ubiquitous form of functional brain plasticity. It has been described in most brain regions and is regarded as the neurobiological correlate of learning and memory. Recent experimental work has consistently shown that simple behavioral learning induces LTP in the hippocampus and that learning can be impaired by inhibition of synaptic plasticity in the hippocampus [22]. Literally thousands of publications describe the mechanisms of synaptic plasticity. A complex cascade of receptors, proteins and ion channels detects the induction paradigms of synaptic plasticity and converts this information into a persistent modification of synaptic power. In a late phase of synaptic plasticity, morphological changes follow the functional alterations; new synapses are generated.

Given their central role for learning and memory, the mechanism for LTP and LTD are primary targets for the development of neuroenhancing drugs. Pioneers in this field are the Nobel laureates Eric Kandel and Walter Gilbert. Their research focuses on the modulation of calcium channels and the CREB protein. So far, no drugs have been approved for clinical use to increase learning and memory in healthy humans; however, some interesting preliminary results have been published.

Rolipram is a phosphodiesterase inhibitor and increases the intracellular concentration of the regulatory protein cAMP response element-binding protein (CREB). CREB is crucial for LTP and regulates the transcription of genes which stabilize an increase in synaptic efficacy. CREB is activated by cyclic adenosine monophosphate (cAMP) which by itself is degraded by phosphodiesterase. When CREB is increased in drosophila by genetic manipulations, the animals learn the location of food source within a single trial whereas wildtype flies need ten or more repeats to learn an identical task [20]. Application of rolipram has caused a dramatic increase in learning performance in mice [2]. Several phosphodiesterase inhibitors are in the early stage of clinical testing in humans.

Donepezil is approved for the treatment of Alzheimer dementia. In a double-blind, placebo-controlled study, Yesavage et al. have tested the efficacy of this substance in elderly pilots with an average age of 52 years. They were tested in a flight simulator before and after a 30-day intake of donepezil. Confronted with complex flight situations, the pilots in the donepezil group showed a highly significant increase in performance [23].

D-cycloserine is a partial agonist at the *N*-methyl-D-aspartate (NMDA) glutamate receptor. The substance facilitates LTP in brain slices and promotes fear extinction in behavioural animal experiments. D-cycloserine is approved in the United States as an antibiotic drug to treat tuberculosis. In several placebo-controlled clinical trials, D-cycloserine has been demonstrated to augment exposition-based psychotherapy. In one of the first of these trials, a single dose of D-cycloserine or placebo was used prior to exposition therapy in a virtual glass elevator in patients

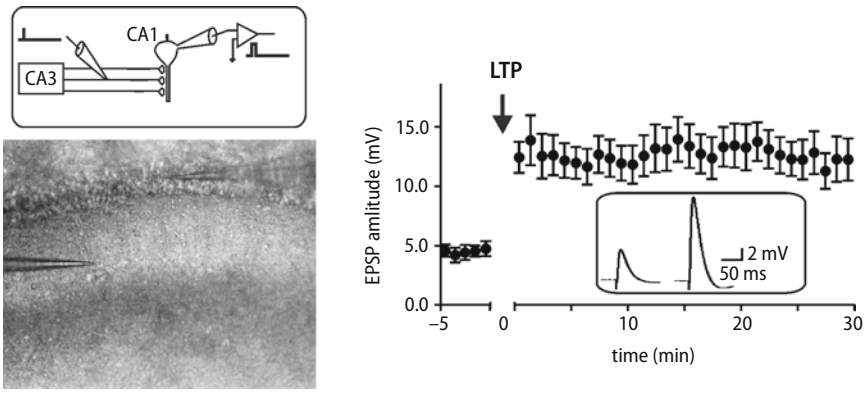

Fig. 1 Induction of long-term potentiation (LTP). EPSPs are evoked by extracellular stimulation of the Schaffer collateral pathway and recorded by whole-cell patch clamp measurements of CA1 pyramidal cells in hippocampal brain slices from adult rats. The *right panel* shows the time course of averaged experiments where LTP was induced by theta-burst stimulation and persistently increased EPSP amplitudes were recorded for 30 min after LTP induction. Modified after [12]

with height phobia. The efficacy of exposition therapy was improved dramatically and sustained differences in the outcome between the D-cycloserine and the placebo group could be detected months later [18].

More innovative approaches to increase brain plasticity include *ampakines* which work by allosterically binding to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors [15, 17]. This boosts the activity of glutamate, a neurotransmitter, and makes it easier to encode memory and to learn. In addition, some members of the ampakine family of drugs may also increase levels of trophic factors such as brain-derived neurotrophic factor (BDNF). Ampakines are tested in phase-II clinical trials for memory enhancement. Another strategy for neuroenhancement is calcium channel modulation which is thought to promote LTP.

These examples demonstrate a potential pharmacological enhancement of learning and memory. However, it is unclear if this sort of pharmacological manipulations of cognitive processes might provoke unwanted adverse effects. Learning should be selective; it is highly undesirable to enhance the learning of adversive or traumatic contents. It could be expected that cognitive enhancers stimulate learning and memory globally; therefore, this class of drugs has a theoretical potential to deteriorate certain psychiatric disorders such as anxiety, obsessive-compulsive disorder or posttraumatic stress disorder.

Ginkgo biloba formulations are extensively used as prescription or over-the-counter medications to improve memory. In US, consumers spend more than 1 billion US$ per year for these drugs. Ginkgo biloba is supposed to have antioxidative effects. This high use is in contrast to the lack of evidence for any efficacy of Ginkgo. In several randomized clinical trials, Ginkgo has not been effective in the treatment of different forms of dementia. After a 6-week course of Ginkgo or placebo, healthy persons did not report any significant change in cognitive performance or self-rating of learning and memory abilities [19].

Attention and vigilance

Apart from learning and memory skills, attention is indispensable to solve cognitive tasks. Focused attention and motivation activate cognitive resources. The most commonly used substance to increase attention and vigilance is *caffeine*. Caffeine binds to a number of different receptors; its activating effect might be explained by its agonistic effects at adenosine receptors.

Modafinil is approved for the treatment of narcolepsia and sleep disorders of shift workers. Despite this narrow indication, Modafinil has a market share of more than 700 million US$/year which indicates a high degree of off-label use. Modafinil can be bought from many websites, mostly from Asian countries. The substance has gained a bad reputation when the runner Kelly White was tested positive for Modafinil at the Athletics World Championships 2003 in Paris and lost her two gold medals. The mode of action of Modafinil is unknown; the substance increases vigilance and prevents fatigue. Other modes of cognitive enhancement could not be demonstrated. Modafinil is massively abused to prevent fatigue after long working hours [1]. Part of the research on this drug is sponsored by military sources as Modafinil is used to allow long periods without sleep in combat situations.

Another highly abused drug is *methylphenidate*. Approved for the treatment of attention-deficit hyperactivity disorder, preliminary studies suggest that a high percentage of US-american college students use methylphenidate to improve their performance in exams. In controlled studies, it has proved difficult to consistently demonstrate a neuroenhancing effect of this drug in healthy probands. A study reported a better solving of spatial tasks after methylphenidate in young adults. However, in a second trial of the same task, probands with placebo scored higher; indicating that learning might even be impaired by the substance [6]. In a similar study, no advantage of methylphenidate could be shown for elderly people [21]. Until now, the high degree of

methylphenidate abuse cannot be completely explained by scientific evidence.

Mood and social interaction

At any given time, every eleventh US-american adult is taking an *antidepressant* which is far beyond the point prevalence of major depression. Selective serotonin reuptake inhibitors (SSRIs) are indicated for a number of other psychiatric conditions such as social phobia, premenstrual syndrome or anxiety disorders but even then, a large number of healthy people seem to abuse antidepressants. The experimental evidence for the use of antidepressants in healthy controls is even more limited than for the use of methylphenidate. There are no studies which show an increase in mood after antidepressant therapy in people without depression. Some very limited efficacy can be demonstrated by more indirect approaches: after a 7-day treatment with two different antidepressants or placebo, healthy probands with antidepressants rated the mood of models on photographies more positive, performed worse on detecting negative emotions and remembered the positive content of stories better than placebo-treated controls [9].

Another class of substances which are highly used to improve mood and social interaction in healthy people are *illegal stimulating drugs* like mescaline, ecstasy or other designer drugs. These drugs have in common that they increase a sense of attachment to the self and others and reduce social anxiety but are devoid of hallucinatory effects. "Entactogens" such as MDMA (3,4-methylenedioxy-*N*-methylamphetamine) and mescaline have even be used as a therapeutic tool in psychoanalytic psychotherapy, in Switzerland as long as 1993 [8].

Sexual performance

Sildenafil is a classical example of a life-style drug which is used to a higher degree by healthy men than by patients with medical conditions. Sildenafil inhibits penile cyclic guanosine monophosphate-specific phosphodiesterase (PDE-5) but is devoid of any central action. Despite an intensive clinical trial program, no effects in females could be demonstrated until now. The pharmaceutical industry urgently seeks drugs which could increase libido and sexual desire in women. After the failure of PDE-5 inhibitors, a number of different compounds are tested in clinical trials. One of the most promising of these drugs is *PT-141*, a synthetic analog of melanocortin. This melanocyte-stimulating hormone regulates the tanning of the skin; PT-141 has been tested as an oral sun screen. During the clinical trials, study participants reported a positive effect on penile erectility, but also an increased sexual desire in both sexes. In animal experiments in rats, female rats showed a dramatic increase in sexual activities and mating. At high doses, female rats even mounted male animals [16].

Conclusions

There is a large market for neuroenhancers. Many healthy people are ready to use and to abuse different classes of drugs, even in the absence of significant evidence for their efficacy and without complete clinical testing. In controlled clinical trials, it has been difficult to prove more than moderate neuroenhancing effects for most of these compounds. A systematic pharmacological enhancement of complex brain functions such as learning, memory, attention or social interactions will be difficult to achieve as long as the neurobiological foundations of these functions are not fully understood. Many experimental models are limited to animal research; it might be difficult to transfer findings from rodents or even fruit flies to humans. Moreover, clinical science is just beginning to realize putative adverse effects of neuroenhancing drugs.

Until now, there has been no adequate discussion in society on the ethical implications of neuroenhancement. Knowledge in this field will certainly increase and more effective substances will be available. It is absolutely necessary to start now thinking about opportunities, dangers and limitations of neuroenhancement.

Conflict of interest statement The authors declare no competing financial interests.

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