

I. Neuroenhancement – a short introduction on medical options

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1. Definition

In its broadest sense, the term ›neuroenhancement‹ refers to different types of measures taken by healthy people with the aim of increasing their performance, for example with regard to cognitive or emotional skills.¹ In contrast to the term ›enhancement‹, which also includes every kind of physical performance improvement (e.g. doping in sports), ›neuroenhancement‹ specifically refers to interventions that influence neurobiological processes in the brain. The focus of the discussion about neuroenhancement mostly lies on biochemical enhancement strategies, especially on the intake of pharmaceutical substances. Apart from that, there are many other ways to influence performance or behaviour, ranging from elements of daily life such as sleep or coffee consumption to physical measures such as brain stimulation. Although there are also considerations to influence other human behaviours such as moral behaviour,² targets of enhancement are primarily cognitive, motivational or emotional functions. This brief introduction will mainly focus on the enhancement of cognitive functions.³

¹ For a detailed overview of the definition of enhancement cf. section 4 (»What is enhancement? On the definition of enhancement«) of part 2 (Ethics of Neuroenhancement) of this expert report.

² For an example that covers this issue, cf. Sellaro et al. 2015. In this article, Sellaro et al. examined whether increasing cognitive control through brain stimulation helps overcome negative bias toward members of social out-groups.

³ A short discussion of three targets of enhancement, cognition, mood and moral, is also provided in section 2 (»What can be enhanced? On the targets of (neuro-)enhancement«) of part 2 (Ethics of Neuroenhancement) of this expert report.

2. Possible targets of neuroenhancement and the measurability of its effects

The human mind consists of a broad variety of cognitive functions. Generally, cognitive performance is classified into different cognitive domains, which are again divided into subdomains.⁴ The cognitive domains that are particularly interesting in the context of neuroenhancement are attention and concentration as well as memory which on their part have an impact on other, more complex domains such as executive functioning (e.g. reasoning and problem solving). There are no cognitive enhancers that augment every cognitive function in equal measures. Each enhancer or enhancing strategy, whether biochemical (e.g. pharmaceutical substances), behavioural (e.g. meditation or mnemonic strategies) or physical (e.g. brain stimulation), has a specific profile regarding its efficacy for different cognitive domains. For example, attention is enhanced by meditation, but not by mnemonic strategies. In contrast, memory can be enhanced through mnemonic strategies, but not by meditation.⁵ Besides, there are cases where the enhancement of one domain by a certain enhancer goes along with the impairment of another cognitive domain. For example, methylphenidate, a prescription drug used to treat attention deficit hyperactivity disorder (ADHD), improves the ability to resist distraction, but impairs cognitive flexibility.⁶

The examination of different enhancement effects on cognitive functions relies on tests and methods used in clinical neuropsychology. Despite being designed to measure cognitive function in a standardised manner, there is a variety of neuropsychological test batteries. Studies show that the effects of pharmacological enhancement on different cognitive domains might differ depending on the cognitive test battery used.⁷ Besides, not only the tests that are used might have an impact on the observable effects, but the effects are also influenced by personal factors, such as the cognitive skills of the individual prior to the enhancement intervention (the so-called *baseline performance*). Most pharmaceuticals

⁴ There are different ways to conceptualise and organise cognitive ability domains. Cognitive functions can be classified either by the general process involved (e.g. attention, memory, or language), or by regional brain functions which are connected to certain cognitive functions, or in a hierarchy based on the complexity of the operations. Inconsistencies described in the clinical and research literature especially concern broad domains that may include multiple component processes. Cf. Harvey 2019: 227.

⁵ Cf. Dresler et al. 2019: 1140.

⁶ Cf. *ibid.*, where they refer to Fallon et al. 2017.

⁷ Cf. *ibid.*, where they refer to Lees et al. 2017.

that are designed to treat conditions like dementia or ADHD primarily show their effects on individuals which have a low baseline performance, whereas for those subjects with a high baseline performance the pharmaceuticals show either no effect or can cause impairments of cognitive functions. This can be explained by the inverted U-model. It shows how optimal performances are achieved with intermediate levels of the targeted neurochemicals while impairments are caused by levels that are either too low or too high.⁸ Basic biological and psychological factors, such as the genotype, gender, hormonal status, age or personality of a person⁹, as well as social and socio-environmental factors, such as social resources, family composition or parental occupation, may also affect the efficiency of a cognitive enhancer.¹⁰

To sum up, the idea of a single pill or intervention improving all our cognitive skills at once and equally in every individual is not tenable. Every enhancer or enhancement strategy is targeted at a different set of cognitive functions and therefore influences different types of brain processes. Their efficiency depends on a variety of personal factors and may vary depending on the measurement method.

3. Enhancement strategies

There are several ways of conceptualising the wide variety of enhancement strategies. For example, one can distinguish between pharmaceutical and non-pharmaceutical methods, between invasive and non-invasive methods, between psychopharmaceuticals / herbal medicine / dietary supplements and endogenous substances or between psychopharmaceuticals, neurostimulation and genetic manipulation.¹¹ In order to get the broadest possible overview of the different enhancement strategies, one can follow Martin Dresler et al. (2019) and differentiate between biochemical, physical and behavioural enhancement strategies.

⁸ Cf. *ibid.* According to Dresler et al., a general baseline-dependency can also be observed in other enhancement strategies. In the cases of computer games, cognitive training or brain stimulation, individuals with a low baseline performance benefit more than individuals with a known high performance. Sleep, in contrast, rather improves memory functions for individuals with a previously detected higher baseline performance in memory or intelligence.

⁹ A study by Smillie and Gökçe shows, for example, that caffeine enhances working memory especially in extraverted individuals. Cf. Smillie / Gökçe 2010 and Dresler et al. 2019: 1140.

¹⁰ Cf. Dresler et al. 2019: 1140.

¹¹ Cf. also part 2 (Ethics of Neuroenhancement) of this expert report.

3.1 *Biochemical strategies*

3.1.1 *Everyday substances and dietary supplements*

There is a wide range of biochemical enhancement strategies. In the field of non-prescription daily substances, the widely socially accepted stimulants caffeine, taurine or glucose are most popular.¹² Numerous studies have shown that the consumption of sugar, coffee or other beverages from caffeine-bearing plants has cognition-enhancing effects.¹³ In case of caffeine, for instance, its cognitive enhancing effects depend on the examination conditions. When information is learned passively, caffeine has performance-enhancing properties. However, this is not the case with regards to intentional learning. The substance can also increase the performance of working memory, but only if the level of difficulty is moderate; in complex tasks, caffeine even tends to reduce performance. Long-term memory does not seem to be affected by caffeine either. However, caffeine increases attention and vigilance and reduces response times; it develops its effects especially in sleep-deprived or exhausted subjects and also in repetitive cognitive tasks.¹⁴ Other drugs that are typically used recreationally have also shown potential enhancement effects on cognition: nicotine might enhance attention;¹⁵ alcohol, while impairing certain cognitive functions, might enhance creative processes.¹⁶

Additionally, there are numerous dietary supplements that promise positive effects on cognitive functions, e. g. preparations containing herbs like salvia,¹⁷ *Bacopa monnieri* (in Indian herbal medicine known as brahmi),¹⁸ ginseng or ginkgo biloba. So far, especially the last two have failed to show ascertainable positive effects on a range of targeted cognitive functions in healthy individuals.¹⁹ Ginkgo biloba, for example, contains high concentrations of flavonoids and terpenoids, which were assumed to

¹² However, there are several controversial debates on possible health-damaging effects of these substances. Cf. for example Cappelletti 2015.

¹³ Cf. Dresler et al. 2019: 1138, where they refer to Smith et al. 2011; Glade 2010 and Nehlig 2010.

¹⁴ Cf. Gründer / Bartsch 2014: 1539.

¹⁵ Cf. Dresler et al. 2019: 1139, where they refer to Warburton 1992 and Valentine / Sofuoglu 2018. Cf. also Gründer / Bartsch 2014: 1540.

¹⁶ Cf. on this Jarosz / Colflesh / Wiley 2012 and Benedek et al. 2017.

¹⁷ Cf. Dresler et al. 2019: 1138, who refer to Tildesley et al. 2003.

¹⁸ Cf. Kongkeaw et al. 2014.

¹⁹ Cf. Dresler et al. 2019: 1129, who refer to Laws / Sweetnam / Kondel 2012 and Geng et al. 2010.

counteract oxidative stress as antioxidants. However, according to a systematic literature review carried out by Andreas G. Franke and Klaus Lieb in 2010, ginkgo biloba showed no positive effects on reaction time and mood of healthy people and no consistent effects on vigilance, attention, memory, and subjective self-assessment.²⁰

3.1.2 (Psycho-)Pharmaceuticals

Much of the discussion about neuroenhancement revolves around the use of drugs that were designed to treat conditions such as dementia, ADHD or depression. In the media, medications that are used off-label to improve cognition are often referred to as ›intelligent drugs‹. For various reasons, determining how broadly intelligent drugs are used is only possible to a limited extent. Results might vary depending on the definition of neuroenhancement, heterogeneous investigation populations or the type of investigation (samplings, tolls etc.). Although determining the prevalence of illegal substances and medication used for enhancing purposes is linked to certain difficulties, there have been tolls and surveys examining how widespread biochemical neuroenhancement strategies are.²¹ Since 2009, there have been three representative surveys on neuroenhancement in Germany carried out by the Robert Koch Institute and the Deutsche Angestellten-Krankenkasse (German employee health insurance, DAK).²² According to the population-based study (Studie zum Konsum leistungsbeeinflussender Mittel in Alltag und Freizeit, KOLIBRI) by the Robert Koch Institute in 2010, 1.5% of the German population used medication without medical indications or illegal substances for enhancement purposes.²³ The study also reveals that younger people and people with high weekly working hours are more likely to take intelligent drugs.²⁴ In 2009 and 2015, the DAK conducted online surveys on 3,000 and 5,000 DAK insured persons. The evaluation of the online surveys shows that about 5% (2009) and 6.7% (2015) of employees between the ages of 20 and 50 take medication or other substances for enhancement purposes without medical indications. In their second study from 2015,

²⁰ Cf. Franke / Lieb 2010: 858.

²¹ The discussion was mainly initiated by a poll carried out by *Nature* magazine in 2008, cf. for this Maher 2008.

²² Cf. Müller / Freude / Kersten 2019.

²³ Cf. Schilling et al. 2012: 2.

²⁴ The usage of substances like methylphenidate seems to be especially high among students. Cf. on this Carton et al. 2018 and Cândido et al. 2019.

they conclude that especially employees with simple or insecure jobs belong to the risk groups for medication abuse linked to enhancement.²⁵

Especially D-amphetamine and methylphenidate have well documented cognitive-enhancing properties in healthy test subjects.²⁶ Amphetamines and methylphenidate, both used to treat ADHD,²⁷ block presynaptic norepinephrine and dopamine transporters. As a result, they increase monoaminergic neurotransmission due to a lack of negative feedback.²⁸ Amphetamine is known for increasing long-term attention, counteracting the reduction of performance after sleep deprivation and overall reducing the need for sleep.²⁹ A review of single dose studies conducted by Anke Linssen et al. (2014) comes to the conclusion that methylphenidate improves cognitive performance especially in the domains of working memory and speed of processing; to a lesser extent it may also improve verbal learning and memory, attention and vigilance as well as reasoning and problem solving.³⁰ However, according to Dresler et al., the empirical evidence for the efficacy of synthetic stimulants for enhancing brain function and cognition in healthy subjects is often markedly lower than assumed in theoretical discussion. As mentioned before, the effects of methylphenidate and other synthetic stimulants are not only baseline-dependent, but placebo effects must be considered as well.³¹

Another drug that is considered as potential neuroenhancer is modafinil, a medication originally used to treat sleepiness due to narcolepsy, shift work sleep disorder, or obstructive sleep apnoea; depression in bipolar disorder, fatigue syndrome in depression and ADHD are also examined as further potential indications.³² The exact therapeutic effect mechanism of modafinil is still unknown. However, studies have shown that it induces an increase in various monoamines such as dopamine, noradrenaline and serotonin. It was also proven that modafinil causes a histamine release into the central nervous system, which promotes vigilance. Yet, its effectiveness as a neuroenhancer in healthy, non-sleep-deprived subjects remains controversial among experts. A meta-analysis by Ruair-

²⁵ Cf. Deutsche Angestellten-Krankenkasse 2009; id. 2015.

²⁶ Cf. Gründer / Bartsch 2014: 1540.

²⁷ Under German law, amphetamines, which are an approved medication to treat ADHD in the US, are classified as illegal substances. In Germany, mainly methylphenidate, best known under its trading name Ritalin, is used for the treatment of ADHD and less frequently for narcolepsy.

²⁸ Cf. Franke / Lieb 2010: 854.

²⁹ Cf. Gründer / Bartsch 2014: 1539.

³⁰ Cf. Linssen 2014: 973.

³¹ Cf. for example Cropsey et al. 2017.

³² Cf. Förstl 2009: 843.

idh Battleday and Anna-Katharine Brem (2015) concluded that modafinil has genuine cognitive enhancing effects on some cognitive domains without causing severe side effects or changes in mood. In studies that used complex assessments, modafinil appears to improve attention, executive functions and learning consistently. In contrast, only half of the studies included in the meta-analysis that used basic testing paradigms came to similar results.³³ Zackary Cope et al. (2017) also describe modafinil as an effective cognitive enhancer in healthy adult subjects. Compared to other stimulants, the cognitive enhancing effect is achieved at doses that do not result in hyperactivity.³⁴ In this sense, one can conclude that it acts similarly to methylphenidate, nevertheless, without the adverse side effects of the amphetamine-like substances.³⁵ In addition, studies indicate that no substantial baseline-dependent effects appear to be caused.³⁶

Antidementia drugs, such as acetylcholinesterase inhibitors and memantine, are also considered to initiate cognitive enhancing effects in healthy subjects. So far, only few studies exist on the issue. Most of them examine the medication donepezil.³⁷ Donepezil is a potent acetylcholinesterase inhibitor; by blocking the acetylcholinesterase, the enzymatic breakdown of acetylcholine in the synaptic cleft is inhibited and the concentration of acetylcholine in the synaptic cleft is increased.³⁸ In subjects suffering from dementia, this appears to reduce symptoms of the disease. However, a meta-analysis by Dimitris Repantis et al. (2010) on acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals indicates that there is no consistent evidence for a cognitive enhancing effect of donepezil in healthy people. According to six small trials, donepezil might improve the retention of training on complex aviation tasks and verbal memory for semantically processed words. Nevertheless, results were especially inconsistent regarding positive effects on episodic memory.³⁹ A reduction of memory and attention deficits was only observed in subjects with a 24-hour sleep deprivation but not in rested individuals.⁴⁰

³³ Cf. on this Battleday / Brem 2015.

³⁴ Cf. on this Cope et al. 2017.

³⁵ Cf. Förstl 2009: 843.

³⁶ Cf. d'Angelo / Savulich / Sahakian 2017: 3260.

³⁷ Cf. *ibid.*

³⁸ Cf. Brewster et al. 2019: 159.

³⁹ Cf. d'Angelo / Savulich / Sahakian 2017: 3260, who refer to Repantis / Laisney / Heuser 2010.

⁴⁰ Cf. Repantis / Laisney / Heuser 2010, who refer to Chuah / Chee 2008.

3.1.3 Microdosing

Besides the use of widespread illegal substances that are not only taken for recreational, but also for performance enhancing purposes—e.g. amphetamines (speed or crystal meth), cocaine and novel psychoactive substances (NPS, also called designer drugs)—, a trend has emerged in recent years which promotes the intake of minimal doses of mostly illegal psychedelic substances, referred to as microdosing. The idea behind this is that the regular ingestion of very small quantities of psychedelic substances like lysergic acid diethylamide (LSD) and psilocybin might lead to mental health benefits such as an improvement of creativity and attention and a reduction of depression and anxiety. Research on psychedelics has been performed for decades and despite highly controversial debates, it provides evidence for therapeutic effects of full-doses.⁴¹ In contrast, since microdosing is quite a young phenomenon there is barely any empirical research. Vince Polito and Richard J. Stevenson (2019) have summarised the results of the four scientific articles on microdosing existing to date.⁴² Three of them, describing qualitative interview studies and observational studies, report positive outcomes, namely an improvement of mood, energy levels and cognition, open-mindedness and creativity as well as a reduction of negative attitudes and emotions.⁴³ These results are based on interviews or small-scale non-blinded, non-placebo-controlled experiments; one must assume that there are significant placebo effects. The only randomised, double-blind, placebo-controlled trial on LSD microdosing by Steliana Yanakieva et al. (2019) concludes that microdosing LSD can lead to changes in time perception. However, benefits on health, cognition or well-being were not investigated.⁴⁴ In summary, in view of promising results of existing research on full-dose psychedelics it has yet to be shown whether small doses of psychedelics could have cognitive enhancing effects. Further empirical research is required to determine the effectiveness of microdosing.

3.1.4 Genetic editing

For some years, a new generation of genetic engineering techniques, including CRISPR-Cas9, has been revolutionising the whole field of genetic editing, promising more precise, more effective and more economic

⁴¹ Cf. Prochazkova et al. 2018: 3402–3403; Anderson et al. 2019: 732.

⁴² Cf. Polito / Stevenson 2019.

⁴³ Cf. Johnstad 2018; Prochazkova et al. 2018 and Anderson et al. 2019.

⁴⁴ Cf. Yanakieva et al. 2019.

interventions in the human genome.⁴⁵ These innovations have made the once seemingly distant, unrealistic idea of improving cognitive performance through genetic engineering more probable. However, apart from the ethical problems that would accompany such interventions, this research area is still in its early days. So far, the question of which cognitive functions are influenced by which gene expressions has been the subject of basic research. The idea of cognitive enhancement through genetic editing is thus only subject of hypothetical considerations. An article by Andrea Lavazza (2018) examines the possibilities and critical issues related to enhancement via genetic engineering.⁴⁶ He describes certain difficulties besides ethical issues that arise in this context. Although it is a well-established belief that genes are not only the basis of inheritable traits but also of cognitive abilities, the idea of one gene or a small set of genes that can be identified with a certain cognitive function might be misleading. Although certain cognitive functions can be linked to a single gene or a small group of genes, complex brain processes do not seem to depend on these alone. The main cognitive functions involve different brain areas and probably a cascade of neuronal activations which requires the expression of many genes.⁴⁷ Besides, research on complex epigenetic mechanisms shows that the expression of genes also depends on their interaction with the development and on the external environment of the individual.⁴⁸

In addition to the fact that it is difficult or maybe even impossible to discover a specific gene (or a small set of genes) that is responsible for a specific cognitive function, there are certain risks regarding the insertion of modified gene sequences into the cells of the human body. In gene therapy, mainly viruses are used as vectors to deliver genetic material into cells. This technique bears several risks, for example, the risk of an immune reaction or the incorrect integration of the modified genetic material into the genome. Although techniques like CRISPR-Cas9 appear to be more accurate, the risk of incorrect gene-cuts or inaccurate insertion events remains. Moreover, for cognitive enhancement, vectors or other insertion techniques would have to traverse the blood-brain barrier to reach the neurons where the target genes are mainly expressed.⁴⁹

⁴⁵ First described by Doudna / Charpentier 2014.

⁴⁶ Cf. Lavazza 2018.

⁴⁷ Cf. *ibid.*: 390.

⁴⁸ Cf. *ibid.* Lavazza refers to Bonduriansky / Day 2018.

⁴⁹ Cf. *ibid.*: 389.

In order to get from hypothetical considerations to actual possible applications, significant amount of research is still required, which can only be partly justified to this date. Considering the current state of knowledge about gene therapy, experimental applications of genetic editing should only be authorised on patients likely to pass away due to a severe disease that cannot be treated otherwise or on patients suffering from other serious diseases. Since genetic editing techniques intervene in complex processes that are not yet completely understood, modifying the expression of one gene could lead to unwanted, serious, and irreversible effects. Accordingly, non-clinical applications of new gene editing techniques can currently be ruled out because of general safety issues.⁵⁰

3.2 *Physical strategies*

3.2.1 Brain stimulation

In the field of physical enhancement strategies, especially brain stimulation techniques are discussed regarding their potential cognitive enhancement effects on healthy subjects. Brain stimulation techniques have been developed for therapeutic purposes in psychiatry and neurology. Today they are used to treat conditions such as Parkinson's disease, epilepsy, chronic pain, or major depression. Some of these methods also show enhancing effects on the cognition of healthy individuals.⁵¹ A distinction is generally made between two main types of brain stimulation: invasive and non-invasive methods.

Deep brain stimulation (DBS) is an invasive brain stimulation technique. It requires a neurosurgical procedure, during which a medical device—a neurostimulator which sends electrical impulses (also called *brain pacemaker*)—is placed inside the brain. It is considered as a promising treatment for a variety of neurological and psychiatric conditions.⁵² Besides, studies have shown that DBS might enhance the memory of patients with intractable epilepsy.⁵³ However, since it requires a neurosurgical procedure and is, therefore, associated with a risk that is not proportionate without medical indication, it is restricted to subjects with pathological conditions.

⁵⁰ Cf. Lavazza 2018: 391.

⁵¹ Cf. Dresler et al. 2013: 335. Cf. also McKinley et al. 2011.

⁵² Cf. Aum / Tierney 2018.

⁵³ Cf. Inman et al. 2018 and Suthana et al. 2012.

There are also several non-invasive methods that are associated with rather low risks and minor side effects, for example electrical stimulation methods such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial pulsed current stimulation (tPCS), or transcutaneous vagus nerve stimulation (tVNS).⁵⁴ In the case of these non-invasive electric stimulation methods, usually electrodes that are connected with a battery-powered device are placed on the head. This enables the stimulation of the human brain using electrical impulses. There are other, similar methods that work with magnetic impulses (e.g. transcranial magnetic stimulation, TMS). Those methods use a magnetic coil that is applied tangentially to the skull and creates a short magnetic field. Either way, brain activity is influenced by modulating the membrane potential to provoke cognitive, emotional, and behavioural changes. The stimulation is intended to increase or inhibit the activity, connectivity and sensitivity of nerve cells. These techniques are, for instance, used in research. In combination with imaging methods, they allow an investigation into causal relationships between brain areas and behaviour. A small number of them are also used in clinical practice (mostly tDCS and TMS).⁵⁵ However, recent studies have questioned whether some of the commonly used techniques (like tDCS) have neurophysiologically meaningful effects at all.⁵⁶ Although there are a number of studies that suggest enhancing effects on cognitive functions such as memory and learning,⁵⁷ it is impossible to assume that brain stimulation methods in general have clear and simple enhancing effects.⁵⁸ Thus, their efficacy strongly depends on applying the devices and electrodes to the correct region; individual variation in anatomy and response often occurs.⁵⁹ Another problem concerns the clear identification of brain areas and cognitive functions. To achieve a response linked to certain cognitive skills, it is crucial to understand which area must be stimulated. This area of research must be further investigated.⁶⁰ Besides electrical and magnetic stimulation methods, techni-

⁵⁴ Cf. Dresler et al. 2019: 1139. Transcranial means ›through the skull (cranium)‹; transcutaneous ›through the skin (cutis)‹.

⁵⁵ Cf. Science Media Center Germany 2019.

⁵⁶ Cf. Dresler et al. 2019: 1139, who refer to Lafon et al. 2017; Thibaut et al. 2017; Parkin et al. 2018 and Grossman et al. 2017.

⁵⁷ Cf. Dresler et al. 2013: 536.

⁵⁸ Cf. Dresler et al. 2019: 1139.

⁵⁹ Cf. Dresler et al. 2013: 536.

⁶⁰ Cf. *ibid.*: 536.

ques that use optical stimulation via lasers or acoustic stimulation⁶¹ are also assumed to have a potential for cognitive enhancement.

3.2.2 Biohacking devices

In recent years, a new debate on physical tools that assist cognitive functioning arose in the context of biohacking communities. The term ›biohacking‹ describes a do-it-yourself citizen science that merges body modification with technology. Although this community of hobbyist software developers is primarily interested in tracking their daily physical and biochemical activities in order to maintain a healthy lifestyle based on the data they gain, there are also attempts to create devices that enhance cognitive functions directly.⁶² These include technical devices such as wearable electronic memory aids, augmented reality gadgets or neural implants that—under controlled laboratory settings—showed enhancing effects on human memory.⁶³ However, do-it-yourself enhancement methods bear specific risks that should not be underestimated. In this context, clear regulations must yet be determined.

3.3 *Behavioural strategies*

In addition to biochemical and physical methods, there are methods and activities belonging to our everyday or cultural activities that help improve certain cognitive skills. These include sleep, physical exercise, learning a second language as well as meditation, computerized training, or mnemonic techniques.

3.3.1 Sleep

The neural mechanisms underlying the effects of sleep on cognitive functions like memory consolidation are not yet completely understood. However, research literature suggests that enhancing cognitive functions, especially memory and creativity, is one important function of sleep.⁶⁴ Accordingly, sleep deprivation impairs neurocognitive functioning, parti-

⁶¹ Cf. Dresler et al. 2019: 1139.

⁶² Cf. Yetisen 2018: 744.

⁶³ Cf. Dresler et al. 2019: 1139, who refer i.a. to Warwick 2014 and Hampson et al. 2018.

⁶⁴ Cf. Dresler et al. 2013: 532, who refer to Diekelmann / Born 2010. On the effects of sleep on memory consolidation also cf. Chambers 2017.

cularly within the domains of sustained attention and executive function. At the same time, there are studies that suggest that the neurocognitive effects of sleep restriction are differentially tolerated by different age groups. Elderly subjects are affected more than younger adult subjects.⁶⁵

3.3.2 Physical exercise

It is well known that regular physical activity helps to stay healthy in general. Furthermore, there is evidence suggesting that regular aerobic exercise has beneficial effects on brain functions and cognition.⁶⁶ A meta-analysis of randomised controlled trials by Patrick J. Smith et al. (2010) concluded that aerobic exercise training enhances attention, processing speed and executive function.⁶⁷ Although data on the neural mechanism underlying the effects of physical exercise on human cognition is still relatively sparse, there is sufficient evidence that physical exercise enhances cognitive functions throughout the lifespan.⁶⁸

3.3.3 Cultural activities

Several studies have shown that music training has a broad range of positive effects on cognition. Playing an instrument requires constant training of highly specialised sensorimotor, auditory, and auditory-spatial skills. It was observed that the brains of people who play an instrument differ from those who do not. This leads to the question if music training or pre-existing biological dispositions for musicality are responsible for this difference. A meta-analysis by Assal Habibi et al. (2018) concludes that music training induces brain and behavioural changes in children, which are not attributable to pre-existing biological traits.⁶⁹ In addition, music training also shows cognition enhancing effects on older adults. Sofia Seinfeld et al. (2013) describe a significant improvement of executive functions, inhibitory control and divided attention, a trend indicating an enhancement of visual scanning and motor ability and finally a decrease of depression and an evocation of positive mood states linked to regular

⁶⁵ Cf. Lowe / Safati / Hall 2017: 600.

⁶⁶ Cf. Dresler et al. 2013: 532, who refer to Hillman / Erickson / Kramer 2008.

⁶⁷ Cf. Smith et al. 2010. For other meta-analyses on cognition enhancing effects of physical exercise that come to similar results cf. Chang et al. 2012; Roig et al. 2013 and Hötting / Röder 2013.

⁶⁸ Cf. Dresler et al. 2013: 532.

⁶⁹ Cf. Habibi et al. 2018.

piano lessons given to older adults.⁷⁰ Besides instrumental training, learning a second language similarly shows enhancing effects. For example, a study by Ellen Bialystok, Fergus I. M. Craik and Gigi Luk (2012) concludes that bilingualism might protect against cognitive decline in older age.⁷¹ And even contemporary dance improvisation might be a useful way to improve cognitive flexibility in aging. A study by Olivier A. Coubard et al. (2011), for example, suggests that high attentional dance improvisation improves switching attention in older adults.⁷²

3.3.4 Cognitive training techniques

There are several training techniques such as mnemonic techniques or meditation that have been developed and used for centuries to enhance certain cognitive functions. Mnemonic training might lead to superior memory performance⁷³ while meditation training enhances attention processes and mindfulness.⁷⁴ While these results are widely accepted, the effects of computerised training and commercial computer games are rather controversial. There are concerns that especially violent computer games might have a negative impact on social behaviour, leading to an increase of aggression and reduction of empathy.⁷⁵ However, there is a growing interest in computerised training programs that are designed to enhance long term memory or brain plasticity in healthy or mildly impaired older adults to prevent conditions such as dementia.⁷⁶ However, recent studies give rise to doubt concerning the efficacy of computer training programs and the transferability of their positive effects on cognitive skills outside the computer game or training program.⁷⁷

In contrast to biochemical or physical enhancement strategies, behavioural methods are hardly ever linked to health risks and ethical concerns. In some cases, their impact on human cognition seems to be greater than the impact of pharmaceutical or physical interventions. In addition, they are easily accessible to a large majority of people, for example in the case

⁷⁰ Cf. Seinfeld et al. 2013.

⁷¹ Cf. Bialystok / Craik / Luk 2012.

⁷² Cf. Coubard et al. 2011.

⁷³ Cf. Dresler et al. 2017.

⁷⁴ Cf. Dresler et al. 2019: 1139, who refer to Chiesa / Calati / Serretti 2011 and Sedlmeier et al. 2012.

⁷⁵ Cf. Dresler et al. 2013: 535, who refer to Kirsh / Mounts 2007 and Anderson et al. 2010.

⁷⁶ Cf. Dresler et al. 2013: 535, who refer to Tardif / Simard 2011. Also cf. Hill et al. 2017.

⁷⁷ Cf. Dresler et al. 2019: 1139, who refer to Simons et al. 2016; Melby-Lervåg / Redick / Hulme 2016 and Stojanoski et al. 2018.

of physical exercise and meditation. However, they are time-consuming, which is why research on more efficient means of improving human performance will certainly continue to be conducted.

References

- Anderson, C. A. / Shibuya, A. / Ihori, N. / Swing, E. L. / Bushman, B. J. / Sakamoto, A. / Rothstein, H. R. / Saleem, M. (2010): Violent video game effects on aggression, empathy, and prosocial behavior in eastern and western countries: a meta-analytic review. In: *Psychological Bulletin*, 136 (2), 151–173.
- Anderson, T. / Petranker, R. / Dinh-Williams, L.-A. / Rosenbaum, D. / Weissman, C. / Hapke, E. / Farb, N. A. S. (2019): Microdosing Psychedelics: Personality, mental health, and creativity differences in microdosers. In: *Pharmacology* 236, 731–740.
- d'Angelo, L. C. / Savulich, G. / Sahakian, B. J. (2017): Lifestyle use of drugs by healthy people for enhancing cognition, creativity, motivation and pleasure. In: *British Journal of Pharmacology* 174, 3257–3267.
- Aum, D. J. / Tierney, T. S. (2018): Deep brain stimulation: foundations and future trends. In: *Frontiers in Bioscience* 23, 162–182.
- Battleday, R. M. / Brem, A.-K. (2015): Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. In: *European Neuropsychopharmacology* 25 (11), 1865–1881.
- Benedek, M. / Panzierer, L. / Jauk, E. / Neubauer, A. C. (2017): Creativity on tap? Effects of alcohol intoxication on creative cognition. In: *Consciousness and Cognition* 56, 128–134.
- Bialystok, E. / Craik, F. I. M. / Luk, G. (2012): Bilingualism: Consequences for mind and brain. In: *Trends in Cognitive Sciences* 16 (4), 240–250.
- Bonduriansky, R. / Day, T. (2018): *Extended Heredity: A New Understanding of Inheritance and Evolution*. Princeton: Princeton University Press.
- Brewster, J. T. / Dell'Acqua, S. / Thach, D. Q. / Sessler, J. L. (2019): Classics in Chemical Neuroscience: Donepezil. In: *ACS Chemical Neuroscience* 10 (1), 155–167.
- Cândido, R. C. F. / Perini, E. / Pádua, C. M. / Junqueira, D. R. (2019): Prevalence of and factors associated with the use of methylphenidate for cognitive enhancement among university students. In: *Einstein (Sao Paulo)*, eAO4745.
- Cappelletti, S. / Piacentino, D. / Sani, G. / Aromatario, M. (2015): Caffeine: Cognitive and Physical Performance Enhancer or Psychoactive Drug? In: *Current Neuropharmacology* 13, 71–88.
- Carton, L. / Cabé, N. / Ménard, O. / Deheul, S. / Caous, A.-S. / Devos, D. / Cottencin, O. / Bordet, R. (2018): Pharmaceutical cognitive doping in students: A chimeric way to get-a-head? In: *Therapies* 73 (4), 331–339.
- Chambers, A. M. (2017): The role of sleep in cognitive processing: focusing on memory consolidation. In: *Wires Cognitive Science* 8 (3), e1433.
- Chang, Y. K. / Labban, J. D. / Gapin, J. I. / Etnier, J. L. (2012): The effects of acute exercise on cognitive performance: a meta-analysis. In: *Brain Research* 1453, 87–101.

- Chiesa, A. / Calati, R. / Serretti, A. (2011): Does mindfulness training improve cognitive abilities? A systematic review of neuropsychological findings. In: *Clinical Psychology Review* 31 (3), 449–464.
- Chuah L. Y. / Chee, M. W. (2008): Cholinergic augmentation modulates visual task performance in sleep-deprived young adults. In: *The Journal of Neuroscience* 28 (44), 11369–11377.
- Cope, Z. A. / Minassian, A. / MacQueen, D. A. / Milienne-Periot, M. / Geyer, M. A. / Perry, W. / Young, J. W. (2017): Modafinil improves attentional performance in healthy, non-sleep deprived humans at doses not inducing hyperarousal across species. In: *Neuropharmacology* 125, 254–262.
- Coubard, O. A. / Duret, S. / Lefebvre, V. / Lapalus, P. / Ferrufino, L. (2011): Practice of contemporary dance improves cognitive flexibility in aging. In: *Frontiers in Aging Neuroscience* 3, 13.
- Cropsey, K. L. / Schiavon, S. / Hendricks, P. S. / Froelich, M. / Lentowicz, I. / Fargason, R. (2017): Mixed-amphetamine salts expectancies among college students: Is stimulant induced cognitive enhancement a placebo effect? In: *Drug and Alcohol Dependence* 178, 302–309.
- Deutsche Angestellten Krankenkasse (ed.) (2009): Gesundheitsreport 2009. Analyse der Arbeitsunfähigkeitsdaten. Schwerpunktthema Doping am Arbeitsplatz. Hamburg: DAK.
- Deutsche Angestellten Krankenkasse (ed.) (2015): DAK-Gesundheitsreport 2015. Hamburg: DAK.
- Diekemann, S. / Born, J. (2010): The memory function of sleep. In: *Nature Reviews Neuroscience* 11, 114–126.
- Doudna, J. A. / Charpentier, E. (2014): The new frontier of genome engineering with CRISPR-Cas9. In: *Science* 346 (6213), 1258096.
- Dresler, M. / Sandberg, A. / Ohla, K. / Bublit, C. / Trenado, C. / Mroczo-Wąsowicz, A. / Kühn, S. / Repantis, D. (2013): Non-pharmacological cognitive enhancement. In: *Neuropharmacology* 64, 529–543.
- Dresler, M. / Shirer, W. R. / Konrad, B. N. / Müller, N. C. J. / Wagner, I. C. / Fernández, G. / Czigis, M. / Greicius, M. D. (2017): Mnemonic training reshapes brain networks to support superior memory. In: *Neuron* 93 (5), 1227–1235.e6.
- Dresler, M. / Sandberg, A. / Bublit, C. / Ohla, K. / Trenado, C. / Mroczo-Wąsowicz, A. / Kühn, S. / Repantis, D. (2019): Hacking the Brain: Dimensions of Cognitive Enhancement. In: *ACS Chemical Neuroscience* 19, 1137–1148.
- Fallon, S. J. / van der Schaaf, M. E. / Ter Huurne, N. / Cools, R. (2017): The Neurocognitive Cost of Enhancing Cognition with Methylphenidate: Improved Distractor Resistance but Impaired Updating. In: *Journal of Cognitive Neuroscience* 29 (4), 652–663.
- Förstl, H. (2009): Neuro-Enhancement. Gehirndoping. In: *Nervenarzt* 80, 840–846.
- Franke, A. G. / Lieb, K. (2010): Pharmakologisches Neuroenhancement und »Hirndoping«. Chancen und Risiken. In: *Bundesgesundheitsblatt* 53, 853–860.
- Geng, J. / Dong, J. / Ni, H. / Lee, M. S. / Wu, T. / Jiang, K. / Wang, G. / Zhou, A. L. / Malouf, R. (2010): Ginseng for cognition. In: *Cochrane Database of Systematic Reviews* 12, CD007769.
- Glade, M. J. (2010): Caffeine—Not just a stimulant. In: *Nutrition* 26 (10), 932–938.

- Grossman, N. / Bono, D. / Dedic, N. / Kodandaramaiah, S. B. / Rudenko, A. / Suk, H. J. / Cassara, A. M. / Neufeld, E. / Kuster, N. / Tsai, L. H. / Pascual-Leone, A. / Boyden, E. S. (2017): Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. In: *Cell* 169, 1029.
- Gründer, G. / Bartsch, T. (2014): Neuroenhancement. In: *Nervenarzt* 85, 1536–1543.
- Habibi, A. / Damasio, A. / Ilari, B. / Sachs, M. E. / Damasio, H. (2018): Music training and child development: a review of recent findings from longitudinal study. In: *Annals of the New York Academy of Sciences* 1423, 73–81.
- Hampson, R. E. / Song, D. / Robinson, B. S. / Fetterhoff, D. / Dakos, A. S. / Roeder, B. M. / She, X. / Wicks, R. T. / Witcher, M. R. / Couture, D. E. / Laxton, A. W. / Munger-Clary, H. / Popli, G. / Sollman, M. J. / Whitlow, C. T. / Marmarelis, V. Z. / Berger, T. W. / Deadwyler, S. A. (2018): Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall. In: *Journal of Neural Engineering* 15 (3), 036014.
- Harvey, P. D. (2019): Domains of cognition and their assessment, In: *Dialogues in Clinical Neuroscience* 21 (3), 227–237.
- Hill, N. T. M. / Mowszowski, L. / Naismith, S. L. / Chadwick, V. L. / Valenzuela, M. / Lampit, A. (2017): Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. In: *The American Journal of Psychiatry* 174 (4), 329–340.
- Hillman, C. H. / Erickson, K. I. / Kramer, A. F. (2008): Be smart, exercise your heart: exercise effects on brain and cognition. In: *Nature Reviews Neuroscience* 9, 58–65.
- Hötting, K. / Röder, B. (2013): Beneficial effects of physical exercise on neuroplasticity and cognition. In: *Neuroscience & Biobehavioral Reviews* 37 (8), 2243–2257.
- Inman, C. S. / Manns, J. R. / Bijanki, K. R. / Bass, D. I. / Hamann, S. / Drane, D. L. / Fasano, R. E. / Kovach, C. K. / Gross, R. E. / Willie, J. T. (2018): Direct electrical stimulation of the amygdala enhances declarative memory in humans. In: *PNAS* 115 (1), 93–103.
- Jarosz, A. F. / Colflesh, G. J. / Wiley, J. (2012): Uncorking the muse: alcohol intoxication facilitates creative problem solving. In: *Consciousness and Cognition* 21 (1), 487–493.
- Johnstad, P. G. (2018): Powerful substances in tiny amounts: An interview study of psychedelic microdosing. In: *Nordic Studies on Alcohol and Drugs* 35, 39–51.
- Kirsh, S. J. / Mounts, J. R. W. (2007): Violent video game play impacts facial emotion recognition. In: *Aggressive Behaviors* 33 (4), 353–358.
- Kongkeaw, C. / Dilokthornsakul, P. / Thanarangsarit, P. / Limpeanchob, N. / Norman Scholfield, C. (2014): Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract. In: *Journal of Ethnopharmacology* 151 (1), 528–535.
- Lafon, B. / Henin, S. / Huang, Y. / Friedman, D. / Melloni, L. / Thesen, T. / Doyle, W. / Buzsaki, G. / Devinsky, O. / Parra, L. C. / Liu, A. A. (2017): Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. In: *Nature Communications* 8, 1199.
- Lavazza, A. (2018): Cognitive Enhancement through Genetic Editing: a New Frontier to explore (and to regulate)? In: *Journal of Cognitive Enhancement* 2, 388–396.

- Laws, K. R. / Sweetnam, H. / Kondel, T. K. (2012): Is Ginkgo biloba a cognitive enhancer in healthy individuals? A meta-analysis. In: *Human Psychopharmacology* 27 (6), 527–533.
- Lees, J. / Michalopoulou, P. G. / Lewis, S. W. / Preston, S. / Bamford, C. / Collier, T. / Kalpakidou, A. / Wykes, T. / Emsley, R. / Pandina, G. / Kapur, S. / Drake, R. J. (2017): Modafinil and cognitive enhancement in schizophrenia and healthy volunteers: the effects of test battery in a randomised controlled trial. In: *Psychological Medicine* 47 (13), 2358–2368.
- Linssen, A. M. W. / Sambeth, A. / Vuurman, E. F. P. M. / Riedel, W. J. (2014): Cognitive effects of methylphenidate in healthy volunteers: a review of single dose studies. In: *International Journal of Neuropsychopharmacology* 17 (6), 961–977.
- Lowe, C. J. / Safati, A. / Hall, P. A. (2017): The neurocognitive consequences of sleep restriction: A meta-analytic review. In: *Neuroscience and Biobehavioral Reviews* 80, 586–604.
- Maher, B. (2008): Poll results: look who's doping. In: *Nature* 452 (7188), 674–675.
- McKinley, R. A. / Bridges, N. / Walters, C. M. / Nelson, J. (2012): Modulating the brain at work using noninvasive transcranial stimulation. In: *NeuroImage* 59, 129–137.
- Melby-Lervåg, M. / Redick, T. S. / Hulme, C. (2016): Working memory training does not improve performance on measures of intelligence or other measures of »far transfer«: Evidence from a meta-analytic review. In: *Perspectives on Psychological Science*, 11 (4), 512–534.
- Müller, G. / Freude, G. / Kersten, N. (2019): Neuroenhancement in Deutschland am Beispiel von vier Berufsgruppen. Neuroenhancement in four occupations in Germany. In: *Gesundheitswesen*, doi: 10.1055/a-1026-6157.
- Nehlig, A. (2010): Is caffeine a cognitive enhancer? In: *Journal of Alzheimer's Disease* 20, 85–94.
- Parkin, B. L. / Bhandari, M. / Glen, J. C. / Walsh, V. (2018): The physiological effects of transcranial electrical stimulation do not apply to parameters commonly used in studies of cognitive neuromodulation. In: *Neuropsychologia* 128, 332–339.
- Polito, V. / Stevenson, R. J. (2019): A systematic study of microdosing psychedelics. In: *PLoS ONE* 14 (2), e0211023.
- Prochazkova, L. / Lippelt, D. P. / Colzato, L. S. / Kuchar, M. / Sjoerds, Z. / Hommel, B. (2018) Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting. In: *Psychopharmacology* 235, 3401–3413.
- Repantis, D. / Laisney, O. / Heuser, I. (2010): Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. In: *Pharmacological Research* 61 (6), 473–481.
- Roig, M. / Nordbrandt, S. / Geertsen, S. S. / Nielsen, J. B. (2013): The effects of cardiovascular exercise on human memory: a review with meta-analysis. In: *Neuroscience & Biobehavioral Reviews* 37 (8), 1645–1666.
- Schilling, R. / Hoebel, J. / Müters, S. / Lange, C. (2012): *Pharmakologisches Neuroenhancement*. In: *GBE kompakt* 3 (3), ed. by Robert Koch-Institut Berlin.
- Science Media Center Germany (ed.) (2019): *Nicht-invasive Hirnstimulation – neue Möglichkeiten in Therapie und Forschung?* Fact sheet. URL <https://www.sciencemediacenter.de/alle-angebote/fact-sheet/details/news/nicht-invasive->

- hirnstimulation-neue-moeglichkeiten-in-therapie-und-forschung/ [25 November 2021].
- Sedlmeier, P. / Eberth, J. / Schwarz, M. / Zimmermann, D. / Haerig, F. / Jaeger, S. / Kunze, S. (2012): The psychological effects of meditation: a meta-analysis. In: *Psychological Bulletin* 138 (6), 1139–1171.
- Seinfeld, S. / Figueroa, H. / Ortiz-Gil, J. / Sanchez-Vives, M. V. (2013): Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. In: *Frontiers in Psychology* 4, 810.
- Sellaro, R. / Derks, B. / Nitsche, M. A. / Hommel, B. / van den Wildenberg, W. P. M. / van Dam, K. / Colzato, L. S. (2015): Reducing Prejudice Through Brain Stimulation. In: *Brain Stimulation* 8 (5), 891–897.
- Simons, D. J. / Boot, W. R. / Charness, N. / Gathercole, S. E. / Chabris, C. F. / Hambrick, D. Z. / Stine-Morrow, E. A. (2016): Do »brain-training« programs work? In: *Psychological Science in the Public Interest* 17 (3), 103–186.
- Smillie, L. D. / Gökçen, E. (2010): Caffeine enhances working memory for extraverts. In: *Biological Psychology* 85 (3), 496–498.
- Smith, P. J. / Blumenthal, J. A. / Hoffman, B. M. / Cooper, H. / Strauman, T. A. / Welsh-Bohmer, K. / Browndyke, J. N. / Sherwood, A. (2010): Aerobic Exercise and Neurocognitive Performance: A Meta-Analytic Review of Randomized Controlled Trials. In: *Psychosomatic Medicine* 72 (3), 239–252.
- Smith, M. A. / Riby, L. M. / Eekelen, J. A. / Foster, J. K. (2011): Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. In: *Neuroscience & Biobehavioral Reviews* 35 (3), 770–783.
- Stojanoski, B. / Lyons, K. M. / Pearce, A. A. A. / Owen, A. M. (2018): Targeted training: Converging evidence against the transferable benefits of online brain training on cognitive function. In: *Neuropsychologia* 117, 541–550.
- 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. In: *The New England Journal of Medicine* 366, 502–510.
- Tardif, S. / Simard, M. (2011): Cognitive Stimulation Programs in Healthy Elderly: A Review. In: *International Journal of Alzheimer's Disease*, 378934.
- Thibaut, A. / Zafonte, R. / Morse, L. R. / Fregni, F. (2017): Understanding Negative Results in tDCS Research: The Importance of Neural Targeting and Cortical Engagement. In: *Frontiers in Neuroscience* 11, 707.
- Tildesley, N. T. / Kennedy, D. O. / Perry, E. K. / Ballard, C. G. / Savelev, S. / Wesnes, K. A. / Scholey, A. B. (2003): *Salvia lavandulaefolia* (Spanish sage) enhances memory in healthy young volunteers. In: *Pharmacology Biochemistry and Behavior* 75 (3), 669–674.
- Valentine, G. / Sofuoglu, M. (2018): Cognitive Effects of Nicotine: Recent Progress. In: *Current Neuropharmacology* 16 (4), 403–414.
- Warburton, D. M. (1992): Nicotine as a cognitive enhancer. In: *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 16 (2), 181–191.
- Warwick, K. (2014): The Cyborg Revolution. In: *NanoEthics* 8, 263–273.
- Yanakeva, S. / Polychroni, N. / Family, N. / Williams, L. T. J. / Luke, D. P. / Terhune, D. B. (2019): The effects of microdose LSD on time perception: a randomised, double-blind, placebo-controlled trial. In: *Psychopharmacology* 236, 1159–1170.
- Yetisen, A. K. (2018): Biohacking. In: *Trends in Biotechnology* 36 (8), 744–747.

