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Drugs, games and devices for enhancing cognition: Implications for work and society

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Abstract

As the work environment changes, the demands on working people change. Particularly cognitive abilities are becoming more and more important for work performance and successful competition in a global environment. However, work-related stress, performance over long hours, lack of sleep, shift work and jet lag affect cognitive functions. Therefore, an increasing number of healthy people are reported to use cognitive enhancing drugs as well as other interventions such as non-invasive brain stimulation to maintain or improve their work performance. This review summarizes research on pharmacological and technical methods as well as cognitive training studies, including game apps for the brain, in healthy people. In neuropsychiatric disorders, impairments in cognitive functions can drastically reduce the chance of returning to work. This review also summarizes research on pharmacological and cognitive training studies in neuropsychiatric disorders.

Introduction

When the financial crisis in Greece was at its climax in July 2015, European politicians such as Angela Merkel, David Cameron and the Greek finance minister Yanis Varoufakis were in close contact, and even US president Barack Obama was involved due to potential global economic consequences of the crisis. They were meeting in small groups, holding phone conferences, debating and negotiating over days into the early morning hours[1]. This might have been a rather exceptional situation, but similarly critical and hectic constellations occur again and again in the life of politicians. It is a highly demanding situation, because the individual politician has to stay sharp, focused, controlled, and be able to make decisions with potentially far-reaching consequences. And he or she often has to keep up this high-functioning state over days and potentially weeks. One historical case where a politician has admitted using pharmacological 'helpers' such as barbiturates and amphetamines to be able to fall asleep and to be fit the next day again is the former British prime minister Anthony Eden [2], which has been shown to have affected his decision making [2].

Although life for most people is not as tightly clocked and does not involve decisions about the fate of states or war, the 9 to 5 Monday to Friday work rhythm assumed to be the norm is changing: In the last 150 years, the employment structure and thus the work environment for the majority of workers has changed dramatically: Until about 1911, about equal proportions of workers in the UK worked in manufacturing and services (40% each), whereas in 2011, more than 80% of workers worked in the service industry with less than 10% in manufacturing and agriculture/fishing[3]. This means that the majority of workers now rather use their brains and their minds instead of their muscles, and now maintaining and improving brain function has come into the focus of education and other Governmental departments [4]. This trend is even increased by the digital technology development which is visibly eroding employment in manufacturing and retail as well as having an impact on highly skilled services in multiple areas [5].

A recent report by the International Labour Organization on the changing nature of jobs [5] describes the changes in work environment over the last 10 years. It identified increasing rates of part-time employment, accompanied by a decrease in full-time employment, and a considerable proportion of workers without permanent contract (about 25% in high-income countries, tendency increasing). In the advanced economies and EU category, these workers in non-permanent contracts are most affected by poverty (between 16 and 40%). Furthermore, the proportion of unemployed workers receiving unemployment benefits in high income economies has decreased from 44% in 2009 to 35% in 2014. This reduction in benefits and insurances for the case of unemployment in turn increases the pressure on those in work to perform and to satisfy work demands. In addition, the increasing trend towards jobs involved in the global supply chain (2014: >30% in the EU, about 10% in the US[5]), e-commerce and extended availability of online and offline services in a (nearly) 24/7 style will increase the demand for 'white collar' workers around the clock[6]. About 22% of workers globally are reported to work more than 48 hours per week (US: 18.1%[7]). Regarding shift work the most recent US data are

from 2004, reporting over 15 million full-time wage and salary workers (14.8%) who are given shift schedules (fallen slightly since 1991 (18%), but clear difference to 1985 (16%)[8]). In Germany, the percentage increased during the late 1990s, and is now at a plateau of about 17% (2013)[9], identical to the percentage in the UK in 2014[10]. Shift work has particularly been associated with negative acute and long-term health effects such as subjective fatigue, reduced quality and quantity of sleep, reduced quality of life[11], increased anxiety, depression, adverse cardiovascular effects[12], increased risk for gastrointestinal disorders[13], metabolic syndrome[14], possibly increased cancer risk[15, 16] as well as higher incidence of accidents and errors during work[17] and a higher risk of commuting accidents (review[6]).

The amount of sick leave days due to mental disorders (notwithstanding the phenomenon of presenteeism) has increased markedly in the last decades: it increased, for instance, by 209% from 1997 to 2014 in the population covered by one of the main German health insurance companies, while the amount of sick leave days due to all disorders increased only by 21% in the same time[18]. Mental disorders are now the second most frequent reason for sick days (after musculo-skeletal problems)[18]. The causality between these two phenomena, the change in workplace conditions and the change in the prevalence and severity of mental disorder, is not clear. However, independent of causality, the direct economic effects of mental problems are becoming an increasing factor for companies and also for national economies.

These changes in work environment and the ever increasing demands on cognition associated with these contribute to the tendency to use strategies to improve work performance. There are several methods to enhance cognitive functions which can be differentiated into pharmacological ('smart drugs', 'neuroenhancers') and non-pharmacological strategies, including physical exercise, diet, sleep meditation as well as technical devices (transcranial stimulation) and computer games and apps aimed at boosting brain function[19-21]. We will focus on pharmacological enhancers using the Neuroscience based Nomenclature system[22]), but not generally consumed widely available substances such as caffeine, in the following section, and discuss the current state of other methods in the last section.

But not only politicians, bankers or academics[23, 24] are taking pharmacological 'helpers'. But this option of using pharmacological 'helpers' or cognitive enhancers to face the ever increasing stress and demands of the work environment appeals also to a wide range of people: A report[25] in 2015, issued by a big German health insurance company, contacted 10213 insured people (age range 20-50 years old) of which 5017 responded (49.1%). Of the respondents, 6.7% reported the life-time use of pharmacological neuroenhancement (increase from 4.7% in the previous report issued in 2009), 3.3% with the aim to improve work-related performance, 4.7% with the aim to improve mood and anxiety. However, the authors report that the rate of 6.7% might underestimate the true value due to response bias. The estimated 1-year prevalence was 5.8% with 63% of users reporting regular, more than once a

month intake. This study focused on the intention of using prescription drugs rather than the specific pharmacological agents. The users reported medications aimed at reducing anxiety/nervousness, antidepressants, stimulants, beta-blocker, and medications aimed at improving memory (antidementiva). Work environments with high prevalence were characterized by high pressure (serious consequences due to small mistakes), work situation with low employments security, a requirement not to show emotions and working at the limit of capabilities. In summary, this report showed an increasing frequency of the use of pharmacological substances with the aim of improving work-related performance, which amounts to up to 5 million people in Germany (population: 82.6 million). Despite repeated alarming headlines in newspapers[26-33], data on the use of cognitive enhancers in work environments from other countries are rare[19]. In student populations, several studies found prevalences between 2 and 25% in various countries, with most studies ranging around 10-15%[19, 34, 35]. Furthermore, most research on the enhancing effects of pharmacological and other enhancing mechanisms such as transcranial electrical or magnetic stimulation (eg. tDCS, tMS) has until now only investigated effects of single (maximum few) intakes on well-defined cognitive tests[36].

From an ethical and policy perspective, however, the use of neuroenhancing interventions should be carefully considered. On the one hand, impaired cognition due to stress, shift work, or other effects can reduce overall GDP of a nation, be it directly by diminishing productivity or indirectly due to the effects of accidents or long-term effects of stress and work-related disorders such as musculoskeletal and mental disorders (e.g. [37]). In addition, chronic stress can also negatively affect cognitive function, particularly forms of memory [38] as well as brain volume[39, 40].

The above mentioned German survey[25] suggests that particularly people who are either worried about their job, working at the limit of their capabilities or in fields where small mistakes can have serious consequences, seem to be particularly prone to using cognitive enhancers[25], and the users reported the following motives for use: for specific situations (such as exams, giving a presentation, important negotiations, etc., reported by 41%), because work is easier (reported by 35%), I can reach my goals easier (32%), more energy and better mood for other interests (27%), competitive edge at work (12%), would not be able to do the work otherwise (25%), need less sleep (9%). This is in parallel to studies investigating the motivation of students who consume cognitive enhancers, reporting mainly increasing performance and 'keeping up' (concentration, vigilance, memory, cognitive potential), staying awake for longer periods and a pressure to succeed as well as a way to maintain an active social life[41-43]. In addition, factors such as overcoming jetlag and improving focus and increasing motivation for tasks over longer times are known reasons for taking drugs such as modafinil[21, 23, 44, 45].

One important point when talking about cognitive enhancers is the differentiation between its use as treatment which is usually understood as aimed at improving a measurable deficit, related to a neuropsychiatric disorder compared to the use of cognitive enhancers with the aim of improving a

normal cognition in a healthy person above their typical function or to maintain cognition for longer times or despite sleep deprivation or jet-lag.

In patients suffering from neuropsychiatric disorders, deficits can be easily measured, and no-one would dispute the use of drugs or other interventions to improve clinical deficits which might enable patients to lead independent lives, return to work and have a better quality of life and wellbeing. However, when looking at cognitive enhancement in people without a clear diagnosis of a mental disorder, it is difficult to define the terms "normal cognitive function" and "deficit" (e.g. [21]): What defines "normal cognitive function"? It might seem rather easy to determine if someone has clear cognitive deficits, for instance, after a stroke or as is the case in chronic schizophrenia. However, it is more difficult in people without a clear medical disorder, but subjective deficits or in people who wish to improve their cognitive performance above their "normal" level or want to maintain their level despite being sleep-deprived or jet-lagged or maybe noticing an aging-related decline. Therefore, it is difficult whether to describe the use of a cognitive enhancing drug in these situations as restoration or as enhancement[21].

In addition to these definitional questions, there are also questions as to which cognitive enhancing methods are really effective and in which populations (healthy/patients) and for which cognitive domains. It is also important to know whether effects measured in an experimental laboratory setting can be translated into everyday performance and functioning. Besides 'smart drugs' a number of other methods aim at improving cognitive function such as cognitive training, possibly using novel technical methods such as games and smartphone applications, electrical or electromagnetic methods such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (TDCS) which aim at directly modulating brain areas or networks to improve cognitive performance.

The aim of this review is to summarize the state of current knowledge on enhancing and restoring cognition in healthy participants and in patients suffering from neuropsychiatric disorders with a particular emphasis on novel findings published in 2014 and in 2015.

Studies on pharmacological cognitive enhancers in healthy volunteers

In general, pharmacological cognitive enhancers used by healthy people can be grouped into several categories: stimulant-types (amphetamines, aimed at improving vigilance, attention, focus, speed of processing), modafinil (which has some similarities to amphetamines, but also differential effects)[46], drugs used to treat dementia (acting on acetylcholine and/or glutamate, aimed at improving memory) [47], and due to the link between motivation/mood and cognitive performance, people are also using drugs that improve sleep, reduce anxiety (e.g. benzodiazepines) and improve mood (SSRIs)[25].

In the years 2014 and 2015 (until October 2015), there were several new studies on cognitive enhancers and particularly a couple of important reviews and meta-analyses aimed at finding evidence in the vast number of small scale studies (summary in table 1). Battleday and Brem[48] performed a

systematic review on 24 studies using modafinil (mixed pharmacology, acting primarily as a blocker of dopamine and noradrenaline reuptake transporters[49] and various effects on other neurotransmitter receptors[46, 50, 51]) on cognitive tasks in healthy not sleep deprived participants, showing no consistent effect on tests of attention, but generally positive effects on inhibitory control and working memory. More clearly beneficial effects of modafinil were found in tests of 'higher' executive function such as planning (e.g. [45, 52]), decision making and fluid intelligence (e.g. [53]). In tests of delayed memory, the authors report about as many positive studies as studies with no or with negative effect. However, in more complex paradigms, which are less standardized, but might be more ecologically valid, a number of studies found improved performances. Some studies have demonstrated baseline-dependent effects with low performing subjects showing improvements in performance following stimulant drugs, but those subjects with an already high baseline performance showing no change or even impairment following stimulant drugs. However, in comparison to studies on typical stimulants (particularly methylphenidate (MPH) and amphetamines, both acting on dopamine, noradrenaline and serotonine reuptake transporters[54-56]), there seem to be no substantial baseline-dependent effects with modafinil. Sleep-deprived healthy subjects show cognitive enhancement with modafinil in tests of executive function (working memory, planning, decision making, flexibility)[57] as well as sustained attention[58]. For prescription stimulants, comprising amphetamines and MPH, the meta-analysis by Ilieva et al.[59] (48 studies) confirmed small but significant effects on inhibitory control and short-term memory, a medium effect on delayed memory, and a borderline significant small effect on working memory in healthy adults. Similarly, the review by Linssen et al.[60] on single dose studies of MPH in healthy volunteers reported clear effects on working memory (particularly with a medium dose (10-20 mg)) and processing speed, weaker effects on learning and memory, attention, and an even weaker effect on decision making and problem solving. Visual learning and memory were not affected across studies, and studies in older adults showed weaker to no beneficial effects compared to younger adults (with the limitation of fewer studies). One study investigated the effect of MPH on the interaction between salience and attentional control, showing that MPH actually increased the distractor cost, i.e. the effect of a salient distractor on attention is increased[61]. The main motives for healthy people to consume pharmacological cognitive enhancers are various (see above)[25, 41]. One study reported that people with subclinical traits related to ADHD, impulsivity and novelty seeking were more prone to using cognitive enhancers[62]. However, it is possible that people self-medicate or at least try to self-medicate for undiagnosed ADHD traits or subjective cognitive deficits[63] as well as for motivational problems[45, 64] and diminished inhibitory control resulting in increased impulsivity[65]. Another study reported similar subjective attention impairments/ADHD symptoms, but also increased omission errors in an attention test in users of (unprescribed) stimulants[66]. However, there is evidence from a number of studies that poor baseline performance predicts cognitive improvement in response to stimulant intake (e.g. [67-70]), which might correspond to the dopamine state in the thalamocorticostriatal network[71, 72].

One recent review summarized over 50 studies on other drugs that potentially could enhance cognition such as those exerting actions through other pharmacological mechanisms, including through other catecholaminergic mechanisms, action on glutamate, acetylcholine, and histamine[47]. Of these, most were negative (no enhancing effects) or conflicting studies, except for some positive effects by tolcapone (inhibits dopamine degradation in the brain) and Levodopa on memory. Further pharmacological interventions acting on melatonine or anti-inflammatory drugs showed positive cognitive effects, but only in single studies.

There are other interventions at the border between pharmacology and nutrition, one being poly-unsaturated fatty acids (PUFAs) which are thought to enhance brain function. One recent meta-analysis of studies in healthy volunteers and in patients suffering from attention-deficit hyperactivity disorder (ADHD) showed a potential beneficial effect on working memory in ADHD, but no significant consistent effects across both healthy and ADHD participants, except for a small effect in PUFA deficient participants in the domains of working memory and short term memory. The authors concluded that more studies are needed. Another supplement, resveratrol, which is thought to have neuroprotective effects, showed no benefits for cognitive performance in healthy volunteers[73].

Non-pharmacological interventions to enhance cognitive performance in healthy subjects

First, there are a number of well established methods which can help maintaining optimal cognitive performance (summary see table 2). The UK Government's Foresight Report on Mental Capital And Wellbeing[74] has recognized and summarized a number of well-founded strategies for the individual and for policy makers to maintain and optimize wellbeing and performance in general and in workplace environments, based on research that wellbeing is related to better cognitive function[75]. The Foresight report formulated five basic ways to improve wellbeing based on scientific evidence:

- Physical exercise (*be active*),
- *Keep learning* – referring to the concept of lifelong learning, ongoing challenges and the improved confidence when conquering the challenge,
- *Connect* – valuing and fostering social contacts,
- Mindfulness (*take notice*) – being open to new experiences, and also being aware of your environment and your own wellbeing,
- *Give* – the rewarding effects of a positive attitude towards others and the positive effect of helping someone.

For all these factors, there are multiple studies showing beneficial effects at the neurobiological level (general reviews[76, 77]; studies on aerobic exercise resulting in increased brain derived neurotrophic factor (BDNF)[78, 79], increased neurogenesis in mice[80] and improved cognition and increased

hippocampus size in humans[81] (however, also [82]); extensive literature on enrichment enhancing cognition in rodents, reviews[76, 83]). Furthermore, interventions in early childhood can help improving resilience against future adverse influences and also mitigate the effects of early low socioeconomic status on cognitive and emotional development[84-86] (examples of interventions: [87, 88], review of family-based interventions: see [89]).

In addition, it is well known which factors affect cognition and wellbeing negatively, such as lack of (quality) sleep, poor nutrition, chronic stress effects, inadequate levels of demand (either excessive or not sufficient, i.e. boredom). Furthermore, a number of disorders and disturbances in somatic function can affect cognition negatively, for instance sensory impairments (vision, hearing), metabolic and endocrine imbalances, neurotoxic substances such as alcohol and other solvents, traumatic brain injuries, including even mild brain injury. Avoiding or reducing the effect of these negative influences represents therefore a very basic mechanism to preserve cognitive performance. Furthermore, interventions such as mindfulness, meditation and relaxation training could prevent the building up of stress and thus prevent the impairment of cognition by stress in addition to possibly direct improvements in domains such as attention, executive function and memory (e.g. [90], review in [91]).

More specific cognitive training approaches have used various methods ranging from paper and pencil based interventions, book reading (e.g. [92]) to computerized training to training programmes integrated into video games (e.g. [93, 94]). The target of this training varies from circumscribed functional domains such as attention[95] to broad multi-domain cognition[96]. The video-game industry, worth more than £3.9 billion in the UK (2014)[97], and more than $6.2 billion in the USA (2012)[98], has developed great strategies to grab the player's attention, create and maintain motivation to play over long time periods and even to tap into brain networks associated with reward and addiction[99-101]. Certain video games, while not having the explicit aim to improve cognition, seem to have some similar broad effects on cognitive function as specific, targeted "brain training" games[102], in terms of improving reaction time, speed of response and in some cases attention. In addition, both brain training games and video games are now more and more accessible via the internet, providing a training opportunity for large parts of the population[103]. However, a larger meta-analysis found that the effects of computerized cognitive training in older adults were significant, but relatively small[104]. From a conceptual and scientific perspective and also to target more specific cognitive domains, research has in the last decade aimed at integrating directed cognitive training into video games, using the strategies of "professional" commercial video games and thereby having the potential to overcome the motivational problems evident with classical cognitive trainings (e.g. non-completion rates of > 50% in study settings in a rehabilitation program[105]). Overall, however, it is not clear yet how factors such as motivation, fun and adaptivity of the game best come together to result in maximal improvement of the trained functions, and, even more important, in a transfer of the training effect into other, related, but not directly trained functions, and in the best case into everyday functioning[106, 107]. Some models propose that one

important aspect of successful training in video games is that the players "learn to learn"[108, 109] or the improvement of multitasking and general cognitive control[110] which might explain the different degrees of transfer or generalization found with different games.

In the field of working memory and executive function training, a small but significant improvement of fluid intelligence has been shown in a meta-analysis[111] as well as into academic performance in children with low baseline performance and, although to a lesser degree, in children with average baseline performance[112]. However, the relevance of baseline performance to the possible gain with training is not totally clear. For example, children with lower baseline may benefit more from training, whereas in older adults those with higher baseline education seem to perform better with training[112]. In older adults, one specific everyday domain has received some attention: the development of specific training programs for improving car driving performance and safety with rather consistent successful results[113-115].

One potentially important but yet underresearched question, however, is the optimal "dosage" of all these interventions: If a person tries to improve cognition by doing a lot of cognitive training, this might, if excessive and highly time consuming, may be associated with a significantly increased sedentary time, reduced physical exercise and reduced social interaction, which all can then counteract the beneficial effect of the cognitive training. There are few studies looking at combinations of different interventions (mostly combinations of exercise and cognitive training, in some studies additional nutritional interventions), and most of these are done in cohorts of older adults. There is some evidence that the combination of cognitive and physical training is more efficacious than cognitive training alone (e.g. [116]). In most of these studies, interventions were done in a group setting, such that the social interaction (if within the group or with members of the teams) was enhanced with any intervention (e.g. [117]) and can therefore not be separated as factor. In younger adults, however, there is nearly no research on this question. Future studies should focus on, the optimal balance of activities and interventions on cognition, which has until now been neglected.

In the last decades, methods of directly modulating brain activity have been developed with the intention to enhance cognitive performance directly or to increase the efficacy of cognitive training. One such group of interventions are non-invasive brain stimulation methods, particularly transcranial magnetic and electrical stimulation. Transcranial Magnetic Stimulation (TMS) has direct effects on the activity of circumscribed (mostly cortical) neuronal populations resulting in either a direct activation (depolarization, excitation) or an inhibition ('virtual lesion')[118]. This effect interacts at least partially with the individual's cognitive and physiological state[119]. In cognitive research, TMS has been shown to have quite robust effects in a variety of domains (depending on the targeted brain region) such as motor learning, sensory discrimination, attention, inhibition, working memory[120, 121]. Nevertheless, due to the more complex application and the higher costs of TMS machines, this method is not expected to hit applications for use outside research or clinical environments. Transcranial electrical stimulation

methods, particularly transcranial direct current stimulation (tDCS), aim at changing the excitability of larger brain areas by modulating the neuronal response threshold, but not inducing action potentials. At the functional level, this intervention is thought to facilitate or inhibit brain processes and to modulate brain plasticity[118]. Transcranial alternating current stimulation (tACS) aims at influencing frequency-specific brain activations whereas transcranial random noise stimulation (tRNS) is thought to apply a repeated subthreshold stimulation and therefore boosting the overall sensitivity of neuronal networks[118]. Particularly tDCS has gained media attention again and again with headlines such as 'Headset zaps video gamers' brains for better reflexes'[122], 'Keep Calm and Carry on'[123] or 'Zap Your Brain to Health with an Electrode Cap'[124], but also warnings such as 'Warning over electrical brain stimulation'[125] and an impairing effect of a commercially available tDCS headset on working memory[126]. However, despite some positive reports and even higher hopes in the beneficial effects of tDCS (e.g. [36, 127]), a recent meta-analysis came to the conclusion that it has, if at all, only a weak effect on cognition in healthy subjects[128] and, for instance, in stroke patients[129], although the former meta-analysis has been criticised for being overly conservative[130, 131]. This finding, however, might in addition be due to heterogeneity associated with a lack of knowledge about, for instance, differential effects of electrode placement and other stimulation parameters[119]. Therefore, research is urgently needed to investigate mechanisms, optimal parameters and objective effects as well as effects of repeated and long-term use, because the unregulated application of DIY neurostimulation devices in this field is increasing[132].

Using a related and non-invasive approach, methods such as EEG and fMRI based neurofeedback have been shown to enhance the control over or the function of specific brain circuits[133-136] and enhance cognitive-perceptual processes[137, 138]. However, while the relation between signal (i.e. activity of a brain region or connectivity between brain regions) and function is rather well understood in the case of fMRI neurofeedback, this direct correlation is much less understood in EEG neurofeedback[139, 140].

Nevertheless, one field that requires more research is the optimal design of training programs (dosage, duration, etc.) and how to ensure the transfer of a practiced skill, if using neurofeedback or other training methods, onto other, more or less related cognitive tasks and, more importantly, into everyday life.

Studies on pharmacological cognitive enhancers in neuropsychiatric disorders (table 1)

Neuropsychiatric disorders are highly prevalent in the general population (18.5% 1-year prevalence in the adult US population)[141]. These disorders and the cognitive disturbances associated with them represent major problems for the ability to work, be productive and the society as a whole[18, 142, 143]. Neuropsychiatric disorders are characterized by cognitive disturbances including biased attention,

aberrant learning, dysregulated motivation and emotion and impaired top-down control of our multiple processes typically attributed to the prefrontal cortex[20, 21, 144]. Many neuropsychiatric disorders start early in life, some with a prodromal stage, they affect young people disproportionally (75% of mental illnesses begin before the age of 24 years)[145] and they have serious consequences for the functionality and wellbeing of the individual and the economic development of the society[4, 146]. In some of the neuropsychiatric disorders, cognitive deficits are obvious and have long been targets of treatment, most clearly in dementias and also in ADHD. In others such as depression and schizophrenia, most treatments available until now target the more acute symptoms such as mood or psychosis. However, the cognitive symptoms often persist after remission of the acute symptoms[147-153] and are associated with serious effects on social and interpersonal functioning, such as fewer than 20% of patients with schizophrenia returning to work after a first psychotic episode[154]. It is now clear that cognitive impairment in schizophrenia and depression is an unmet need and a target for treatment ([155]. One problem in studies on cognitive enhancing interventions in neuropsychiatric disorders is that a number of studies used clinical scales summarizing global functions associated with cognitive deficits or cognition in everyday situations (e.g. CGI, MMSE in dementia, PANSS in schizophrenia) rather than using specific cognitive tests.

In Alzheimer's disease (AD) and other dementias (or neurocognitive disorders as they are now called in the DSM-5[156]), cognitive symptoms are the main aspects[157]. Therefore, research has already since the late 1970s investigated drugs to enhance or even restore cognitive function, particularly memory, using cholinergic mechanisms (e.g. [158, 159]) resulting in tacrine as the first acetylcholinesterase inhibitor (AChEI, blocking the degradation of synaptic acetylcholine) approved for use in AD[160]. Since then these drugs have been the most successful treatments in AD, even if they are primarily aimed at symptomatic treatment, rather than at the underlying pathology of the disorder. In parallel, research has been trying to develop causal treatments, which would halt the underlying disease processes are, however, still in clinical trials. In the last year, one meta-analysis confirmed the clear positive effects of the AChEIs donepezil, galantamine and rivastigmine as well as the NMDA-receptor antagonist memantine (acting on the glutamate system) on cognition and general functional outcome in AD[161]. However, using less sensitive subjective measures such as clinical global impression, only donepezil was clearly superior to placebo, with rivastigmine improving only clinical impression. Three recent studies[162-164] have shown that treatment with cholinesterase inhibitors not only improves functional outcome, but also is cost-effective. Therefore early detection and early effective treatment with AChEIs is important. Early detection will become even more important when neuroprotective drugs and drugs targeting the disease process causally will become available. From a health-economic perspective, a recent study showed that treatment with cognitive enhancing drugs (ACHEI and memantine) in AD clearly reduced total costs (direct and indirect) compared to no treatment[165]. In one study, the beneficial effect of donepezil on cognition and overall outcome was not correlated with hippocampal volume[166]. In contrast, in untreated patients cognitive deficits and hippocampal atrophy

were correlated, whereas this was not the case in donepezil treated patients[166]. One study showed also improvement in gait performance due to donepezil treatment in AD[167]. In 2014 and 2015, there were furthermore a handful of studies using galantamine confirming its beneficial effect on some cognitive domains for a duration of 6-12 month, and thereafter the drug slowed the progression of deterioration[168-170]. In terms of novel treatment approaches published in 2014 and 2015, particularly histamine H3 receptor antagonistic approaches have been tested[171-173], as well as rapid acting insulin[174]. Further studies investigated the effects of benzoate (aiming at enhancing NMDA receptor function) showing an improved cognitive performance and global clinical impression in a randomized placebo-controlled study over 24 weeks in 60 patients[175].

In Dementia with Lewy Bodies, a neurodegenerative disorder with a different pathophysiology and different symptom profile compared to AD, a recent meta-analysis[176] found a beneficial effect of the ACHEIs donepezil and rivastigmine for cognitive functioning as well as for other symptoms such as visual hallucinations, but only limited evidence for other drugs targeting cognition such as galantamine and memantine.

Next to the dementias, schizophrenia is the neuropsychiatric disorder where cognitive deficits have long been described[177, 178] and are considered to be an important target for treatment[179] due to their relationship to functionality. However as yet, the relationship between antipsychotic treatment and cognition in schizophrenia is mixed[180], with some antipsychotics coming out as being superior in certain domains but apparently impairing function in another domain. For example, verbal fluency was shown to be improved by clozapine, but in contrast, verbal memory was impaired by clozapine (atypical antipsychotic drug primarily acting on serotonine receptors, 5HT2A[181]), in comparison to other antipsychotics[180, 182-184]. Recently, research has aimed at developing drugs that reduce so-called positive symptoms (i.e. hallucinations, psychosis) and also improve cognition. The first drug promising to fulfil these aims is lurasidone, which has a mixed pharmacology with antagonistic effects on dopamine D2 receptors and the 5-HT7 serotonergic receptor, and partial antagonistic effects on the 5-HT1A serotonergic receptor[185]. In comparison to quetiapine, it has been shown to dose-dependently improve cognition measured with a composite measure as well as skills-based everyday functioning[186]. However, the long-term effects of this novel drug on cognition and everyday functioning, and particularly work and social functioning, have not yet been shown although it was only approved in the US in 2010 and in the EU in 2014. The last 10 years have seen a number of trials using drugs initially developed as antidementive drugs (ACHEIs) in schizophrenia. However, the initially positive reports could not be replicated in bigger samples or the effects in memory, attention and processing speed were relatively small [187-190]. Similarly, compounds aiming more specifically at nicotinic acetylcholine receptors and their subtypes showed relatively small effects in attention, working memory, planning and memory [191, 192]. In parallel, research tried to modify the glutamatergic system in the hope of improving cognitive deficits in schizophrenia based on the hypothesis that a glutamatergic

dysfunction might underlie or at least contribute to the pathogenesis of schizophrenia (e.g. [193]). However, amongst others, a couple of recent meta-analyses showed no significant effect of drugs that positively modify glutamatergic signalling or acting as agonists or co-activators on glutamatergic receptors[188, 194-196]. Similarly, the use of antidepressants aiming at manipulating the serotonergic system to improve cognition in schizophrenia was not successful in improving cognition, but did improve depressive symptoms (e.g. [197]). Similar negative results were reported on other pharmacological mechanisms such as a H3 histamine receptor antagonist[198], monoamineoxidase B-inhibitor rasagiline[199]. One study in 71 patients showed improvements using the estrogen receptor modulator raloxifene in measures of memory in a placebo-controlled cross-over study[200] which, however, remains to be replicated (see no significant effect in a recent study in 42 women[201]). One other review collated support for a combined treatment with galantamine and memantine, although this suggestion has yet to be conclusively tested[202]. Modafinil showed in a meta-analysis of 8 randomized-controlled studies including 372 patients a small improvement in negative symptoms without worsening positive symptoms, but also without strong difference from placebo in direct tests of cognition[203]. One study combined cognitive training in schizophrenia patients with modafinil compared to placebo, but without an additional effect of modafinil[204]. Using modafinil in patients with schizophrenia who are high functioning or early in the course may well yield beneficial effects[205-207]. However, to date, most of the studies were conducted using chronically ill patients with relatively severe cognitive deficits. There are reasons to believe that with earlier treatment the development of cognitive impairments can be stopped or even reversed which might be easier to achieve than to repair damage that has already occurred[208]. And in addition, the lack of consistent results could be due to the neurobiological heterogeneity of schizophrenia as diagnostic category, meaning that with neurobiological criteria for subcategories treatment responders to specific and different cognitive treatments might be identified.

In affective disorders, including particularly major depressive disorder (MDD) and bipolar disorder, there has been a strong move to finding mechanisms that can help alleviate the cognitive symptoms[155] that frequently remain even after the main affective symptoms are remitted[151, 209] and which strongly impact on functional outcome (review in [210]). A recent review[211] summarised 26 studies focusing on the treatment of cognition in depression. In this review, the NMDA-receptor antagonist memantine did not show a cognition enhancing effect. Two other drugs typically used in the treatment of cognitive deficits in dementia, galantamine and donepezil, did not suggest a clear benefit for cognitive impairments in depressed older patients (with the limitation that more studies are needed for these drugs). Vortioxetine, a serotonergic antidepressant with reuptake-inhibiting and specific 5HT receptor activity, has received approval from the European Medicines Agency (EMEA) supporting the beneficial effect on cognitive functions in depression based on a big multicenter study in 602 patients[212] and it is currently in the process of being assessed by the US Food and Drug Administration for the specific indication of improving certain aspects of cognitive function in adults with MDD[213].

The review by Solé[211] mentions two studies[214, 215] with positive effects of vortioxetine on attention, executive function, processing speed and verbal learning and memory independent from the improvement in mood, which is supported by an additional study comparing vortioxetine to the serotonin-noradrenaline reuptake inhibitor duloxetine[212] with vortioxetine showing superiority over duloxetine in terms of improving cognition. However, it is not yet clear if vortioxetine also improves cognitive function in the absence of depression. In preclinical studies, selective serotonin reuptake inhibitors (SSRI) reversed the negative effects of stress and other models of depression on memory, whereas the effects of SSRI on memory in normal animals are rather mixed (review: [216]). Vortioxetine, however, had rather consistent beneficial effects on memory in stressed and normal animals[216]. In animal models of executive function, both serotonergic and noradrenergic mechanisms have shown to improve stress-induced impairments[216]. Yet another mechanism of improving cognition in depression is the application of erythropoietin, which in one study showed a potential beneficial effect on clinical outcome as well as verbal learning (RAVLT) in MDD[217] and on reaction time in remitted bipolar disorder[218]. In parallel to the idea to use stimulants to improve cognition in healthy people and in schizophrenia, a couple of studies have investigated if stimulants alone or as add on to antidepressants can improve clinical and cognitive outcome: In one study in elderly depressed patients the authors used citalopram, methylphenidate or the combination of both drugs in a placebo-controlled double blind design in nearly 150 patients[219]. The patients receiving the combination treatment showed a trend towards a faster and more pronounced clinical improvement compared to the other two treatment arms, but no clear difference between the treatments regarding cognitive improvement. A similar study used lisdexamfetamine (prodrug, converted into dextroamphetamine upon ingestion) as add on to SSRI treatment in partially remitted patients with self-reported executive dysfunction (placebo-controlled) resulting in a stronger improvement in executive function, although reaching significance only in the self-report measure[220]. Except for the application as an add-on to improve antidepressant effects as summarized in a recent meta-analysis[221], there are no studies clearly addressing a potential cognition enhancing effect of modafinil in depression. Ketamine is a NMDA receptor antagonist, whose rapid antidepressant effect was discovered in 2000[222] and which has come more into the focus of research and clinical application in the last 5 years. Being originally an anaesthetic, it has been investigated regarding safety showing no negative neurocognitive effects in a number of studies[211], and regarding potential neuroprotective effects during electroconvulsive therapy (ECT), but the few available studies have not resulted in a clear picture yet[211]. Based on the stress and inflammation hypothesis of depression one review summarizes a number of potential targets to improve cognition in depression[223], but most of the compounds have not been tested yet in this respect. Goss, Kaser et al.[221] recommended modafinil as an add-on to antidepressant medication in depression. Similarly, a recent review on the effects of modafinil and other stimulants in unipolar and bipolar depression recommended modafinil as augmentation for depressive symptoms[224].

In the field of addiction, the use of modafinil and stimulants has until now been mainly investigated for the treatment of the primary symptoms, i.e. addiction, craving, rather than for cognitive effects[225].

Attention-deficit-hyperactivity (ADHD) disorder is a paradigmatic disorder where stimulants (amphetamines), have long been used and are established treatments for the primary symptoms as well as for cognitive symptoms[226, 227] – cognitive and primary symptoms are very closely linked in ADHD. Problems in sustained attention are core cognitive deficits, which can be improved by methylphenidate in both ADHD patients and healthy volunteers[228, 229]. In adult ADHD patients, stimulants have been shown to improve sustained attention, inhibition and verbal learning[227]. In 2014 and 2015, the most prominent research investigated an ongoing discussion about effects of stimulant treatment on general development, particularly reduced height and/or weight. Some studies resulted in small effects of stimulant treatment on the development of height and/or weight[230, 231] in children, but some studies also found no effect[232], review[233]. Considering that ADHD itself seems to be associated with increased body weight[234], it could mean that the medication may normalize body development in ADHD. However, there is insufficient evidence to determine this as yet.

A few studies investigated the effect of cognitive enhancers in other neuropsychiatric disorders such as Fragile X-syndrome[235] (beneficial effect of 1-year treatment with memantine on cued verbal memory recall, but not free recall), traumatic brain injury[236] (beneficial effect of methylphenidate on fatigue and psychomotor speed), post-radiation impairments in cancer patients[237] (24 week treatment with donepezil, improved in some cognitive domains, stronger effect in more impaired patients) and a meta-analysis of 10 (mostly small) studies using modafinil in neurological disorders (Parkinson's disease, multiple sclerosis, traumatic brain injury) reported rather inconsistent effects (trend towards improved excessive daytime sleepiness, but no effect on depression), concluded that more research in this field is needed[238].

One field that is gaining more attention is the combination of cognitive enhancers with psychotherapy, for instance in anxiety disorders. Particularly D-cycloserine (modulating (enhancing) the NMDA glutamate receptor) has been investigated with overall more positive than negative studies, but also other drugs are showing some positive effects (recent reviews: [239-243]). Another approach is the combination of pharmacological cognitive enhancers with cognitive training. A recent study in patients with schizophrenia combined modafinil with cognitive training in a placebo-controlled design over 10 days[204]. There was a clear effect of cognitive training on measures of attention, working memory, learning and executive function, but no additional effect of modafinil compared to placebo. However, both these applications of cognitive enhancers (psychotherapy, cognitive training) are still in an experimental stage, requiring more systematic and randomized controlled studies.

In the preclinical field, studies are focusing on finding new targets with possible cognitive enhancing effects such as NMDA-receptors[244], Phosphodiesterase inhibitors[245, 246] (general review [247]), D4 dopaminergic receptor[248], and serotonergic 5-HT 6 receptor[249].

Non-pharmacological interventions to enhance cognitive performance in neuropsychiatric disorders

In the field of neuropsychiatric disorders, there are fewer studies investigating the effects of cognitive training and other interventions on cognition, although at least in mild to moderate neurocognitive disorders the benefits of, for instance, physical exercise combined with computerized cognitive training seem to be comparable or only moderately weaker than the improvements in healthy older adults[250-252], and that even in patients with manifest, up to moderate AD a training of specific memory functions is possible and can be maintained over months[253, 254], although the effects of specific cognitive training compared to multi-domain cognitive stimulation in a recent meta-analysis were weaker (moderate effect size for multi-domain cognitive stimulation)[255].

In the field of schizophrenia, there have been a couple of studies applying computerized as well as app-based and video-game based trainings with mostly beneficial effects such as an improvement in cognitive flexibility as well as in everyday functioning after cognitive training using a specifically designed video game for 4 weeks. The recent study by Sahakian et al.[21] used a neuroscientific approach to brain app development, combined with an integrative approach, including neuroscientists, a game developer and service users with schizophrenia. Game play with the Wizard memory app improved episodic memory and learning and patients' social, occupational and psychological functioning. In addition, motivation remained high throughout the 8 hours of training over 4 weeks[21]. In general, the evidence is quite strong that cognitive training (also known as cognitive remediation) can improve cognition and everyday outcome in schizophrenia[256-258], resulting in neuroplastic changes in brain activation[259, 260]. A recent study showed improvements even in patients diagnosed with schizophrenia without clear insight into their cognitive deficits[261]. In addition, research has recognized the importance of cognitive training particularly in patients early in the course of schizophrenia, after a first psychotic episode, to maintain and strengthen the patients' resources already early in the course and to enable a rapid re-integration into social and work environments[262-264], with some studies successfully targeting also social cognitive functions such as theory of mind directly[265], whereas a recent review showed transfer effects of cognitive training onto social functions[266]. However, despite this rather strong overall body of evidence, only few treatment guidelines include neurocognitive training into their recommendations[267], whereas the American Psychiatric Association, for instance, considers cognitive remediation therapy as 'experimental and cannot yet be recommended as part of routine practice' (although the last guideline is from 2004)[268]. However, one study in a group of

patients with mixed mental disorders showed that in patients who had failed in a trial of supported employment a specific cognitive training could increase their chance of employment to 60%[269].

In other neuropsychiatric disorders, there are fewer studies investigating the effects of cognitive training (e.g. in PTSD[270], stress-related exhaustion[271], etc.) whereas in mood and anxiety disorders, for instance, training modules still have to be developed[272].

RTMS as non-invasive stimulation method in depression has proven efficacious to improve clinical symptoms[273, 274]. In contrast, in studies investigating the effect of rTMS on cognition in depression the findings are more mixed (meta-analysis [275], newer study [276]), with executive functions, memory and attention each being improved in two or more studies. One study suggested a baseline effect, with patients with higher executive function performance at baseline benefitting more[276] than patients with lower baseline performance.

Summary and conclusion

Overall, maintaining, restoring and improving cognitive performance is of increasing relevance with respect to work and economic environments as well as general quality of life and health.

From a neuroethical perspective, it is important to consider both the positive but also the negative forces, for example excessive stress or indirect coercion, on healthy individuals to enhance themselves at school, university or work[277].

In people suffering from neuropsychiatric disorders, the evidence for potential pharmacological interventions for improving cognition is growing, but fewer studies have investigated non-pharmacological interventions. However, the potential gains due to interventions might even be larger than in healthy volunteers. It may be that combining pharmacological and non-pharmacological means of enhancement might produce greater benefits in terms of cognition and wellbeing for those with neuropsychiatric disorders.

Viewing the increasing lifestyle use of cognitive enhancing drugs from a policy perspective, there is an urgency for a public-private partnership between the government and the pharmaceutical industry to evaluate the long-term safety and efficacy of drugs such as modafinil in healthy people. These types of study could eliminate the potential harms of the dangerous practice of internet purchasing of prescription only cognitive enhancing drugs, with its potential harms.

As a society, we need to consider how to improve brain health and wellbeing to ensure a sustainable economy and a flourishing society for all.

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Legend for tables:

Table 1: Pharmacological cognitive enhancers discussed here

Abbreviations: AChEI Acetylcholineesterase inhibitors, AD Alzheimer's Dementia, ADHD attention deficit hyperactivity disorder, BD bipolar disorder, DLB dementia with Lewy bodies, MDD major depression, n-AChR nicotinic Acetylcholine Receptor, PD Parkinson Disease, MS multiple sclerosis, TBI traumatic brain injury, SSRI Selective Serotonine Reuptake Inhibitors, SZ Schizophrenia, PUFA poly-unsaturated fatty acids.

Table 2: Non-pharmacological cognitive enhancement interventions discussed here

Abbreviations: MCI mild cognitive impairment, AD Alzheimer's Dementia, ADHD attention deficit hyperactivity disorder, SZ schizophrenia, MS multiple sclerosis, PD Parkinson's Disease, TBI traumatic brain injury, PTSD post-traumatic stress disorder, CFS/ME chronic fatigue syndrome/myalgic encephalitis, HD Huntington's Disease, TMS transcranial magnetic resonance stimulation, tDCS transcranial direct current stimulation, tACS transcranial alternating current stimulation, tRNS transcranial random noise stimulation, EEG electroencephalography, fMRI functional magnetic resonance imaging

Table 1: Pharmacological cognitive enhancers discussed here

Substance	Cognitive domain/ function	Condition

• Amphetamines
  • (Dex)Amphetamine
  • Methylphenidate
  • Lisdexamfetamine
• AChEI
  • Donepezil
  • Rivastigmine
  • Galantamine
• Benzoate
• Clozapine
• Erythropoetin (EPO)
• H3 receptor antagonist
• Ketamine
• Levodopa
• Lurasidone
• Memantine
• Modafinil
• n-AChR agonists
• Raloxifene
• Rapid acting insulin
• Rasagiline
• Resveratrol
• SSRI
• Tolcapone
• Vortioxetine
• PUFA
	• Attention
	  • spatial
	  • selective
	  • sustained
	• Executive function:
	  • mental addition
	  • fluid intelligence
	  • cognitive control
	  • cognitive flexibility
	  • working memory
	  • inhibition
	  • planning
	  • decision making
	  • logical reasoning
	  • problem solving
	• Memory
	  • short term
	  • long term
	  • implicit
	  • spatial
	  • visual
	  • verbal
	• Gait
	• Processing speed, reaction time
	• Salience/distraction
	• Speed, fatigue
	• Creativity
	• Self monitoring
	• Emotion processing
	• Multi-domain tasks
		• Healthy adults
		• Healthy adults with PUFA deficiency
		• AD
		• ADHD
		• Addiction
		• BD
		• DLB
		• Fragile X syndrome
		• MDD
		• MS
		• PD
		• Post-radiation impairment
		• SZ
		• TBI

Abbreviations: AChEI Acetylcholineesterase inhibitors, AD Alzheimer's Dementia, ADHD attention deficit hyperactivity disorder, BD bipolar disorder, DLB dementia with Lewy bodies, MDD major depression, n-AChR nicotinic Acetylcholine Receptor, PD Parkinson Disease, MS multiple sclerosis, TBI traumatic brain injury, SSRI Selective Serotonine Reuptake Inhibitors, SZ Schizophrenia, PUFA poly-unsaturated fatty acids.

Table 2: Non-pharmacological cognitive enhancement interventions discussed here

Intervention	Cognitive domain/ function	Condition
•cognitive training •methods: •reading •group •computer-based •app-based •game-based •aim/domain •specific •gist training •general •aerobic exercise •combination cognitive training + aerobic exercise •Meditation/relaxation •social engagement •sleep hygiene •family-based interventions •non-specific cognitive (affective) engagement •Electrical/electro-magnetical methods •TMS •tDCS •tACS •tRNS •neurofeedback •EEG •fMRI •biofeedback	•motor learning •sensory discrimination •executive function •switching/flexibity •interference •working memory •reasoning •planning •inhibition •memory •verbal •spatial •attention •sustained •switching •fluid intelligence •spatial abilities •car driving performance	•Healthy •older healthy people •Children •Intellectual disabilities •AD •ADHD •Addiction •anxiety disorders •cancer •CFS/ME •combat-related cognitive symptoms •HD •Hearing loss •MCI •MDD •MS •PD •PTSD •stress-related exhaustion •stroke •SZ •TBI •Tinnitus

Abbreviations: MCI mild cognitive impairment, AD Alzheimer's Dementia, ADHD attention deficit hyperactivity disorder, SZ schizophrenia, MS multiple sclerosis, PD Parkinson's Disease, TBI traumatic brain injury, PTSD post-traumatic stress disorder, CFS/ME chronic fatigue syndrome/myalgic encephalitis, HD Huntington's Disease, TMS transcranial magnetic resonance stimulation, tDCS transcranial direct current stimulation, tACS transcranial alternating current stimulation, tRNS transcranial random noise stimulation, EEG electroencephalography, fMRI functional magnetic resonance imaging