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Invited review

Non-pharmacological cognitive enhancement

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ABSTRACT

The term "cognitive enhancement" usually characterizes interventions in humans that aim to improve mental functioning beyond what is necessary to sustain or restore good health. While the current bioethical debate mainly concentrates on pharmaceuticals, according to the given characterization, cognitive enhancement also by non-pharmacological means has to be regarded as enhancement proper. Here we summarize empirical data on approaches using nutrition, physical exercise, sleep, meditation, mnemonic strategies, computer training, and brain stimulation for enhancing cognitive capabilities. Several of these non-pharmacological enhancement strategies seem to be more efficacious compared to currently available pharmaceuticals usually coined as cognitive enhancers. While many ethical arguments of the cognitive enhancement debate apply to both pharmacological and non-pharmacological enhancers, some of them appear in new light when considered on the background of non-pharmacological enhancement.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Humans have always striven to increase their mental capacities. From symbolic language, writing and the printing press to mathematics, calculators and computers: Mankind has devised and employed tools to record, store and exchange thoughts and hence, in a more abstract sense, to enhance cognition. Such external devices aiding cognition do not seem to raise any ethical concerns, at least not in regard to the aim of enhancing cognitive functions. In contrast, the introduction of means to enhance cognition internally by intervening in the brain in a more straightforward way has raised ethical and legal concerns and is regarded by (some parts of) the public as highly suspicious. The prospects and perils of cognitive enhancers have prompted wide discussion in ethics, law and politics. Cognitive enhancement has become a trend topic both in academic and public debate – however the discussants bring a very diverse background and motivation to this debate. The aim of many empirical researchers of cognitive enhancement is to understand the neurobiological and psychological mechanisms underlying cognitive capacities (McGaugh and Roozendaal, 2009), while theorists are rather interested in their social and ethical implications (Savulescu and Bostrom, 2009). While in basic research very specific mechanisms are studied (mostly in animal models), many theoretical discussions start from the counterfactual idea of a highly effective drug that makes its consumer super smart. In contrast, there is a surprising paucity of research that evaluates the effects of currently existing cognitive enhancers in healthy individuals. A widely cited definition characterizes cognitive enhancement as interventions in humans that aim to improve mental functioning beyond what is necessary to sustain or restore good health (Juengst, 1998). While the current bioethical debate on cognitive enhancement shows a strong focus on pharmacological ways of enhancement, according to the given characterization, enhancement of mental capabilities also by non-pharmacological means has to be seen as cognitive enhancement proper. In this paper we aim to draw attention to several non-pharmacological

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cognitive enhancement strategies that have been largely neglected in the debate so far. We will first summarize studies on the efficacy of psychopharmacological enhancers and then present data on the cognition enhancing effects of a number of non-pharmacological methods. We will start with broadly used interventions that are not commonly recognized as enhancement strategies such as nutrition, physical exercise and sleep, and then will go over to more specific methods such as meditation, mnemonic techniques, computer training, and brain stimulation technologies. We will restrain our review to methods that currently exist and won't speculate on future technologies. While many ethical arguments of the cognitive enhancement debate apply to both pharmacological and non-pharmacological enhancers, some of them appear in new light when considered on the background of non-pharmacological enhancement.

2. Pharmaceuticals

The bioethical debate on enhancement mainly concentrates on psychopharmaceuticals. In particular psychostimulants are increasingly popular among healthy people seeking cognitive enhancement (Talbot, 2009; Smith and Farah, 2011). Beside amphetamines, which are not reviewed here, two particular substances have frequently been in the spotlight of both the scientific (de Jongh et al., 2008; Sahakian and Morein-Zamir, 2007) and popular press (The Economist, 2008; Talbot, 2009) because of their assumed enhancing properties, namely methylphenidate and modafinil. The first, a stimulant used to treat attention-deficit hyperactivity disorder (ADHD), is known to have been extensively misused, especially by college students as a "study aid" (McCabe et al., 2005; Wilens et al., 2008). The second, modafinil, a wakefulness promoting agent licensed for the treatment of excessive daytime sleepiness associated with narcolepsy, is already used by military personnel for missions of longer duration to counteract fatigue after sleep deprivation (Bonnet et al., 2005; Caldwell and Caldwell, 2005; Moran, 2007). It also seems to become increasingly popular in both business and in academia. In a non-representative online poll conducted by Nature magazine (Maher, 2008), 20% of the 1400 responding readers reported use of methylphenidate, modafinil or beta-blockers for non-medical reasons: 62% of users reported taking methylphenidate and 44% modafinil. Indirect evidence for the non-medical use of methylphenidate and modafinil can also be gained by companies constantly raising sales and by comparing their disproportionately high prescription numbers to the numbers of patients suffering from the disorders for which these substances are approved or used off-label (Mehlman, 2004).

Methylphenidate is a dopamine reuptake blocker that also enhances dopamine and norepinephrine release with pharmacologic mechanisms similar to those of amphetamines (Sulzer et al., 2005). The mechanisms of action of modafinil are not well understood but are believed to differ from those of methylphenidate and amphetamines. Although there is mounting evidence that the effects on dopamine and norepinephrine are primary, effects on γ-aminobutyric acid, glutamate, histamine and orexin/hypocretin are also theorized (Volkow et al., 2009; Minzenberg and Carter, 2008; Ballon and Feifel, 2006). Although these drugs are supposed to affect cognition mainly, the widespread neurochemical systems they implicate suggest that they might also have an impact on emotional and motivational functions. In a systematic review on the effects of these stimulants on healthy individuals it has been shown that there is a lack of studies addressing this issue (Repantis et al., 2010b). Regarding methylphenidate, the analysis of the few existing studies provided no consistent evidence for enhancing effects, though evidence for a positive effect on memory (mainly spatial working memory) was found. While such memory benefits seem to be in the large effect size range, the popular opinion that methylphenidate enhances attention was not verified (Repantis et al., 2010b). Some studies reported even negative effects, such as a disruption of attentional control (Rogers et al., 1999).

In a systematic review modafinil was found to have some positive, though moderate, enhancing effects on individuals who were not sleep deprived, namely on attention (Repantis et al., 2010b). No effect was found on memory, mood or motivation in the few studies that examined these domains, but the results of the studies were not unequivocal. Moreover, there is evidence that the effect of modafinil depends to some extent on the individual baseline performance (Randall et al., 2005).

In the above mentioned systematic reviews also side effects of methylphenidate and modafinil on healthy individuals have been reviewed (Repantis et al., 2010b). Since most of the included papers reported small studies and not large-scale clinical trials, no standardized method of assessing adverse reactions and reporting drop-outs due to adverse effects was used. In a number of studies (26 for methylphenidate and 26 for modafinil), no comment on side effects was made, which leaves us to assume that no severe adverse effects appeared that would deserve a comment in the limited space of a publication. In the majority of the trials, the drugs were well tolerated. There were some side effects reported, but these were benign and only in few cases lead to drop-outs. For modafinil adverse reactions were primarily headache, dizziness, gastrointestinal complains (e.g. nausea, abdominal pain, dry mouth), increased diuresis, palpitations, nervousness, restlessness, and sleep disturbances and especially in studies with non-sleep deprived individuals, insomnia (Baranski and Pigeau, 1997; Caldwell et al., 1999, 2000, 2004; Dinges et al., 2006; Eddy et al., 2005; Gill et al., 2006; Hart et al., 2006; Lagarde et al., 1995; Pigeau et al., 1995; Wesensten et al., 2002; Whitmore et al., 2006). For methylphenidate a frequently reported side effect (reported in 13 out of 14 trials reporting side effects) was increased heart rate, while increase in blood pressure was not consistently found (Bray et al., 2004; Brumaghim and Klorman, 1998; Clark et al., 1986; Fitzpatrick et al., 1988; Hink et al., 1978; Mehta et al., 2000; Peloquin and Klorman, 1986; Rogers et al., 1999; Strauss et al., 1984; Volkow et al., 1999a, 1999b; Wetzel et al., 1981). Besides these, typical complaints were headache, anxiety, nervousness, dizziness, drowsiness and insomnia. In total, these drugs seem to be well-tolerated even by this population where the trade-off between side effects and improvement may be less clear. Finally, since the majority of the studies that have been performed were short-term and single-dose studies, no comment can be made on the reinforcing effects, dependence development, and drug tolerance of MPH or modafinil in healthy individuals.

Prescription drugs currently available for the treatment of dementia provide a further possibility for cognitive enhancement. Of interest are the drugs used for the treatment of dementia due to Alzheimer's disease, namely the acetylcholinesterase inhibitors and memantine. The first category comprises three substances – donepezil, galantamine, rivastigmine – that are recommended for clinical use for the treatment of patients with mild to moderate Alzheimer's disease (Racchi et al., 2004). Memantine is a NMDA receptor antagonist and is registered for the treatment of moderate to severe Alzheimer's disease (Sonkusare et al., 2005). Studies with anti-dementia drugs were found to be lacking. In a systematic review (Repantis et al., 2010a) only ten trials with donepezil, one with rivastigmine and seven with memantine have been reported. No randomized controlled trials examining the effects of galantamine in healthy individuals were found. Anti-dementia drugs show their effect after intake for several weeks. All memantine and the one galantamine trial were however single dose trials. Hence, based on these few and insufficient data, no adequate analysis of their potential as cognitive enhancers can be performed. Repeated trials have been conducted only with donepezil. These were six small scale trials, lasting 14–42 days. From these, only two (Beglinger et al., 2005; Fitzgerald et al., 2008b) had older persons as participants. The rest of the trials included young healthy participants. This factor complicates the comparison between the results and makes it difficult to generalize the results of the latter studies for the main population of interest, namely the growing elderly population.

These few existing studies provide no consistent evidence for a cognitive enhancement effect. In one study it was found that donepezil improved the retention of training on complex aviation tasks (Yesavage et al., 2002). In an another case, verbal memory for semantically processed words was improved (Fitzgerald et al., 2008a). Donepezil might also improve episodic memory (Gron et al., 2005), but interestingly, two studies reported transient negative effects on episodic memory (Beglinger et al., 2004, 2005). A newer study found also an impairment of working memory in older healthy participants taking donepezil for six weeks (Balsters et al., 2011). In a sleep deprivation study, donepezil had no effect when participants were well-rested. Nevertheless, the memory and attention deficits resulting from 24 h of sleep deprivation were attenuated after donepezil intake. This effect however, was seen only in individuals whose performance declined the most after sleep deprivation (Chuah and Chee, 2008; Chuah et al., 2009), and could not be confirmed in a recent study (Dodds et al., 2011). Another point that should be made is that in most of the studies a large neuropsychological test battery was applied. However, an effect could be shown in only a few, if not only one, of the tests applied. This could speak either for a selective effect of donepezil or for small effects that in these relatively underpowered studies could only be revealed in only one (maybe the most difficult) task. Another possible explanation could be that acetylcholinesterase inhibitors require a pathology of diminished cholinergic transmission to show their effects, and, therefore, it is not possible to optimize performance in healthy individuals that already have an optimal concentration of acetylcholine. In conclusion, evidence for cognition enhancing effects of currently available psychopharmaceuticals in healthy subjects is sparse.

In the majority of the trials, donepezil was well tolerated, however some authors warn that sleep disturbances might become apparent in larger populations (Yesavage et al., 2002). Reported side effects were benign and only in few cases led to drop-outs. The adverse reactions were mainly gastrointestinal complaints (e.g. nausea), but also headache, dizziness, nightmares and insomnia.

3. Nutrition

Numerous food products and dietary supplements claim effects like “increase energy” or “enhance memory” despite scarce, controversial or even lacking scientific evidence. Nutritional enhancers are consumed, intentionally or unintentionally, in everyday situations and they can reduce fatigue, e.g. through a coffee after lunch, and help maintain full cognitive capacities, e.g. through sweet snacks during an exam. Here, we review the acute effects of two commonly consumed dietary constituents, namely caffeine and sugar (glucose).

Caffeine is an adenosine receptor antagonist; it reduces inhibition of neural firing by large through an increased turnover of noradrenaline in the brain (Smith et al., 2003; Ferre, 2008). It exerts its stimulating effects within less than an hour after administration through altering the biochemistry of the brain. Typical behavioral effects of caffeine include elevated mood, increased alertness, and better sustained attention (Smith et al., 1991, 2005; Hewlett and Smith, 2007). It improves motor-skill performance on tasks that are impaired when arousal is low, e.g. during simulations of driving (Reyner and Horne, 1997) and increases speed of encoding and response to new stimuli (Warburton et al., 2001; Riedel et al., 1995). Caffeine effects on more complex and cognitively demanding tasks are, however, controversial in that some authors report better performance (Heatherley et al., 2005) but also null-findings effects (Rogers and Dernoncourt, 1998). The effects of caffeine on memory and learning are particularly disputed and positive effects can be in large attributed to indirect effects from elevated attention to the stimuli during encoding (Nehlig, 2010). Another debate concerns the question whether and in how far differences in prior caffeine consumption and their lack of experimental control thereof contribute to these conflicting observations. Caffeine tolerance has been demonstrated (Evans and Griffiths, 1992) and is more likely to occur in habitual, heavy coffee drinkers. Coffee drinkers represent, however, the group that is most prone to intentionally exploiting the enhancing effects of caffeine. Caffeine withdrawal after heavy coffee consumption has been associated with headaches, increased subjectively perceived stress and feelings of fatigue and reduced alertness in some studies (Ratcliff-Crain et al., 1989; Schuh and Griffiths, 1997; Dews et al., 2002; Juliano and Griffiths, 2004). However, withdrawal effects can, at large, be explained by psychological rather than pharmacological factors of reduced caffeine intake (Dews et al., 2002). In line with this, it has been shown that expectancy mimics effects of caffeine when consumers believe they consume a caffeinated beverage (Fillmore, 1994), thus further corroborating a psychological component of the caffeine effect following both consumption and withdrawal. While psychological aspects of caffeine withdrawal appear to be relevant particularly in subjective report of mood and energy, evidence suggests that caffeine enhances task performance independent of whether consumed in the abstained or normal caffeinated state in coffee drinkers (Smit and Rogers, 2000; Addicott and Laurienti, 2009). On the other hand, it appears that caffeine yields similar effects when administered in a coffee, in a tea, or as a capsule, supporting a pharmacological rather than a psychological mechanism when participants' expectations are controlled for (Smith, 2002).

Glucose is the primary breakdown product of carbohydrates and the fuel for our cells. It is provided through the blood constantly and measured as the level of blood sugar. In an attempt to keep the blood sugar level constant, excess glucose must be stored and released later, which is achieved by the pancreatic hormones insulin and glucagon. Insulin is released with high levels of blood sugar and stimulates the synthesis of glycogen. Glucagon is released with decreasing blood sugar; it targets the liver to break up glycogen into glucose. Hypoglycemia, i.e. when the blood glucose level falls to very low values, can affect cognitive functioning negatively and is associated with slower reaction times in task that require attention. In healthy individuals, however, the blood glucose level appears to be fairly stable during the day. Subjective reports of “increased mental energy” have been associated with higher glucose metabolism in the brain (Posner et al., 1988; Reivih and Alavi, 1983), and this effect occurs within several minutes after glucose administration. With regard to objective cognitive performance, glucose improves attention (Benton et al., 1994), response speed (Owens and Benton, 1994) and working memory (Scholey et al., 2001), the latter occurring under conditions of high but also under low glucose depletion (Owen et al., 2012; Jones et al., 2012). The most pronounced effects of glucose on cognition are found for declarative memory (Messier, 2004; Smith et al., 2011), where effect sizes in the large range have been demonstrated in particular for demanding tasks (e.g.

Sünram-Lea et al., 2001, 2002a, 2002b; Meikle et al., 2004). High blood-glucose level are associated with improved memory function (Benton and Owens, 1993), and glucose administration before and after learning similarly improves memory performance, indicating that attentional or other non-memory specific processes during encoding alone cannot be responsible for the memory enhancing effects of glucose (Sünram-Lea et al., 2002a). Memory effects are more pronounced in elderly as compared to young adults, and glucose tolerance was predictive for declarative memory performance (Manning et al., 1990; Meikle et al., 2004; Messier, 2004). On a neural level, the hippocampus has been proposed as the main brain region mediating the memory enhancing effects of glucose, with more specific mechanisms involving glucose effects on cerebral insulin, acetylcholine synthesis, potassium adenosine triphosphate channel function, and brain extracellular glucose availability (Smith et al., 2011).

Taken together, the findings show that caffeine and sugar enhance mood, subjectively perceived energy, vigilance, attention, and memory, and may even exert their effects in a synergistic fashion if administered together (Adan and Serra-Grabulosa, 2010). Individual differences, e.g. in glucose tolerance or nutritional habits such as caffeine consumption, influence the extent and direction of these effects.

4. Physical exercise

It is common knowledge that regular physical activity is a highly beneficial factor for preventing cardiovascular diseases and staying healthy in general. Already in the first half of the 20th century it was demonstrated that athletes outperform physically inactive individuals also in cognitive functions (Burpee and Stroll, 1936), and an emerging body of evidence suggests that regular aerobic exercise indeed has beneficial effects on brain function and cognition (Hillman et al., 2008). The focus of most studies on physical exercise effects on cognition is on developmental issues: Either children of different age groups or elderly adults were examined. In school-age children, physical exercise was demonstrated to benefit e.g. academic achievement, intelligence, perceptual skills, and verbal and mathematical ability (Sibley and Etnier, 2003). In older adults with and without pathological cognitive decline, beneficial effects of various physical exercise programs on different aspects of cognition were observed (Richards et al., 2003; van Uffelen et al., 2008). A recent meta-analysis of randomized controlled trials demonstrated that aerobic exercise training improves attention, processing speed, executive function and memory, while effects on working memory were less consistent (Smith et al., 2010). Even if methodological issues in measuring the impact of exercise on cognition in particular for studies with elderly subject populations remain (Miller et al., 2012), the conclusion that physical activity helps to preserve mental abilities throughout aging seems to be warranted.

In contrast to research in children and older adults, there is a paucity of studies on physical exercise effects on the cognition of younger and middle age adults. Most data on these age groups can be found in studies on older adults, where they were examined as control groups for comparison with the elderly. An exception of this pattern constitute studies focusing not on chronic effects of regular physical activity, but on acute effects of exercise. For example, brief bouts of physical exercise improved long-term memory in young adults (Coles and Tomporowski, 2008). Intense exercise in the form of high impact anaerobic running was shown to strongly enhance learning speed in an vocabulary memorizing task (Winter et al., 2007). A recent meta-analysis demonstrated that in particular mental speed and memory processes are consistently enhanced after acute exercise, while the effects during acute exercise seem to depend on the specific exercise mode. In general, however, cognition enhancing effects of acute exercise seem to be in the small to medium range (Lambourne and Tomporowski, 2010). Besides motivational factors, an increase in general arousal level related to physical exertion has been hypothesized as a potential mechanism (Brisswalter et al., 2002).

Data on the neural mechanisms underlying the effects of physical exercise on human cognition is rather sparse. Regular physical exercise training improved resting functional efficiency in higher-level cognitive networks including the frontal, posterior, and temporal cortices of older training participants compared to a control group (Voss et al., 2010). In particular greater task-related activity in fronto-parietal networks is associated with both general cardiovascular fitness and exercise training effects on cognition (Colcombe et al., 2004). Also hippocampal cerebral blood flow and hippocampal connectivity exhibit significant increases through physical exercise (Burdette et al., 2010). Structurally, cardiovascular fitness within the healthy elderly correlates with preserved gray matter areas that typically show age-related decline (Gordon et al., 2008), in particular hippocampal volume was found to be associated with physical fitness in older adults (Erickson et al., 2009), but also in children (Chaddock et al., 2010). Significant brain volume increases in both gray and white matter regions were also demonstrated to be associated with aerobic exercise training (Colcombe et al., 2006). In particular the size of the anterior hippocampus was shown to increase through physical exercise, which was related to enhanced spatial memory and increased serum brain-derived neurotrophic factor (BDNF) levels, a mediator of hippocampal neurogenesis in the dentate gyrus (Eriksson et al., 2011). This is in line with data derived from animal models, showing that physical exercise increases BDNF gene expression in the hippocampus (Neeper et al., 1995), and that hippocampal BDNF indeed mediates the effects of physical exercise on cognition (Vaynman et al., 2004; Gomez-Pinilla et al., 2008). Also the enhancing effects of intense acute exercise seem to be mediated by BDNF increases (Winter et al., 2007). Finally, parallel studies in mice and humans demonstrated that cerebral blood volume measurements provide an imaging correlate of neurogenesis in the dentate gyrus and that physical exercise had a primary effect on dentate gyrus cerebral blood volume that correlated with cognitive function (Pereira et al., 2007). In conclusion, there is converging evidence on several levels of observation that physical exercise enhances cognitive function throughout the lifespan.

5. Sleep

Humans spend a third of their lifetime in sleep. From an evolutionary standpoint, this phenomenon helps to save energy — but also leaves the sleeper in a potentially dangerous state of inattention. Sleep therefore has to provide the organism with important advantages to compensate for this disadvantage. A rapidly growing body of literature suggests that an important function of sleep is to enhance cognitive capacities, in particular memory (Diekelmann and Born, 2010) and creativity (Dresler, in press).

First empirical reports on the positive effects of post-learning sleep on memory consolidation were published almost a century ago: Jenkins and Dallenbach (1924) demonstrated that memory for nonsense syllables over retention periods including sleep is less prone to forgetting compared to an equivalent time of wakefulness. Since then, hundreds of studies testing different memory systems have confirmed the positive effects of sleep on memory consolidation (Diekelmann and Born, 2010). It might be argued that regular sleep is just a general biological prerequisite to ensure cognitive functioning and therefore sleep trivially favors memory consolidation in comparison to sleep deprivation. However, also in experimental designs without sleep deprivation as a control condition sleep positively effects memory consolidation compared to wakefulness, e.g. when retention intervals during the day are compared with nocturnal retention intervals of similar length (Fischer et al., 2002; Walker et al., 2002). Furthermore, a growing number of studies demonstrates that also additional sleep in the form of daytime naps benefits memory function in non-sleep-deprived subjects (e.g. Mednick et al., 2003; Korman et al., 2007). Of note, even a nap as short as 6 min has been shown sufficient to promote memory performance (Lahl et al., 2008), and for some memory systems the benefit of a daytime nap is comparable to a whole night of sleep (Mednick et al., 2003). In general, the size of the sleep effect on memory consolidation seems to depend on the involved memory system: While for declarative learning effect sizes of sleep are in the medium range (e.g. Gais et al., 2006), sleep effects on procedural or perceptual learning are large (Fischer et al., 2002) or very large (Karni et al., 1994). Besides its stabilizing function, sleep boosts certain kinds of memories even above the level of initial acquisition: Procedural memories like motor skills typically reach a plateau after some time of training – however after a night of sleep motor performance starts from a higher level despite the absence of further training (Walker et al., 2002). Interestingly, the sleep-memory relationship is specifically influenced by personal factors like gender, hormonal status or mental health (Dresler et al., 2010; Genzel et al., 2012).

The neural mechanisms underlying the effects of sleep on memory consolidation are still poorly understood. A major point of discussion is the question if newly formed memories profit from rather passive homeostatic processes (Tononi and Cirelli, 2003) or are actively consolidated during sleep. While several animal studies demonstrated a neuronal replay of activation patterns during sleep that were associated with recent memories (Wilson and McNaughton, 1994; Ji and Wilson, 2007), a study with humans utilizing memory-related odor cues during sleep could demonstrate a causal role of sleep for memory consolidation (Rasch et al., 2007). For several years it was thought that rapid eye movement (REM) sleep supports the consolidation of procedural memories while non-REM sleep supports declarative memories like verbal information, however recent studies suggested that this model was too simplistic (Genzel et al., 2009; Rasch et al., 2009; Dresler et al., 2011). Instead of global sleep stages, the role of physiological microprocesses during sleep gained attention. In particular the interaction of hippocampal sharp wave ripples, thalamo-cortical sleep spindles, and cortical slow oscillations is thought to play a physiological key role in the consolidation of memories (Mölle and Born, 2011).

Anecdotal reports on scientific discovery, inventive originality, and artistic productivity suggest that also creativity can be triggered or enhanced by sleep. Several studies confirm these anecdotes, showing that sleep promotes creative problem solving compared to wakefulness. For example, when subjects performed a cognitive task, which could be solved much faster through applying a hidden rule, after a night of sleep more than twice as many subjects gained insight into the hidden rule as in a control group staying awake (Wagner et al., 2004). Like sleep-related memory enhancement, active processes during sleep seem to promote creativity: If applied during sleep, olfactoric stimuli that were associated with creativity tasks before sleep trigger insights overnight (Ritter et al., in press). In particular REM sleep, the sleep stage most strongly associated with intense dreaming, enhances the formation of associative networks in creative problem solving (Cai et al., 2009). Selective deprivation of REM sleep but not of other sleep stages impairs post-sleep performance in creativity tasks that are presented to the subjects before sleep (Cartwright, 1972; Glaubman et al., 1978). Subjects show greater cognitive flexibility in creativity tasks immediately after awakenings from REM sleep compared to awakenings from other sleep stages (Walker et al., 2002).

Both theoretical models and empirical research of creativity suggest that sleep is a highly effective creativity enhancer (Dresler, in press). The historical standard model proposes a passive incubation phase as an essential step to creative insights (Helmholtz, 1896). Psychoanalytical models emphasize primary process thinking for creative cognitions – which is explicitly conceptualized as dream-like (Kris, 1952). Cognitive models propose that flat association hierarchies and a state of defocused attention facilitate creativity (Mednick, 1962). Hyper-associativity and defocused attention are phenomenal features of most dreams, physiologically probably caused by prefrontal cortex deactivation (Hobson and Pace-Schott, 2002). Physiological models suggest a high variability in cortical arousal levels as beneficial for creativity (Martindale, 1999), and the sleep cycle can be considered as a prime example of such arousal variability. The chaotic activation of the cortex in REM sleep through brainstem regions in absence of external sense data leads to a much more radical renunciation from unsuccessful problem solving attempts, leading to co-activations of cognitive data that are highly remote in waking life. These co-activations, woven into a dream narrative in a self-organizing manner, repeatedly receive further innervations by the brainstem, leading to bizarre sequences of loosely associated dream topics that might eventually activate particular problem-relevant cognitions or creative cognitions in general (Hobson and Wohl, 2005). In conclusion, the phenomenological and neural correlates of sleep provide ideal incubation conditions for the genesis of creative ideas and insights.

6. Meditation

Meditation has been emphasized as a discipline that promotes mental well-being, however recent research also suggests that it benefits several cognitive capacities. Meditation has been conceptualized as a family of complex emotional and attentional regulatory training regimes (Lutz et al., 2008). Such approaches include ancient Buddhist mindfulness meditations such as Vipassana and Zen meditations, but also several modern group-based standardized meditations (Chiesa and Malinowski, 2011). In the focus of current research are two rather traditional approaches: focused attention meditation and open monitoring meditation, which involve voluntary focusing of attention on a chosen object or non reactive monitoring of the content of experience from moment to moment (Lutz et al., 2008). During recent years, the effects of meditation practice were systematically studied also in western laboratories, and a rapidly growing body of evidence demonstrates that meditation training enhances attention and other cognitive capacities. For example, in comparisons of experienced meditators with meditation-naive control subjects, meditation practice has been associated with increased attentional performance and cognitive flexibility (Moore and Malinowski, 2009; Hodgins and Adair, 2010). In longitudinal studies, three months of meditation training could be shown to enhance attentional capacity (Lutz et al., 2009), perception and vigilance (MacLean et al., 2010). Even a brief training of just four meditation sessions was sufficient to significantly improve visuo-spatial processing, working memory and executive functioning (Zeidan et al., 2010). A recent systematic review associated early phases mindfulness meditation training with significant improvements in selective and executive attention, whereas later phases were associated with improved sustained attention abilities. In addition, meditation training was proposed to enhance working memory capacity and some executive functions

(Chiesa et al., 2011). A recent meta-analysis of the effects of meditation training reported medium to large effect sizes for changes in emotionality and relationship issues, medium effect sizes for measures of attention and smaller effects on memory and several other cognitive capacities (Sedlmeier et al., in press).

Also the neurophysiological mechanisms underlying meditation practice and its relation to cognition have been addressed. Electroencephalographic (EEG) studies have revealed a significant increase in alpha and theta activity of subjects that underwent a meditation session (Kasamatsu and Hirai, 1966; Murata et al., 1994). Neuroimaging studies have shown that meditation practice activates or deactivates brain areas comprising the prefrontal cortex and the anterior cingulate cortex (Holzel et al., 2007), the basal ganglia (Ritskes et al., 2003), the hippocampus, the pre- and post-central gyri as well as the dorsolateral prefrontal and parietal cortices (Lazar et al., 2000). Focusing on attention studies, it has been demonstrated that long-term meditation supports enhancement in the activation of specific brain areas, while also promoting attention sustainability (Davidson et al., 2003). Different studies have also emphasized the role of meditation as a mental process that modulates plasticity in neural circuits commonly associated to attention (Davidson and Lutz, 2008). fMRI studies have demonstrated a reduction of neural responses in widespread brain regions that are linked to conceptual processing, which suggests enhanced neural efficiency, probably via improved sustained attention and impulse control (Pagnoni et al., 2008; Kozasa et al., 2012). Moreover, PET studies have demonstrated an increase of dopamine release in the ventral striatum as a result of yoga meditation, which in turn suggest regulation of conscious states at the synaptic level (Kjaer et al., 2002). In addition, some studies have suggested that meditation practice is associated with structural brain changes. Compared to meditation-naive control subjects, long-term meditators showed significant larger volumes of the right hippocampus and orbitofrontal cortex (Luders et al., 2009) and significant greater cortical thickness in brain regions associated with attention, interoception and sensory processing, including the prefrontal cortex and right anterior insula (Lazar et al., 2005). In a longitudinal study with meditation-naive subjects undergoing an 8-week meditation program, gray matter increases in the hippocampus and other brains regions have been observed (Hölzel et al., 2011).

7. Mnemonics

In modern society, the ability to cope with verbal or numerical information becomes increasingly important. However, our learning skills evolved to handle concrete visuo-spatial rather than abstract information: While we can easily remember our last birthday party in great detail and typically don't have any problems recalling a once walked route including dozens or even hundreds of single sights and branches, most of us have a very hard time memorizing telephone numbers, foreign vocabularies or shopping lists. The most common way to memorize such information is rote learning: We take up the information to be remembered into our short-term memory and repeat it over and over again. However, such a procedure is slow and inefficient – in particular due to a severe limitation of short term memory capacity: As Miller (1956) observed more than half a century ago, the number of arbitrary information chunks an average human can hold in short-term memory is seven, plus or minus two. In contrast, some few individuals show memory skills far beyond this normal range: Already a century ago some case reports mention exceptional memorizers with memory spans of several dozens digits (Brown and Deffenbacher, 1975). In a seminal case study, a normal college student was trained over the course of two years, eventually reaching a memory span of 82 digits read at the pace of one digit per second (Ericsson et al., 1980). Since the early 1990s, the top participants of the annual World Memory Championships regularly prove memory spans of hundreds of digits (Konrad and Dresler, 2010). However, such superior memorizers do not seem to exhibit structural brain changes or superior cognitive abilities in general, but acquired their skills by deliberate training in the use of mnemonic techniques (Brown and Deffenbacher, 1988; Maguire et al., 2003; Ericsson, 2009).

To cope with the limitations of natural memory, humans have always used external remembering cues (D'Errico, 2001). The term *mnemonics* is typically used to denote internal cognitive strategies aimed to enhance memory. Parallel to their success in memory artistry and memory sports, several mnemonics have been shown to strongly enhance memory capacity in scientific studies (Bellezza, 1981; Worthen and Hunt, 2011a, 2011b). Probably most prominent is the so called *method of loci*, an ancient technique used extensively by Greek and Roman orators (Yates, 1966). It utilizes well established memories of spatial routes: During encoding, to-be-remembered information items have to be visualized at salient points along such a route, which in turn has to be mentally retraced during retrieval. A second powerful mnemonic is the *phonetic system*, which is designed to aid the memorization of numbers: Single digits are converted to letters, which are then combined to form words. Both the method of loci and the phonetic system have been shown to be very effective and even increase their efficacy over time, i.e. at delayed recall after several days compared to immediate recall (Bower, 1970; Roediger, 1980; Bellezza et al., 1992; Hill et al., 1997; Higbee, 1997; Wang and Thomas, 2000). A third mnemonic that has to be shown effective is the *keyword method*, designed specifically to enhance the acquisition of foreign vocabulary (Raugh and Atkinson, 1975), but also helps to learn scientific terminology (Rosenheck et al., 1989; Brigham and Brigham, 1998; Balch, 2005; Carney and Levin, 1998). It associates the meaning of a to-be-remembered term with what the term sounds like in the first language of the learner.

A recently published broad overview on mnemonics demonstrates that research into these techniques has lost attention since 1980 (Worthen and Hunt, 2011b). In particular neurophysiological data on mnemonics is sparse. A seminal study on expert mnemonics users found that during mnemonic encoding brain regions are engaged that are critical for spatial memory, in particular parietal, retrosplenial and right posterior hippocampal areas (Maguire et al., 2003). Likewise, the superior digit memory of abacus experts was associated specifically with visuo-spatial information processing brain regions (Tanaka et al., 2002). Here, abacus skill can be interpreted as a mnemonic for digit memorizing. In two studies with novices taught in the method of loci, mnemonical encoding led to activation increases particularly in prefrontal and occipito-parietal areas, while mnemonic-guided recall led to activation increases particularly in left-sided areas including the parahippocmpal gyrus, retrosplenial cortex and precuneus (Nyberg et al., 2003; Kondo et al., 2005).

Another strategic method to enhance memory retention that has gained attention in recent years is retrieval practice. While retrieval of learned information in testing situations is traditionally thought to simply assess learning success, repeated retrieval itself has been shown to be a powerful mnemonic enhancer, producing large gains in long-term retention compared to repeated studying (Roediger and Butler, 2011). For example, when students have to learn foreign vocabulary words, repeated studying after the first learning trial had no effect on delayed recall after one week, while repeated testing produced a surprisingly large effect on long-term retention (Karpicke and Roediger, 2008). Besides vocabulary learning, also text materials profit from repeated retrieval (Karpicke and Roediger, 2006, 2010). Interestingly, study participants seem to be unaware of this effect, overestimating the value of repeated study and underestimating that of repeated retrieval (Karpicke and Roediger, 2006, 2008). Effects of retrieval practice were even shown to produce greater success in meaningful learning than elaborative studying strategies, which are designed to lead to deeper learning and therefore hold a central place in contemporary education (Karpicke and Blunt, 2011). On the neural level, repeated retrieval leads to higher brain activity in the anterior cingulate cortex during retest, which was interpreted as an enhanced consolidation of memory representations at the systems level (Eriksson et al., 2011).

In conclusion, mnemonic strategies can be seen as strong and reliable enhancers of learning and memory capacity. While their immediate benefits for easy-to-learn material seem to be in the small to medium effect size range, the effectiveness of mnemonics strikingly grows with task difficulty or retention time and can reach effect sizes in terms of Cohen's d of larger than 3 or 4 (e.g. Higbee, 1997; Karpicke and Roediger, 2008). Of note, the benefits of mnemonics in population groups with particular cognitive training needs as e.g. in age-related cognitive decline seem to be less pronounced (Verhaeghen et al., 1992), however still can reach large effect sizes if memory is assessed after prolonged retention time (Hill et al., 1997).

8. Computer training

The rapid growth of computer game popularity in adolescents has generated concern among practitioners, parents, scholars and politicians. For violent computer games, detrimental effects have been reported in the social domain, namely increases in aggression and reductions of empathy and prosocial behavior (Kirsh and Mounts, 2007; Anderson et al., 2010). But favorable effects of frequent computer game playing have also been observed. Computer games allow repeated, sometimes rewarding, training of various mental tasks with variation and interactivity. While improved performance on the tasks inside the games is unsurprising, they may also be able to transfer their effects to other cognitive domains or enhance general cognitive abilities.

Much interest has been focused on enhancing long term memory or brain plasticity in healthy or mildly impaired older adults using training programs, especially to prevent dementia and age related cognitive decline (Cotelli et al., 2012; Tardif and Simard, 2011). Computerized training programs have shown moderate improvements of memory that are sustained 3 months after end of training (Mahncke et al., 2006). Other studies have found improvements in memory and attention (Smith et al., 2009; Zelinski et al., 2011), executive function and processing speed (Nouchi et al., 2012; Basak et al., 2008) and working memory and episodic memory in young and older adults (Schmiedek et al., 2010). However, a large six-week online study did not find evidence for transfer (Owen et al., 2010). Also, although computerized brain training games have become a major industry it is not clear that the commercial games transfer to untrained tasks (Fuyuno, 2007; Ackerman et al., 2010).

Computer games appear to be able to train visual skills, such as visuo-spatial attention, number of objects that can be attended and resolution of visual processing (Achtman et al., 2008; Hubert-Wallander et al., 2011). Playing the game Tetris improved mental rotation and spatial visualization time (Okagaki and Frensch, 1994), and computer game training improved contrast sensitivity (Li et al., 2009), spatial visual resolution (Green and Bavelier, 2007) and task-switching (Strobach et al., 2012). However, these enhanced abilities, although not tied directly to the gaming task, might nevertheless be limited to similar domains. For example, a study found that games enhance navigation performance in desktop and immersive virtual environment but not real environments (Richardson et al., 2011).

Regular or expert gamers show various improvements in mental ability compared to non-gamers. For example, first-person-shooter game players showed greater cognitive flexibility than non-players (Colzato et al., 2010), players enumerate better (Green and Bavelier, 2006), have faster visual search (Castel et al., 2005), have better visual attention (Green and Bavelier, 2003), track object color and identity better (Sungur and Boduroglu, 2012), and have improved psychomotor skills (Kennedy et al., 2011). However, 20+ hour training on computer games did not improve non-video gamers on mental tasks (visual short term memory, task switching, mental rotation) where expert video gamers excelled (Boot et al., 2008). Either pre-existing group differences (or self-selection) make the experts more skilled or amenable to training, or a longer training period is needed. This appears to be a general problem in studying enhancing game effects that need to be circumvented in further studies (Boot et al., 2011).

A cognitive domain that has raised increasing attention in recent years is working memory. Working memory is useful for a variety of cognitive tasks, including intelligence. It can also be trained using computerized tasks such as the n-back task, where the difficulty is increased to remain challenging for the player. Working memory training has been tried for various therapeutic purposes, partially because of its correlation with executive function, but also has also been applied in preschool children, where it transferred to improvement of a fluid intelligence-related task (Thorell et al., 2009; Nutley et al., 2011). Also in healthy adults transfer to fluid intelligence from working memory training has been observed (Jaeggi et al., 2008, 2010). However, the evidence of transfer has been questioned by some authors (Shipstead et al., 2010) and some attempts at replication of transfer effects outside working memory have been unsuccessful (Dahlin et al., 2008; Holmes et al., 2010; Redick et al., in press). Individual differences in training performance predict the transfer effects (Jaeggi et al., 2011). Short- and long-term benefits of cognitive training and different types of training (training core working memory or strategy) might have different transfer effects (Morrison and Chein, 2011). Neurobiologically, working memory training does appear to increase prefrontal and parietal activity (Olesen et al., 2004), white matter volume (Takeuchi et al., 2010), and prompt changes in the density of dopamine D1 receptors (McNab et al., 2009).

Cognitive enhancement through games and computerized training is a promising method, but not all commercial games will have optimal cognitive effects (Hubert-Wallander et al., 2011). Effect sizes of computerized training strongly depend on the cognitive domain trained and tested, with processing speed and perceptual measures showing medium to large effect sizes, while effects for different memory domains are only in the small or medium range (Mahncke et al., 2006; Smith et al., 2009; Schmiedek et al., 2010; Zelinski et al., 2011). What forms of training produce reliable and strong transfer to useful domains remains to be determined. The availability and self-motivating aspects of games is an important advantage over many other methods of cognitive enhancement.

9. Brain stimulation

Several forms of electrical brain stimulation have been developed, acting by non-specifically influencing regions of the brain rather than sending physiological signals. They were developed for therapeutic purposes in psychiatry or neurology, but have in some cases exhibited enhancing effects on cognition of healthy individuals (Hoy and Fitzgerald, 2010; McKinley et al., 2012). Some of these methods are non-invasive, while other achieve greater target specificity by placing electrodes inside or on the brain.

Transcranial direct current stimulation (tDCS) involves sending a small electric current (typically 1–2 mA) between two electrodes placed on the scalp (Been et al., 2007). The technique seems to work by changing the likelihood of neural firing in superficial parts of the cortex: neurons under the anode neurons become hyperpolarized and less excitable, while neurons under the cathode become depolarized and more excitable. This produces different effects depending on polarity and electrode placement, which can outlast the stimulation by more than an hour (Nitsche et al., 2005). The method appears to have few adverse effects (Poreisc et al., 2007). Transcranial magnetic stimulation (TMS) employs a coil to deliver brief magnetic pulses to the scalp, inducing electric currents in the brain. Various modalities (single-pulse, paired-pulse, high and low frequency repetitive) are available and have different cognitive effects, including interference with activity as well various forms of enhancement (Rossi and Rossini, 2004). The effects are likely mediated by similar changes in excitation and inhibition as in tDCS, which in turn might involve changes in synaptic plasticity (Nitsche et al., 2003a, 2003b). TMS has a low number of reported side effects in healthy subjects, typically headaches or local pain, and is generally regarded as quite safe. The most serious risk is the occurrence of seizure, often due to incorrect stimulation parameters or use of medications that lower the seizure threshold (however, even in epileptic patients the crude risk during high frequency rTMS is 1.4%; Rossi et al., 2009). Invasive methods for brain stimulation include deep brain stimulation (DBS) and direct vagus nerve stimulation (dVNS). In DBS electrodes are implanted in deep brain structures and used to modulate their activity through high frequency stimulation. dVNS exploits that stimulation of afferent vagal fibers appears to modulate the central nervous system, perhaps by stimulating brainstem structures (Krahl et al., 1998; Groves and Brown, 2005). The stimulating signal is typically generated by a pacemaker-like device placed under the chest skin. These methods have the drawback of requiring surgery (Kuhn et al., 2010; Ben-Menachem, 2001), but can also provide continual stimulation unlike the non-invasive methods.

Several studies demonstrated enhancing effects of various brain stimulation methods on learning and memory. Learning enhancing effects have been reported for tDCS (Chi et al., 2010; Clark et al., 2012; Javadi et al., 2011; Kincses et al., 2003; Reis et al., 2008), DBS (Williams and Eskandar, 2006; Hamani et al., 2008; Suthana et al., 2012) and dVNS (Clark et al., 1999). These results suggest that the changes in excitability induced by tDCS, TMS and dVNS can help memory encoding, while DBS has the potential to directly affect the modulation of memory systems. Anodal tDCS during slow wave sleep also enhanced memory consolidation (Marshall et al., 2004), perhaps by boosting slow wave oscillations (Marshall et al., 2006). Recall of names of famous people (but not landmarks) was improved by anterior temporal lobe tDCS (Ross et al., 2010). Speed of recall could also be enhanced by galvanic stimulation of the vestibular nerves (Wilkinson et al., 2008) and paired pulse TMS stimulation during encoding (left dorsolateral prefrontal cortex) or retrieval (right dorsolateral prefrontal cortex) (Gagnon et al., 2010). Learning and recall of words were enhanced by anodal (hyperpolarizing) tDCS stimulation of left dorsolateral prefrontal cortex during encoding and cathodal stimulation during retrieval (Javadi and Walsh, 2011). tDCS has been found able to enhance performance on working memory tasks (Fregni et al., 2005; Luber et al., 2007; Teo et al., 2011; Ohn et al., 2008). Sleep-deprivation induced impairment of a visual working memory task was reduced by rTMS (Luber et al., 2008). Low frequency TMS and tDCS applied to the temporal lobe can reduce the incidence of false memories (Gallate et al., 2009; Boggio et al., 2009). The improvement of associative learning from tDCS appears able to carry over to implicit learning (Kincses et al., 2003) and numerical learning (Kadosh et al., 2010). In the latter case arbitrary symbols were shown, and subjects developed long-lasting (6 months) automatic numerical processing and number-to-space mappings for them similar to ordinary numbers.

Also for procedural skills there has been much interest in the ability of TMS to influence brain plasticity, mainly in order to help rehabilitation and therapy (Schabrun and Chipchase, 2012). TMS appears able to modulate short-term motor cortex plasticity (Ziemann et al., 1998). Brain stimulation of the motor areas using TMS and tDCS has been found to enhance learning motor tasks (Nitsche et al., 2003a, 2003b; Reisa et al., 2009). The enhancement can often be ascribed to reducing intra-hemispherical “rivalry” by disrupting the opposite side (Kobayashi et al., 2004; Bütefisch et al., 2004).

Also other cognitive domains were shown to be enhanced by brain stimulation. Verbal fluency was increased by left prefrontal tDCS (Iyer et al., 2005), picture-word verification speeded up by rTMS in Broca’s area (Dräger et al., 2004) and picture naming by rTMS of Wernicke’s area (Mottaghy et al., 1999). rTMS can improve visual spatial attention on one side by impairing the other side (Hilgetag et al., 2001; Thut et al., 2004). Brain stimulation may also have beneficial effects for more complex mental functions. rTMS delivered to the frontal or parietal lobe improved accuracy on the mental rotation task (Klimesch et al., 2003). rTMS over the prefrontal cortex speeded up analogic reasoning, but did not change the error rate (Boroojerdi et al., 2001). tDCS inhibition of the left anterior temporal lobe improved the ability to solve matchstick problems, apparently by reducing mental set and allowing more loose associations (Chi and Snyder, 2011). In one of the few ecologically relevant tests of brain stimulation, tDCS of the dorsolateral prefrontal cortex promoted a more careful driving style in a car simulation (Beeli et al., 2008). This might represent a lowering of risk-taking rather than better planning.

Cognitive processes can be enhanced by inhibiting other brain regions that would otherwise have an interfering effect. TMS can reduce interference between similar-sounding words in phonological memory, improving recall (Kirschen et al., 2006) and reduce distractors in visual search (Hodsoll et al., 2009). It has been claimed that rTMS inhibition of the frontotemporal region produces (besides reduction in immediate recall) savant-like abilities in drawing, mathematics, calendar calculating and proofreading (Young et al., 2004; Snyder et al., 2003). However, individual variations were large compared to the sample size, undermining statistical power. Other experiments along the same lines have hinted at improved number estimation (Snyder et al., 2006).

The efficacy of brain stimulation strongly depends on applying it to the right region; the most successful studies are in general fMRI guided so that they can place electrodes over the right part of the cortex. Individual variation in anatomy and response appear large. Enhancement also depends on selecting the stimulated area to fit the task: there does not exist any generally enhancing effects (beyond, arguably, increases in arousal). Understanding what areas should be inhibited or excited is nontrivial. The effect sizes of the enhancement appear small to modest, however single studies report also larger effects (e.g. Chi et al., 2010). From a risk perspective non-invasive brain stimulation appears unproblematic, while a significant number of patients with long-term DBS have hardware-related complications (Oh et al., 2002) beside complications from the initial surgery. Implants are costly, making equal distribution hard, while TMS and especially tDCS are far less expensive. In fact, the potential low cost and ease of tDCS might be cause for concern in the form of amateur use/abuse. While there are so far no indications that any ethically dubious or risky applications have been found, anecdotal evidence suggests that amateurs are trying to perform tDCS (e.g. http://flowstateengaged.com). There is also a risk of premature use of the technology based on hype or speculation, including on vulnerable groups such as children. Since long-term effects on brain plasticity and development are unknown this is a cause for concern (Kadosh et al., 2012).

10. Ethical issues

Just as diverse as the many enhancement strategies are in terms of their effectiveness, potential side-effects and mode of functioning, so are the ethical worries they may raise. In respect to safety and side-effects, every method requires detailed analysis of its own. Most interventions benefit only specific cognitive domains and have little or no effects on others. Some interventions such as physical exercise or meditation might exert rather small benefits on cognitive capacities when compared to other enhancers, however have additional benefits such as enhanced mental or physical health without known side effects. Some methods like brain stimulation or pharmaceuticals might be save if applied by an experienced practitioner, however can be misused by unexperienced users. Some highly effective methods such as mnemonic training or sleep are safe and available to everybody, however are rather time consuming. Defining an adequate cost-benefit ratio for the use of neurotools is one of the central open questions in the enhancement debate. Reasonable minds come to different conclusions about the scope of acceptable risks for non-medically indicated interventions, and it remains to be argued whether this decision should be left entirely to physicians and patients or be regulated on the political level.

Also apart from questions of risks and benefits, the ethical debate on cognitive enhancers has to compare pharmacological and non-pharmacological interventions. For instance, the use of pharmaceutical enhancers is often portrayed as an undesirable shortcut (Manninen, 2006; Freedman, 1998). Shortcuts as such are nothing to be concerned about – on the contrary, using more effective tools to reach goals is one of the main reasons for economic and personal development. Sometimes, however, taking the longer (non-pharmacological) route may have additional benefits. Supporting cognition in form of appropriate nutrition, mnemonic training or meditative practice requires a lot of planning, self-discipline, dedication and strength of will. Therefore, their use may foster secondary virtues, the feeling of self-mastery and achievement, endurance, self-confidence and may confer self-knowledge (Kipke, 2010). In respect to personal development and the ethics of a good life, understood not just as experiencing happiness but rather as having conscious contact with reality and being aware of one's own strengths and weaknesses (Nozick, 1974), these are additional benefits which should be taken into account in decisions on how to form and sculpture one's personality.

These benefits of some non-pharmacological means, however, may come at the price of efficacy – provided of course that pharmacological shortcuts turn out to be more effective. Comparing different cognitive enhancers in this regard is difficult because of a striking paucity of studies testing different interventions with comparable tasks. As measured targets are often broad categories such as vigilance, attention or memory, and as it is likely that different means affect various subfunctions of cognition, one can draw only weak inferences. Mnemonics, for instance, may improve specific memory systems while pharmaceuticals may improve others. What would be needed are studies designed to compare different interventions in a straightforward manner and preferably in real-life tasks. At the moment, the hype around pharmaceutical enhancers can hardly be backed up scientifically, whereas some non-pharmacological methods are proven to be highly effective in certain cognitive domains.

On the social level, pharmaceuticals raise the worry of pharmacologization of life, as Healy (2008) put it: "Birth, Ritalin, Prozac, Viagra, Death". Increasing numbers of neuro-interventions may indeed be the inevitable consequence of increasing knowledge about brain processes. Most likely, neuroscientific progress will reveal not only benefits, but also drawbacks of such interventions, enabling potential users to balance reasons for or against a given enhancer. The real objection might rather be that people who want to live a more natural life or are unwilling to take the risks of pharmaceuticals are pressured into doing so. On a first glance, the same may be held against non-pharmacological enhancement methods. However, a more fine-grained look at social pressure is necessary. Every society partially structured in competitive terms exerts pressure on the individual. Ethical problems arise in respect to the intensity of this coercion and its negative consequences for the individual's life. Job markets in mental economies demanding high cognitive performance are troublesome if they pressure persons into consuming substances with undesirable side effects only for job reasons. We may indeed not welcome a society in which cognitive powers are boosted on the expense of, say, emotional skills or general health. In this light, several non-pharmacological enhancement strategies seem to fare better: It seems a far more reasonable burden to make use of e.g. proper nutrition, mnemonics, sports or meditation, which have only positive side effects if any, than of currently available pharmaceuticals, for which side effects are currently unknown particularly for long-term use. At least, the social pressure on those who do not want to use traditional methods seems not of a kind that could warrant prohibitive regulations.

A related worry is that cognitive enhancers may undermine fairness in social competition ("mind doping"). The often drawn analogies to sports, however, are short-sighted. The world of sports is characterized by competition for its own sake and promotes its own values (the "spirit of sports") and hence cannot serve as a model for social cooperation at large. From an egalitarian perspective, it is noteworthy that some non-pharmacological enhancers (e.g. mnemonics) may even widen the cognitive gap as they are more effective in cognitively already high-functioning individuals, while many pharmaceuticals, by contrast, mainly seem to compensate acute or chronic cognitive impairments. Likewise, physically disabled individuals cannot profit much from physical exercise; people with certain allergies cannot profit from certain nutritional enhancers. So more generally, just as pharmaceuticals raise worries about equal access (Farah et al., 2004), so may non-pharmacological methods. Thus, in regard to almost every enhancement method, some people may benefit more than others, and hence, arguments over equality are not confined to pharmaceuticals.

After all, pharmaceutical or other enhancers are not intrinsically ethically dubious. Rather, the problem individuals and societies may increasingly face in the future is finding the right balance between efficient direct interventions and traditional methods which may be more resource consuming but may hold additional benefits. In a world of limited resources, society will have to strike balances between optimizing human cognition and preserving valuable emotional propensities and individuals' peculiarities. This is a complex task without a firm default position. To make good decisions, a stable empirical basis is needed. Therefore, more research should be devoted to both pharmacological and non-pharmacological interventions, preferably in a way that allows comparing efficacy and side-effects. In light of the latter, a presumption in favor of traditional methods is a prudent position. Thus, the "gold standard" for cognitive enhancers should not be the best pill among pills, but better than other neurotools, first and foremost, traditional ways. Concededly, financial interests seem to favor development of patentable and marketable pharmaceuticals over developing or refining the ancient *ars memoriae*, promoting smart foods, getting enough sleep or other mental or physical exercise. For society at large, however, the latter may be the better way.

11. Conclusions

Does a cup of coffee or a nap wake you up better? Would learning memory techniques or taking a memory enhancing drug improve your study results best – and what would they do to your mood and attention? If methylphenidate affects creativity, what about working memory training? There exist many cognitive enhancement interventions. Some, such as sleep, meditation, exercise or nutrition, are based on traditional and widely accepted habits. Some, such as pharmaceuticals, computer games or brain stimulation, are modern and controversial. Interventions in the mind are, in a wide sense, an everyday and commonplace phenomenon. As Eric Kandel remarked, every conversation changes the brain. But the range of possible techniques to change and enhance the mind, from talking to deep-brain stimulation, is wide. In order to find reasonable ways of using them, their similarities and differences need to be evaluated. It is only a matter of time when brain research and cognitive neurotechnology will pervade our society, presumably this development is irreversible. Surprisingly, not much data exist that would allow relative comparisons of the efficacy of different interventions, although many ethical discussions seem to presume that it is available. The purpose of ethical debates is not only to build possible future scenarios, in which side effect-free smart pills are available to boost any cognitive capacity, but also to evaluate current possibilities and constraints of cognitive enhancement. Comparative and differential research on the variety of currently existing cognitive enhancers is strongly needed to inform the bioethical debate.

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