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Review

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Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories

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Abstract

It has been suggested that the recent rapid developments in the fields of neuroscience and psychopharmacology have increased the possibilities for pharmacological enhancement of mental functioning. Here, evidence is reviewed which shows that drugs acting on a variety of neurotransmitter systems can indeed enhance cognition, and to a lesser extent mood and pro-social behavior. Moreover, it seems possible to interfere with the (re)consolidation of traumatic memories. There are, however, a number of caveats: first, as cognition-enhancing drugs can simultaneously exert both linear and quadratic (U-shaped) effects, doses most effective in facilitating one behavior could at the same time exert null or even detrimental effects on other cognitive domains. Second, individuals with a 'low memory span' might benefit from cognition-enhancing drugs, whereas 'high span subjects' are 'overdosed'. And finally, evidence suggests that a number of trade-offs could occur. For example, increases of cognitive stability might come at the cost of a decreased capacity to flexibly alter behavior. A short overview of ethical issues raised by the use of cognition and mood enhancing drugs demonstrates the tremendous variety in views and opinions regarding the subject.

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Keywords: Cognitive enhancement; Mood enhancement; Memory consolidation; Pro-social behavior; Neuroethics

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1. General introduction

Enhancement can be defined as "interventions designed to improve human form or functioning beyond what is necessary to sustain or restore good health" (E.T. Juengst; in: Parens, 1998, p. 29). Humans appear to have an existential need for self-improvement. Drugs, such as the stimulant caffeine, have been used for this purpose for at least a thousand years (Mehlman, 2004). Some, the socalled *transhumanists*, consider enhancement a laudable goal, or even a moral duty. Human nature, they say, is a 'work-in-progress, a half-baked beginning that we can learn to remold in desirable ways' (Bostrom, 2003). In contrast, *bioconservatives* fear that enhancement technologies will undermine our human dignity, that we might lose what it means to be human.

It has been suggested that the recent rapid developments in the fields of neuroscience and psychopharmacology have increased the possibilities for enhancement of mental functioning, e.g. improving memory, mood, or even intelligence. Here, we review and critically evaluate the available evidence. We will focus only on those drugs that play a major role in ethical discussions, either because they are reported to be effective as cognitive- or mood enhancers, or because they show promise as future targets for enhancement. First, we will focus on cognition-enhancing drugs: to what extent can they improve our short- and long-term memory (LTM), or our executive functioning (a cognitive system that controls and manages other cognitive processes and is involved in planning, cognitive flexibility, abstract thinking and inhibiting inappropriate actions)? Second, we will consider the enhancement of mood and pro-social behavior. And third, we will discuss drugs that prevent the consolidation or reconsolidation of unwanted (traumatic) memories.

From this, we will attempt to extract general principles of cognitive enhancement that underlie the common phenomena occurring across different neurotransmitter systems and with different pharmacological agents. These general principles (such as trade-offs) might prove to be a barrier to the practical or commercial use of pharmacological enhancers and should therefore be taken into account in ethical discussions. Finally, we will consider the ethical concerns that are raised by the use of cognitive and mood enhancers, in light of the perhaps more realistic expectations of the effects of these drugs.

2. Cognitive enhancement

2.1. Currently available enhancers

2.1.1. Donepezil

Widely cited in both ethical discussions and popular scientific articles on cognitive enhancement, is the finding that donepezil improved the retention of training in healthy pilots tested in a flight simulator (Yesavage et al., 2002). Donepezil (Aricept[®]) is an acetylcholinesterase inhibitor indicated for mild to moderate Alzheimer's disease. Acetylcholinesterase inhibitors exert their effects by inhibiting the breakdown of acetylcholine, which increases the amount of acetylcholine in the synaptic cleft that can

bind to muscarinic and nicotinic actetylcholine receptors (Mumenthaler et al. 2003).

Yesavage et al. (2002) trained 18 pilots, with a mean age of 52 years, in a flight simulator. Afterwards, half of the subjects were instructed to take donepezil (5 mg) for 30 days and the other half were given capsules containing a placebo. Both subjects and experimenters were blind to the treatment condition. On day 30, subject returned to the laboratory to perform two test flights. In the donepezil group, the flight performance on day 30 was found to be similar to performance after initial training, whereas in the placebo group, flight performance declined. The authors interpret these results as an improvement of the ability to retain a practiced skill. It seems feasible, however, that the increased performance in the donepezil group, relative to the placebo group, can be explained not by increased retention of the learned skills (LTM), but for example by improved attention or working memory during the test flights on day 30. To make this distinction, the authors should have included groups that received donepezil or placebo for 30 days prior to testing, but not the initial training. Somewhat surprisingly, the authors devote most of their discussion not to explaining the effects of donepezil on retention, but instead suggest that their results can be explained by an effect on visual sustained attention.

Gron et al. (2005) studied the effects of donepezil (5 mg/day for 30 days) on the performance of healthy young male subjects (mean age of 24) on an extensive neuropsychological test battery, which probed attention, executive functioning, visual and verbal short-term and working memory, semantic memory and verbal and visual episodic memory. They found a selective enhancement of episodic memory performance. In the verbal episodic memory task, only immediate recall improved in the donepezil group, whereas on the visual episodic memory task, both immediate and delayed (30 min) recall were improved. In contrast to the suggestion made by Yesavage et al. (2002), donepezil had no effect on attention. Therefore, Gron et al. (2005) propose that the beneficial effect of the drug on flight performance is not due to enhanced visual sustained attention, but to increased episodic memory performance. They write: 'Because the amount of relevant information as well as their temporal extensions during flying a simulated aircraft certainly go beyond working memory capacities, it appears reasonable to assume that some kind of episodic memory buffer could be involved'.

Detrimental effects on cognition have also been reported: both in healthy young participants (Beglinger QJ;et al., 2004) and in healthy elderly volunteers (Beglinger et al., 2005), donepezil administration (5 mg for 14 days and 10 mg for 14 days respectively) caused a slight deterioration of performance on speed, attention and short-term memory tasks. However, as Gron et al. (2005) point out, subjects in those studies took donepezil for 14 days, instead of 30 days in the Gron et al. (2005) and Yesavage et al. (2002) studies. Based on evidence from clinical studies, they suggest that donepezil should be administered for at least 21 days to obtain an effect, and that the changes in the cholinergic system were therefore still suboptimal when the subjects were tested.

To summarize, the available evidence does not appear to support the widely cited conclusion that donezepil improves the retention of training. The experimental design does not allow one to distinguish between drug effects on retention of learned flight simulator skills and drug effects on test performance. Moreover, while the flight simulator task might have a high face validity (Yesavage et al., 2002), it taps into a wide variety of cognitive functions, making it very difficult to determine which specific cognitive function improved after donezepil administration. And finally, if donepezil should indeed be administered for at least 21 days to obtain an effect (Gron et al., 2005), it is difficult to see how the drug could still have a beneficial effect on retention weeks after the training took place. Therefore, a drug effect on performance during testing seems more likely. Based on the Gron et al. (2005) study, it appears that the effects of donepezil are limited to episodic memory, specifically immediate and delayed (30 min) recall.

2.1.2. Modafinil

Provigil[®] is a wake-promoting agent that is FDAapproved for the treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea/hypo pnea syndrome and shift work sleep disorder (www. provigil.com).

The precise mechanism of action of modafinil remains unclear. Histamine is one of the neurotransmitters that control the sleep-wake cycle. Using microdialysis in the anesthetized rat, Ishizuka et al. (2003) found that modafinil (150 mg/kg, intraperitoneally) increased hypothalamic histamine release by 150%. Therefore, they suggest that modafinil may promote waking by (indirect) activation of the histaminergic system. Based on a comparison of the effect of clonidine (0.2 mg) and modafinil (200 mg) on measures of alertness and autonomic functions in healthy male volunteers, Hou et al. (2005) suggest that modafinil 'switches on' activity in the locus coeruleus (LC), a wakefulness-promoting noradrenergic nucleus. However, Wisor and Eriksson (2005) showed that in mice, the noradrenergic projections from the LC to the forebrain are not necessary for the wake-promoting effect of modafinil. Instead, they suggest that the mechanism of action involves dopaminergic stimulation of adrenergic receptors in forebrain areas. Alternatively, it has been suggested that modafinil indirectly inhibits GABA release in the cerebral cortex (discussed in Turner et al. 2003a; Müller et al., 2004).

In normal volunteers, modafinil was found to be a promising countermeasure for sleep loss: it sustained alertness and performance of pilots in a helicopter simulator during a 36 h period of continuous wakefulness (Caldwell et al., 2000). It also improved alertness and cognitive performance in healthy adults that remained awake for 54.5 h, although the effects were comparable to a high dose (600 mg) of caffeine (Wesensten et al., 2002).

In addition to its wake-promoting effects, modafinil was found to improve learning in the serial reversal discrimination task in mice (Beracochea et al., 2003). In healthy human volunteers, modafinil (100–200 mg) improved subjective attention and alertness, but also spatial planning, stop signal reaction time, digit-span and visual pattern recognition memory (Turner et al., 2003a). The authors suggest that modafinil improves accuracy by causing an increased tendency to evaluate a problem before initiating a response.

However, Randall et al. (2003) reported increased 'psychological anxiety' and aggressive mood after administration of 100 mg modafinil, but not 200 mg. Surveying the literature, they also concluded that the effects of modafinil are limited, enhancing performance in only 6 out of 29 cognitive tests (Randall et al., 2004). In a subsequent study, using some of the same tests as Turner et al. (2003a) they also found improvements in digit-span and visual pattern recognition. Moreover, they reported that modafinil (100-200 mg) improved speed of responding and sustained attention. However, modafinil was without effect on spatial working memory, verbal short-term memory, LTM, executive function, visuospatial and constructional abilities, and category fluency (Randall et al., 2005a). They conclude that modafinil enhances performance only in very specific, simple tasks.

Interestingly, while Müller et al. (2004) found modafinil to improve both maintenance and manipulation processes in difficult and monotonous working memory tasks, the effects were most pronounced in lower performing subjects. Moreover, modafinil improved accuracy in a sustained attention task, but only in subjects with a lower (although still above-average) IQ (Randall et al., 2005b). Modafinil therefore appears to be most effective during suboptimal performance, due to either sleep deprivation, or 'lower natural abilities'. So far, no studies have found any deleterious effects of the drug in subjects already performing at optimal levels.

2.1.3. Dopamine agonists: *d*-amphetamine, bromocriptine and pergolide

Amphetamines were popular with the armed forces during World War II and the Korean War (as so called *go pills*) and are still being used by the US military today (Mehlman, 2004). Outside of the military, sales figures of the amphetamine mix Adderall[®], which is prescribed mainly for the treatment of ADHD, suggest it is commonly used for enhancement (Farah, 2005). Among college students, Teter et al. (2006) found a lifetime prevalence rate of 8.3 percent for the illicit use of prescription stimulants. The past-year prevalence rate was 5.9 percent. Of these past-year users, three fourths reported using Adderall. What are the effects on cognition of dopamine agonists such as amphetamine?

The dopamine agonists d-amphetamine (Mattay et al., 2000; Mattay et al., 2003; Barch and Carter, 2005), bromocriptine (Kimberg et al., 1997; Kimberg et al.,

2001; Mehta et al., 2001; Roesch-Ely et al., 2005; Gibbs and D'Esposito, 2005a) and pergolide (Müller et al., 1998; Kimberg and D'Esposito, 2003) have all been been found to improve cognition in healthy volunteers, specifically working memory and executive function. Interestingly, the effect of dopaminergic augmentation seems to depend on the subjects' baseline working-memory capacity. Individuals with a low working-memory capacity improve on dopamine receptor agonists, while high-span subjects are either not affected or get worse (Kimberg et al., 1997; Mehta et al., 2001; Mattay et al., 2000; Mattay et al., 2003; Gibbs and D'Esposito, 2005a; Gibbs and D'Esposito, 2005b; but see: Kimberg et al., 2001 and Kimberg and D'Esposito, 2003).

These studies provide support for an inverted U-relationship between (prefrontal) dopamine levels and working memory performance, as was suggested by Williams and Goldman-Rakic (1995). Interestingly, such a relationship is further supported by studies investigating a functional polymorphism in the catechol O-methyltransferase (COMT) gene. COMT, which inactivates released dopamine, is a key regulator of dopaminergic activity in the prefrontal cortex (Mattay et al., 2003). Individuals with the *val/val* genotype have a high activity enzyme that breaks down synaptic dopamine, which is presumably associated with relatively less prefrontal dopamine. Subjects with the *met/met* genotype, on the other hand, have low activity enzyme, which probably results in high levels of prefrontal cortical dopamine. Egan et al. (2001) reported that the high-dopamine *met/met* subjects show better baseline working-memory ability than the val/val subjects.

Moreover, Mattay et al. (2003) found that in *val/val* subjects, increasing prefrontal dopamine levels with amphetamine improved working memory performance and enhanced efficiency of prefrontal cortex function (as assayed with functional MRI). In contrast, on the most difficult working memory task, amphetamine decreased working memory performance and efficiency of prefrontal cortex information processing in *met/met* subjects. Such findings point to a future role for pharmacogenetics to determine which individuals could benefit from certain types of cognitive enhancers.

2.1.4. Guanfacine

The biopharmaceutical company Shire is seeking FDA approval of Intuniv[®], the α_2 adrenoceptor agonist guanfacine, for the treatment of ADHD symptoms in children (6 to 17 years), with dosage strengths of 1 to 4 mg daily. If approved, is there a risk of abuse by healthy individuals, as is the case with amphetamine (see above) and methylphenidate (discussed below)? Norepinephrine, like dopamine, has marked effects on prefrontal cortex function. Moderate levels of norepinephrine improve prefrontal cortex function by acting on α_{2A} -adrenoceptors, while high levels of norepinephrine impair prefrontal cortex function by also engaging lower affinity α_1 -adrenoceptors (Arnsten and Li, 2005). But what are the effects of guanfacine on the performance of healthy subjects?

2.1.4.1. Animals. In monkeys, the α_2 adrenoceptor agonist guanfacine improved performance on a spatial working-memory task, while also increasing regional cerebral blood flow in the dorsolateral prefrontal cortex (Avery et al., 2000).

2.1.4.2. Human subjects. In healthy volunteers, the specific α_2 adrenoceptor agonist guanfacine (29 µg/kg) improved paired associates learning (a test of visual pattern and visuospatial memory and learning), as indicated by a lower number of trials to reach criterion (Jakala et al., 1999a). In a subsequent study, Jakala et al. (1999b) found that guanfacine improved spatial working-memory and planning in the Tower of London test, but had no effect on attentional set-shifting. The authors therefore suggest that performance on these tasks is differentially sensitive to guanfacine. While they all involve the central executive, they are dependent on partly distinct prefrontal areas. The authors note that the beneficial effects of guanfacine were accompanied by slightly sedating and hypotensive effects, indicating that the effective dose for improving frontal functions also induces side-effects.

In contrast, when Müller et al. (2005) tested healthy male volunteers on an extensive neuropsychological test battery, they did find a mild sedative effect of guanfacine (1-2 mg), but no improvement of memory or executive functioning. There was even a trend for a dose-dependent impairment of backwards digit span, a test of manipulation processes in working memory, and a significant slowing of GO reaction time in the Stop Signal Task.

Some factors which might explain the failure to replicate the Jakala et al. (1999a, b) studies include the use of subjects from the general population instead of students only, the use of a fixed-dose of guanfacine instead of an individual dose and the use of parallel groups instead of a mixed design (Müller et al., 2005). The authors also suggest that there is a possibility of under-dosing. If we look at the Jakala et al. (1999a, b) studies, a Finnish man with an average weight of 82 kg would be administered 2.4 mg of guanfacine ($29 \mu g/kg$). It seems possible therefore that subjects in the Müller et al. (2005) study were slightly under-dosed. It would be interesting to test higher doses of guanfacine, although, as Müller et al. (2005) point out, this would also increase side-effects such as sedation.

2.1.5. Methylphenidate

Methylphenidate (Ritalin[®]) is a stimulant drug related to amphetamine. It increases the synaptic concentrations of dopamine and noradrenaline by blocking their reuptake.

2.1.5.1. Animals. In rats, methylphenidate was found to improve performance on a spatial delayed alternation task, a test of prefrontal cortical function in rodents (Arnsten and Dudley, 2005). It appeared to produce an inverted U dose response curve, with middle doses improving performance, and higher doses impairing performance in most rats. The beneficial effects could be reversed with the α_2

adrenoceptor antagonist idazoxan, and with the dopamine D_1 receptor antagonist SCH23390, indicating that methylphenidate exerts its cognitive-enhancing effects through noradrenergic α_2 adrenoceptor and dopamine D_1 receptor actions (Arnsten and Dudley, 2005).

2.1.5.2. Human subjects. In healthy volunteers, methylphenidate (40 mg) enhanced spatial working-memory performance, which was accompanied by task-related reductions in regional cerebral blood flow in the dorsolateral prefrontal cortex and posterior parietal cortex. As with dopamine agonists, subjects with lower baseline working memory capacity showed the greatest improvement in spatial working memory after methylphenidate administration (Mehta et al., 2000).

However, Elliott et al. (1997) found methylphenidate (20 and 40 mg) to either enhance or impair cognitive performance on tests of spatial working memory and planning, depending on the familiarity and requirements of the task. The authors suggest that methylphenidate enhances executive function on novel tasks, but impairs previously established performance. Moreover, in healthy elderly volunteers (61 years old), methylphenidate (20 and 40 mg) was without effects on working memory, response inhibition and sustained attention, suggesting that it is not a useful countermeasure for age-related cognitive decline (Turner et al., 2003b).

According to surveys as many as 20 percent of college students and 13 percent of high school students have abused methylphenidate at some point (Kapner, 2003). Kapner writes: 'Whereas college students once drank excessive amounts of coffee or took caffeine pills to stay awake while cramming for tests, many now use Ritalin to remain alert. Anecdotal evidence suggests that Ritalin can allow students to stay awake for many hours in a row and maintain abnormally high levels of concentration.' McCabe et al. (2004) examined the prevalence of illicit methylphenidate use in a nationally representative sample of 8th, 10th and 12th graders. They found an annual prevalence of illicit methylphenidate use of 4 percent. White students were over six times more likely than African-American students to abuse Ritalin. Students earning lower grade point averages were also more likely to use the drug illicitly. The authors note that the study likely underestimates the extent of Ritalin abuse, because they focused exclusively on Ritalin and not on other methylphenidate formulations (Concerta).

Among US college students, McCabe et al. (2005) found a life-time prevalence of 6.9 percent, but apart from Ritalin, they included the prescription stimulants Dexedrine and Adderall in their study. Interestingly, illicit use was higher among students who were male and white and who earned lower grade point averages. Rates were also higher at colleges with more competitive admission standards. It appears that college students use these drugs in order to enhance their academic performance. Consistent with this view, Teter et al. (2006) found that the most commonly reported motives for illicit use of prescription stimulants were to enhance concentration, to help with studying and to increase alertness. The authors found a lifetime prevalence rate of 8.3 percent and a past-year prevalence rate of 5.9 percent. Of these past-year users, one fourth reported using methylphenidate.

2.2. Future targets for enhancing cognition

Considerable effort is now directed at the development of memory-enhancing drugs. These drugs target the specific, and to some extent understood mechanisms that underlie memory formation. They aim at enhancing neuroplasticity, either by targeting glutamate receptors (and thus the induction of long-term potentiation), or, further downstream, by increasing the amount of a protein called CREB, which strengthens the synapse and helps to consolidate memories.

2.2.1. AMPA receptors

Ampakines enhance fast excitatory neurotransmission throughout the brain by modulating AMPA-type glutamate receptors (Lynch, 2006). Increasing excitatory transmission promotes the induction of long-term potentiation (LTP), a process which is widely regarded as the cellular basis of learning and memory.

2.2.1.1. Animals. In monkeys, the ampakine CX717 enhanced performance on a working memory task (delayed matching to sample) under normal alert testing conditions. Moreover, it also removed behavioral impairment and returned performance to above-normal levels in sleep-deprived monkeys (Porrino et al., 2005).

2.2.1.2. Human subjects. The ampakine CX516 (900 mg) enhanced memory in healthy elderly volunteers (65–75 years old). The drug produced a more than twofold increase in the number of items (nonsense syllables) recalled after a 5 min delay (Lynch et al., 1997). In young adult subjects, 300 mg of CX516 produced small to moderate improvements in four memory tests, with retention delays ranging from minutes to 24 h (Ingvar et al., 1997).

Recently, Wezenberg et al. (2007) investigated the acute effects of the ampakine farampator (500 mg) on the performance of healthy elderly volunteers (aged 60–75 years, mean age of 66). They found that the drug improved short-term memory, but impaired delayed recall in an episodic memory task. Subsequent analysis revealed that farampator impaired episodic memory only in subjects who had reported side-effects (headache, somnolence and nausea), and that those subjects had significantly higher plasma levels of farampator. The authors note, however, that the absence of a positive effect on episodic memory is surprising in light of the previous findings with the ampakine CX516.

2.2.2. NMDA receptors

Whereas NMDA receptor agonists can have neurotoxic effects and induce seizures (Robbins and Murphy, 2006),

partial agonists, such as D-cycloserine, have been shown to enhance learning and memory without producing neurotoxicity (Walker et al., 2002). D-cycloserine improved avoidance- and maze learning in rats (Monahan et al., 1989), and visual recognition memory in rhesus monkeys (Matsuoka and Aigner, 1996). More recently, the drug has been found to enhance extinction learning in rats (Walker et al., 2002), and to accelerate extinction learning in phobic individuals, producing a faster reduction of their fear of heights (Ressler et al., 2004).

In contrast, the NMDA receptor antagonist ketamine impairs working memory (Honey et al., 2003) and shifting of attention (Krystal et al., 1994) in healthy volunteers. Robbins and Murphy (2006) therefore suggest that it might be possible to improve prefrontal cortex-dependent executive functions by manipulating NMDA receptors.

2.2.3. CREB (cAMP response element binding protein)

Considerable evidence from experiments in *Drosophila*, *Aplysia* and mice suggest that the cAMP response element binding protein (CREB) plays a central role in the formation of LTM. Agents that disrupt the activity of CREB block the formation of LTM, whereas overexpression of CREB activator enhances LTM formation by reducing the requirements for repetition and rest during training (see Yin and Tully, 1996; Barco et al., 2003; Tully et al., 2003). In rats, increases in CREB expression in the basolateral amygdala increased LTM in a fear conditioning paradigm (Josselyn et al., 2001).

However, as Carlezon et al. (2005) point out, there are complications that limit the usefulness of CREB as a target for memory enhancing drugs. Most importantly, it might be difficult to control specific processes and target specific brain regions. While in some brain regions, enhancement of CREB function appears to have beneficial effects on memory, anxiety and depression, in other brain areas, it could actually lead to increased fear and anxiety, depression and drug addiction.

2.2.4. Conclusion

In both popular scientific articles and ethical discussions on cognition enhancing drugs, AMPA receptors, NMDA receptors and CREB are consistently mentioned as promising future targets for enhancing cognition. Of these three targets, the development of the ampakines appears to be furthest along. Even there, however, there has been a paucity of studies on (healthy) human volunteers. Moreover, recent findings with the ampakine farampator (Wezenberg et al., 2007) are inconsistent with previous studies that used the ampakine CX516 (Lynch et al., 1997; Ingvar et al., 1997).

3. Enhancement of mood and pro-social behavior

Compared to cognition, relatively few studies have focused on the enhancement of mood and pro-social behavior in normal individuals. We will first discuss the effects of SSRI's, which have sparked considerable debate in the past concerning the question of personal identity and authenticity, and then turn to oxytocin, a neuropeptide which currently receives a lot of media attention.

3.1. Antidepressants

As Farah (2005) points out, antidepressants are not happy pills, shifting normal people to bliss. In normal volunteers, administration of SSRIs (Paroxetine for 4 weeks) reduced hostility through a more general decrease in negative affect (sadness, anxiety), but did not alter indices of positive affect (Knutson et al., 1998). The SSRI also changed some aspects of social behavior. Specifically, it increased social affiliation in a cooperative task. Tse and Bond (2002) also found SSRIs (Citalopram for 2 weeks) to increase affiliative behavior. Moreover, subjects were rated as being more assertive. In healthy elderly volunteers SSRIs (Paroxetine or Sertraline for 3 weeks) decreased negative affect in response to negative events (Furlan et al., 2004). The authors suggest that SSRIs improve 'hassle tolerance'. Interestingly, Harmer et al. (2004) found that antidepressants induce a positive bias in information processing: when healthy subjects had to recognize facial expressions, the SSRI citalopram and the specific norepinephrine reuptake inhibitor (SNRI) reboxetine decreased the perception of fear and anger from facial expression cues. Moreover, both drugs increased memory for positively valenced emotional material.

These decreases in negative affect come at a price however: memory impairments have been reported in SSRI users, specifically poorer episodic memory (Wadsworth et al., 2005). In healthy subjects, sub-chronic treatment (2 weeks) with the SSRI paroxetine impaired LTM (delayed recall in a word learning test), perhaps due to its anticholinergic effects (Schmitt et al., 2001). The SSRI citalopram impaired vigilance performance acutely at a dose of 20 mg and subchronically at a daily dose of 40 mg (Riedel et al., 2005). In contrast, sub-chronic treatment (2 weeks) with the SSRI sertraline had no effect on vigilance (Riedel et al., 2005; Siepmann et al., 2003), LTM (Schmitt et al., 2001), working memory and reaction time (Siepmann et al., 2003), and even slightly improved verbal fluency, which could be the result of its additional dopaminergic effects (Schmitt et al., 2001).

3.2. Oxytocin

In mammals, the neuropeptide oxytocin, released from the paraventricular nucleus of the hypothalamus, plays an important role in mediating pro-social behavior, such as pair bonding and maternal care (Insel and Fernald, 2004). Does it also promote pro-social behavior in humans?

Kosfeld et al. (2005) studied the effects of a single intranasal dose of 24 IU oxytocin on a financial trust game with real money involved. They found that in the oxytocin group, 45% of the 'investors' showed the maximal trust level (they invested all their money and expected the trustee to honor their trust by sharing the profit), compared to 21% in the placebo group. In contrast, low trust levels were found in only 21% of the subjects in the oxytocin group, but in 45% of the subjects in the placebo group. Intranasal administration of oxytocin therefore appears to lead to an increase in trusting behavior.

Domes et al. (2007a) used a double-blind within-subjects design to investigate the effects of a single intranasal dose of 24 IU oxytocin on the ability to infer the mental state of others ('mind-reading'). Mind-reading ability was measured by the 'Reading the Mind in the Eyes Test' (RMET), which consisted of 36 pictures of the eye-regions of different persons, each accompanied by four alternative labels describing what the person displayed might be thinking or feeling. Oxytocin was found to improve performance on the RMET in 20 out of the 30 subjects, leading the authors to conclude that it caused 'a substantial increase in the ability in affective mind-reading and therefore in interpreting subtle social cues from the eye region of other individuals.' However, while the effect was significant, it was extremely small. Oxytocin increased the mean number of correct responses by only 3%.

As a potential mechanism of oxytocin's effect, Kirsch et al. (2005) found reduced reactivity of the amygdala in response to negative facial stimuli after a single intranasal dose of 27 IU oxytocin. Moreover, they showed a reduced coupling of the amygdala with brainstem regions involved in the autonomic and behavioral consequences of fear. As previous studies showed increased amygdala activity in response to untrustworthy faces, Kirsch et al. (2005) suggest that oxytocin might increase trust by reducing amygdalar danger signaling.

Domes et al. (2007b), however, showed that oxytocin (24 IU) attenuated right-sided amygdala activation in response to angry and fearful faces, but also in response to happy faces. As it has been argued that the amygdala responds to ambiguity and uncertainty, they speculate that the reduced reactivity of the amygdala in response to positive and negative stimuli reflects reduced uncertainty about the predictive value of social stimuli. This reduced uncertainty would subsequently lead to increased approach behavior. The authors argue that this interpretation is supported by their recent finding of increased social cognition ('mind-reading') after oxytocin administration (2007a). They also acknowledge, however, that it is not consistent with studies that suggest the amygdala promotes social behavior by enhancing attention to socially relevant cues.

Clearly, the effects of oxytocin on human social behavior, and the neurobiological mechanisms which underlie these effects, need further investigation.

4. Blunting unwanted memories

Canst thou not minister to a mind diseased, Pluck from the memory a rooted sorrow, Raze out the written troubles of the brain And with some sweet oblivious antidote Cleanse the stuff'd bosom of that perilous stuff Which weighs upon the heart?

Wiliam Shakespeare

While it strictly constitutes a deterioration of memory, the ability to weaken or prevent the consolidation (or reconsolidation) of unwanted memories is generally considered a form of enhancement (The President's Council on Bioethics, 2003; Farah, 2005; Foresight: Drugs Futures 2025, 2005). As anyone can testify, we tend to remember emotionally arousing experiences better than neutral ones. Stress hormones, such as epinephrine and norepinephrine, released during emotional arousal (either pleasant or unpleasant) activate the (basolateral) amygdala and thereby enhances the consolidation of LTM (McGaugh, 2004). Obviously, this is an adaptive mechanism, which ensures that we remember highly significant experiences well.

Post-training disruption of noradrenergic transmission by systemic administration of the β -adrenergic receptor antagonist propranolol has been shown to abolish the enhancement of memory consolidation produced by emotional arousal (Cahill et al., 2000; Debiec and Ledoux, 2004; McGaugh, 2004). Propranolol can even interfere with a memory when it is recalled, such that an altered version is put back in storage. As Lee et al. (2004) write: 'The central dogma of the permanence of LTM [long-term memory] has been challenged by evidence showing the disruption of what are apparently fully consolidated memories when the memory is retrieved, or reactivated. immediately before treatment with various amnesic agents or to behavioral manipulations. The recall of a memory thus appears to place it into an active and labile state, from which it is reconsolidated back into an inactive and stable state'.

4.1. Animal studies

In rats, both systemic administration of propranolol and infusion into the lateral and basal nuclei of the amygdala after retrieval impaired auditory fear memory two days later. Propranolol was even effective in blocking postretrieval reconsolidation of two month old fear memories. Moreover, the disruptive effect of this drug on the reconsolidation of memory appears to be long-lasting, perhaps permanent (Debiec and Ledoux, 2004).

Recently, Doyere et al. (2007) showed that the interference with reconsolidation can be specific for one particular memory trace. In male rats, they paired two conditioned stimuli, a pure tone and a complex frequencymodulated sound, with the same aversive unconditioned stimulus (footshock). One day after training, rats received an intra-lateral amygdala infusion of vehicle or the MAPK inhibitor U0126, a drug which blocks reconsolidation, and were subsequently exposed to only one of the conditioned stimuli. Levels of freezing to both conditioned stimuli were then measured 3 and 24h after that reactivation. After 24h, but not after 3h, rats showed an impairment of fear memory that was specific to the stimulus-response association which had been reactivated after administration of the MAPK inhibitor. Furthermore, when reconsolidation was disrupted, the authors observed a reduction of potentiation at thalamo-amygdala synapses that was specific to the stimulus presented during reactivation, which might suggest an 'erasure of initial encoded plasticity'. They conclude that: 'These findings provide the neurophysiological basis for content-limited modifications during the updating of fear memories.'

4.2. Studies on human subjects

Can we interfere with human memory in the same way? Propranolol (40 mg) was found to impair the LTM of an emotionally arousing story, but did not affect the memory of an emotionally neutral story. Specifically, propranolol was able to block the enhancing effect of arousal on memory (Cahill et al., 1994). Pitman et al. (2002) have postulated that an excess of epinephrine release at the time of a psychologically traumatic event leads to an overly strong emotional memory, which can manifest itself as posttraumatic-stress disorder (PTSD) symptoms. In a pilot study with Emergency Department patients, they found that post-trauma administration of propranolol (40 mg, administered within 6h of the traumatic event and subsequently four times daily for 10 days) reduced physiologic responses during mental imagery of the event 3 months later (Pitman et al., 2002). However, no significant differences were found when the propranolol and placebo groups were compared on the Clinician-Administered PTSD scale (CAPS). But as the authors acknowledge, the study suffered from a small sample size and a number of confounding factors.

Vaiva et al. (2003) did find an effect of post-trauma administration of propranolol (2-20 h after the trauma) on PTSD rates and PTSD symptom scores. They studied the effects of propranolol (40 mg, 3 times a day for 7 days, with an 8-12 day taper period) in trauma victims recruited at an Emergency Department who presented with tachycardia. The tachycardia was taken to reflect prolonged adrenergic activation, which has been shown to increase the risk for PTSD. The placebo group consisted of subjects who refused to take propranolol, but agreed to participate in the study. Results showed that PTSD rates and symptom scores were lower in the propranolol group when assessed two months after the traumatic event. As the authors point out however, the sample size was small and, although the subjects did not differ on variables such as age, gender, and injury severity score, they were not randomly assigned to the experimental or control group.

Brunet et al. (2007) investigated whether propranolol can also interfere with the reconsolidation of traumatic memories in chronic PTSD patients, in which on average 10–11 years elapsed since the traumatic event. Immediately after the patients described the event that caused their PTSD, which reactivated their traumatic memories, they received a dose of 40 mg of short-acting propranolol (or placebo), followed two hours later by a dose of 60 mg of long-acting propranolol (or placebo). A week later, subjects listened to their own traumatic scripts and imagined the event while their heart rate (HR), skin conductance (SC) and left corrugator electromyogram (EMG) were measured. Results showed that HR and SC, but not EMG responses were significantly smaller in the propranolol compared to the placebo group. Moreover, while the placebo group showed physiological responses typical of PTSD patients, the propranolol group showed physiological responses typical of trauma victims without PTSD. These results suggest that propranolol blocked the reconsolidation of their traumatic memories, although, as the study did not include a group that received propranolol in the absence of memory reactivation, non-specific effects of propranolol cannot be ruled out. It would also be interesting to see if the effect is lasting, and if the drug also reduced PTSD symptoms other than physiological reactivity.

5. General principles of enhancement

We now turn to (putative) general principles of cognitive and mood enhancement, namely the inverted U-shape and trade-offs, that might underlie the common phenomena that arise across different neurotransmitter systems and with different pharmacological agents. If these general principles prove to be inherent to the use of cognition and mood enhancing drugs, they might temper the enthusiasm, or worry, about the practical and commercial use of these psychoactive agents, and should therefore be taken into account in ethical debates.

5.1. The inverted U-shape

An inverted U-model, where performance is optimal at intermediate (prefrontal) catecholamine levels and impaired at levels that are either too low or too high, can be encountered in different (albeit highly related) ways. First, drugs can have a U-shaped dose-response curve, where low doses improve and high doses impair performance. Second, a drug's effect can be 'baseline dependent', indicating that low performing individuals find themselves on the up slope of the inverted U (describing the relationship between receptor occupation and performance), and therefore benefit from administration of an agonist. In contrast, high performing subjects are located at or near the peak of the inverted U. As a result, their performance deteriorates if neurotransmitter levels are further increased. We will discuss both possibilities in turn.

5.1.1. Non-linear dose response curves

Depending on the task, the dose-response curves of some cognition enhancing drugs, specifically psychostimulants,

can simultaneously indicate both linear and quadratic (U-shaped) effects. For example, Tannock et al. (1995) studied the effects of methylphenidate (0, 0.3, 0.6 and 0.9 mg/kg) on cognitive flexibility and overt behavior in children with attention deficit-hyperactivity disorder (ADHD). They found that while the effects on behavior showed a linear dose response curve, the function for response inhibition was U-shaped (the high dose was less effective in enhancing response inhibition than lower doses).

Similarly, Konrad et al. (2004) found that in children with ADHD, methylphenidate (0, 0.25 and 0.5 mg/kg)improved alertness and focussed and sustained attention in a linear fashion. But on two executive tasks, response inhibition and set-shifting, the high dose was less effective than the low dose in enhancing performance. As alertness and sustained attention appear to be localized in the frontosubcortical network of the right hemisphere, while executive functions are associated with activity in the prefrontal cortex, the authors speculate that these different brain areas display different dose-response curves. These findings are potentially problematic for the practical use of cognition enhancers in healthy individuals, as doses most effective in facilitating one behavior could simultaneously exert null or even detrimental effects on other cognitive domains.

5.1.2. Baseline dependency

As discussed above, the effects of a number of different cognitive enhancers seem to depend on the subjects' baseline working-memory capacity. Individuals with a low working-memory capacity improve on dopamine receptor agonists, while high-span subjects are either not affected or get worse (Kimberg et al., 1997; Mehta et al., 2001; Mattay et al., 2000; Mattay et al., 2003; Gibbs and D'Esposito 2005a b; but see: Kimberg et al., 2001 and Kimberg and D'Esposito, 2003).

Also, subjects with lower baseline working memory capacity showed the greatest improvement in spatial working memory after methylphenidate administration (Mehta et al., 2000). And while Müller et al. (2004) found modafinil to improve both maintenance and manipulation processes in difficult and monotonous working memory tasks, the effects were most pronounced in lower performing subjects. Similarly, modafinil improved accuracy in a sustained attention task, but only in subjects with a lower (although still above-average) IQ (Randall et al., 2005a, b).

Some of these findings might simply reflect ceiling effects. As pointed out by Müller et al. (2004): '...in relatively high performing subjects without brain pathology or experimentally induced impairment it is difficult to improve cognitive performance with any given drug (ceiling effect)'. High performing subjects might therefore also benefit from dopamine agonists, methylphenidate and modafinil, as long as the task is difficult enough to allow for an improvement of their performance.

However, this does not explain why a number of studies show that 'high-span' subjects are actually impaired by dopamine augmentation. Rather, these findings point to an inverted U-model, which predicts optimal performance at intermediate (prefrontal) catecholamine levels, and impairment at levels that are either too low or too high. Presumably, low performing individuals find themselves on the up slope of the inverted U, and therefore benefit from administration of dopamine agonists. In contrast, high performing subjects are located at or near the peak of the inverted U. Administration of dopamine agonists therefore leads to an 'overdose' of prefrontal dopamine and consequently a deterioration of performance.

Results from Egan et al. (2001) and Mattay et al. (2003) support such a view. Egan et al. reported that *met/met* subjects, with high levels of prefrontal cortical dopamine, show better baseline working-memory ability than *val/val* subjects, with relatively less prefrontal dopamine. And Mattay et al. (2003) found that increasing prefrontal dopamine levels with amphetamine improved working memory performance and enhanced efficiency of prefrontal cortex function in *val/val* subjects, while it decreased working memory performance and efficiency of prefrontal cortex information processing in *met/met* subjects.

Additional support comes from studies using the dopamine D₂ receptor agonist bromocriptine. Using a variant of the Wisconsin Card Sorting task and a test of associative memory, Kimberg et al. (1997) found that the performance of subjects with a lower working memory capacity improved after a dose of 2.5 mg of bromocriptine, while high-span subjects performed more poorly on the drug. As a result, bromocriptine reduced or eliminated the baseline differences between low- and high-span subjects. On a spatial and object delayed recognition task, Gibbs and D'Esposito (2005b) found that a dose of 1.25 mg of bromocriptine reduced the accuracy of their eight highspan subjects, while the drug increased accuracy for the two low-span subjects. In contrast however, while Mehta et al. (2001) showed that 1.25 mg of bromocriptine enhanced the spatial working memory of lower-span subjects, they did not find higher span subject to be impaired by the drug. As different tasks require different optimal levels of dopamine receptor activation (Mehta et al., 2001), perhaps on this specific task, 1.25 mg of bromocriptine was not enough to 'overdose' the higher span subjects. To the best of our knowledge, no studies have found impaired performance in high span subjects after modafinil or methylphenidate administration. Therefore, the baseline dependent effects of these drugs might be better explained by ceiling effects.

It should be noted that one could question the validity of subdividing a random sample of normal, healthy young adults into either 'low or high performing subjects'. Müller et al. (2004) for example obtained their subdivision by taking a median split based on subject's performance on the placebo day. But do these 'poor manipulators' perform poorly on all working memory tasks, or only on this specific task and at that particular time? Kimberg et al. (1997) used scores on a reading span task to divide subjects (by median split) into high- and low-span groups. In light of the low correlation between visuospatial and verbal working memory capacity in their study, they acknowledge that their use of a verbal working memory task to subdivide subjects made it unlikely that those subjects were also adequately divided into groups with high and low spatial working memory capacity. Perhaps not surprisingly then, the group (high- versus low-span) x treatment (bromocriptine versus placebo) interaction did not reach significance for the spatial working memory task.

The subdividing into 'low or high performing subjects' can also be risky from a statistical point of view. That is, an increased performance in 'low-span subjects' and a deterioration of performance in 'high-span subjects' might also reflect regression towards the mean. It should be noted, however, that Kimberg et al. (1997) ruled out this possibility.

5.2. Trade-offs

Some of the caveats and risks associated with the use of memory enhancing drugs are, at least for now, theoretical. For example, Carlezon et al. (2005) has suggested that the use of these drugs might clutter the brain with unimportant information and could lead to stronger memories for traumatic events. Interestingly, a recent case study may provide some insight into potential disadvantages of having a superior memory. In their report, Parker et al. (2006) describe AJ, a woman with superior autobiographical memory. When given a date between 1974 and today, she can tell what day it falls on, what she was doing that day, and she can describe important world events that occurred on that day (if any). She writes:

Whenever I see a date flash on the television (or anywhere else for that matter) I automatically go back to that day and remember where I was, what I was doing, what day it fell on and on and on and on and on. It is non-stop, uncontrollable and totally exhausting.

Because every recollection cues another, her superior memory causes her to spend much of her time remembering her past, instead of focusing on the present and the future. Obviously, it remains to be seen if individuals taking memory enhancing drugs will ever come close to anything like AJ's capabilities. Studies in animals and human subjects do suggest that, even at more modest levels of improvement, the use of cognition enhancing drugs could potentially lead to the following four 'trade-offs', where pharmacological enhancement of one task is associated with impairment in another area.

5.2.1. Long-term memory versus working memory

Research on activation of the cAMP/protein kinase A (PKA) intra-cellular signaling pathway demonstrates one potential trade-off: the opposite 'chemical needs' of the prefrontal cortex, involved in working memory, and the hippocampus, critical for LTM. PKA activity can be

increased by drugs that inhibit phosphodiesterase (PDE) activity, which prevents the breakdown of cAMP. One such drug, rolipram, has been shown to improve LTM consolidation and to facilitate LTP in aged mice, which, among other findings, has prompted pharmaceutical companies to develop drugs that enhance PKA activity as a treatment for age-related cognitive decline in humans (Ramos et al. 2003).

However, while in the hippocampus, PKA activation appears to keep memory fixed and enhance long-term storage of information, updating of working memory in the prefrontal cortex rather calls for erasure of information. Indeed, Ramos et al. showed that in aged rats, activation of PKA in the prefrontal cortex exacerbates (age-related) cognitive deficits. Similarly, they found that rolipram (which indirectly increases PKA activity) impaired prefrontal cortical cognitive performance in aged monkeys.

5.2.2. Stability versus flexibility of long-term memory

A second trade-off could occur between the stability versus the flexible updating of LTM. That memories can become 'too stable' is demonstrated by the effects of the drug Rimonabant (SR141716A), a CB1 cannabinoid receptor antagonist which was launched last year as an anti-obesity- and anti-addictive drug. Animal data suggest it also has cognition enhancing effects: in mice, Rimonabant improved memory acquisition and consolidation (Takahashi et al., 2005), and in food-storing birds, it enhanced LTM for the location of a hidden food supply (Shiflett et al., 2004).

However, while blocking the CB1 receptor led to more robust LTMs, it also disrupted the ability of new information to modify those memories (Shiflett et al., 2004). Similarly, when mice lacking the CB1 receptor were tested in a water maze, they kept returning to the original location of the hidden platform, despite being repeatedly shown the new location (Varvel and Lichtman, 2002).

5.2.3. Stability versus flexibility of working memory

A similar trade-off between stability versus flexibility could arise in working memory. According to the *tonic*/ *phasic dopamine theory*, high amplitude transient *phasic* dopamine release, mediated by dopamine neuron burst firing, may be important for updating or resetting working memory traces. On the other hand, constant low-level 'background' *tonic* dopamine may enhance the stability of memory traces. While behaviorally relevant stimuli trigger the phasic component of dopamine release, tonic dopamine levels regulate the amplitude of the phasic response by acting on autoreceptors on dopamine terminals. That is, increases in tonic dopamine levels suppress the phasic response (Bilder et al., 2004; Nolan et al., 2004).

This suggests that manipulations which increase cognitive stability come at the cost of a decreased capacity to flexibly alter behavior. As Bilder et al. (2004) write: 'Increased cognitive stability benefits certain functions, such as working memory maintenance tasks (i.e. keeping representations 'on line'), sustained attention tasks, and tasks demanding freedom from distraction. On the other hand, excessive stability yields inflexibility and difficulty in responding appropriately to external change by modifying ongoing behavioral programs or shifting attention to new foci. This may result in excessive repetition of maladaptive behaviors, perseveration, stereotypy, and a failure to detect novelty. It may also yield difficulty updating the contents of working memory representations.'

The COMT polymorphism provides a test of the *tonic/* phasic dopamine theory. Presumably, val/val subjects have increased phasic and reduced tonic dopamine transmission subcortically and decreased dopamine concentrations cortically. As a result, there is decreased cognitive stability, but increased flexibility. In contrast, met/met subjects have decreased phasic and increased tonic dopamine transmission subcortically, and increased dopamine concentrations cortically. This leads to an increased cognitive stability, but a decreased flexibility (Bilder et al., 2004).

A meta-analysis of nearly 2000 individuals showed that on the Wisconsin Card Sort Test (WCST), met/met subjects made less, not more perseverative errors than val/val subjects (Barnett et al., 2007). However, Bilder et al. (2004) argue that, while the WCST is widely cited as a measure of cognitive flexibility, it is actually a complex task which involves multiple cognitive functions, such as hypothesis generation, self-monitoring and error correction. Its ability to discriminate between cognitive stability and flexibility would therefore be extremely limited. To adequately distinguish between stability and flexibility, Nolan et al. (2004) used a Competing Programs Task, which required subjects to alternate between two rules of responding: imitation and reversal. Learning and maintenance of the imitation rule required cognitive stability, while flexibility was needed to switch rules in the reversal condition and to inhibit the previously learned response. Compared to val/val subjects, met/met subjects indeed showed better acquisition of the imitation rule (increased stability), but performed worse in the reversal condition (decreased flexibility).

This trade-off is also likely to come into play with the use of cognition enhancing drugs. For example, Bilder et al. (2004) suggests that at low doses, psychostimulants such as amphetamine enhance phasic dopamine transmission by blocking reuptake of released dopamine. In contrast, higher doses may preferentially increase tonic dopamine.

5.2.4. Cognition versus mood

Another trade-off involves the relationship between cognition and mood. If we think of the cognition-impairing effects of drugs such as alcohol or MDMA (Ecstasy), one might conclude that mood enhancers are essentially 'dumbdrugs'. Indeed, as discussed above, some antidepressants also appear to impair cognitive functioning. According to Glannon (2006), the reverse might also hold true: 'A different worry is that altering regions of the brain that control memory and other cognitive functions might disrupt emotional functions. Cognitive and emotional processing are part of an interconnected system in the mind, which is regulated by interconnected cortical/limbic pathways in the brain. Because of these interactions, trying to enhance cognitive processing could impair emotional processing. A drug that made one "smarter" might also make one emotionally flat by blunting one's affective capacities.' Glannon cites anecdotal evidence to support this claim.

But is there an inherent trade-off between cognition and mood? As discussed above, SSRI's enhance mood in the sense that they decrease negative affect (sadness, anxiety). increase 'hassle tolerance' and induce a positive bias in information processing, such as increased memory for positively valenced emotional material. But while the SSRI paroxetine impaired LTM and citalopram impaired vigilance performance, sub-chronic treatment with the SSRI sertraline had no negative effects on vigilance, LTM, working memory or reaction time. It even slightly improved verbal fluency, which could be due to the fact that, at least in vitro, sertraline inhibits dopamine reuptake with one-third the potency of d-amphetamine (Schmitt et al. 2001). Therefore, enhancement of mood does not necessarily have to be accompanied by cognitive impairments.

What about the other side of the equation: do cognition enhancers have the effect of making us emotionally flat? As discussed above, modafinil enhances cognition. As reported by Randall et al. (2003), however, it also increases 'psychological anxiety' and aggressive mood. Recently, modafinil was found to increase both positive and negative affect (anxiety; Taneja et al., 2007). While one might be reluctant to call the cognition enhancer modafinil a mood enhancing drug, due to its anxiogenic effect, it clearly does not appear to blunt one's affective capacities.

5.3. Summary

In summary, a number of findings appear to limit the practical use of drugs that enhance cognition or mood. First, as cognition-enhancing drugs can simultaneously exert both linear and quadratic (U-shaped) effects, doses most effective in facilitating one behavior could at the same time exert null or even detrimental effects on other cognitive domains. Second, studies on dopamine augmentation provide some support for a baseline dependency: individuals with a 'low memory span' benefit from administration of dopamine agonists, whereas 'high span subjects' are 'overdosed' and show a deterioration of performance. And finally, there is evidence that a number of trade-offs could occur: enhancement of LTM could impair working memory, enhancing the consolidation of LTM might disrupt the ability of new information to modify those memories, and increases of cognitive stability (which benefits working memory maintenance) might come at the cost of a decreased capacity to flexibly alter behavior. The claim of an inherent trade-off between cognition and mood, however, seems to lack empirical support.

The use of drugs to enhance human functioning raises considerable ethical concerns, which have been discussed to some extent in the international literature. It is to these concerns that we will now turn, while keeping in mind the 'practical problems' and trade-offs discussed above.

6. Ethical concerns

The use of drugs to enhance human functioning raises considerable ethical concerns. Based on a review of the international literature, one can discern six important ethical questions. We will briefly discuss each of these questions while keeping in mind the findings discussed above.

6.1. Safety

In analyzing whether a (new) technology or drug is morally acceptable, safety concerns are essential. We currently know little about the long-term effects and risks of familiar drugs like Ritalin. What will be the risks and side-effects (e.g. toxicity, physical and psychological dependency) if these drugs are used in healthy persons for enhancement purposes? What will be the risks of new enhancement drugs? Based on the preceding section tradeoffs seem to be very likely. Some argue that as compared to drugs for therapeutic uses, risks and side effects of enhancement drugs are less acceptable (Farah, 2005). However, this may be hard to realize in our current system; drugs may be approved by the FDA for a medical indication e.g. Parkinson disease, but can be used for enhancement purposes due to the off-label use of these drugs and easy access of enhancers through the Internet. Others, however, argue that as long as the person taking them is adequately informed about the risks, prohibiting the use of these drugs may not be justified (DeGrazia, 2000). Nevertheless, it seems not realistic to expect information will be provided adequately if drugs are being purchased on the Internet.

6.2. Societal pressure

The worry about pressure and inducements to use enhancers seems to be warranted in a society that overvalues competitiveness: employers may require employees to use enhancement drugs, the military may induce pilots to use amphetamines before flying combat missions (Mehlman, 2004), surgeons may be required to use enhancement drugs to stay alert during long-continued surgeries (Glannon, 2007), and children may be pressured by their parents to improve their school performances. The preceding section shows that high expectations regarding the effects of enhancement drugs are not warranted. However, societal pressure may occur with respect to drugs that are ineffective or only slightly effective simply because people believe these drugs do improve performance, as the illicit use of methylphenidate and amphetamine shows. Creating realistic expectations appears to be very hard to accomplish.

6.3. Fairness and equality

Enhancement drugs may lead to unfairness between haves and have not's. The use of enhancers may give one a competitive advantage. Interestingly, the inverted U-shape principle suggests that people with lower natural abilities might benefit the most from cognitive enhancement. At first sight this might meet concerns of justice; nevertheless, the wealthy low performing individuals may still be able to afford it while the poor low performing individuals will not. Questions concerning social and economic fairness are therefore still applicable.

Using enhancement drugs is also seen as a form of cheating or as an easy shortcut (Farah, 2002). In sports, there are regulations regarding the use of enhancing substances, in other practices such as education, however, this is not the case. In response to this cheating argument, some question whether there is a moral difference between privately funded extra tutorial lessons and taking cognitive enhancers. The essential question is: if enhancement violates the 'ethos' of a certain practice, such as sports or education, what are the meanings and internal values of practices like sports or education (Schermer, 2007)?

6.4. Enhancement versus therapy

Making a distinction between enhancement and therapy is considered to be important because of three issues: it helps (1) to define the proper goals of medicine and biomedical research, (2) to determine the limits of the health care payment system (what should be reimbursed?), and (3) to discriminate between morally right and morally problematic or suspicious interventions (Parens, 1998). However, drawing a line between enhancement and therapy is problematic, especially with respect to psychiatric or psychological disorders and emotional well-being. Can we draw an undisputed line between therapy for a depression and the medicalisation of grief; between preventing PTSS and blunting bad memories; between treating Mild Cognitive Impairment and enhancing memory in elderly subjects?

We need to respond to the question of how to deal with a variety of psychopharmacological substances that are already being used off-label, like amphetamine and methylphenidate, or that will become available in the 'grey area' between medical treatment and human enhancement. Should they be provided by physicians under certain conditions (Synofzik, 2006)? Or should they be regulated outside of the medical realm, in a commercial setting?

Recently, critical voices have drawn attention to the fact that this grey area can be exploited by 'disease mongerers', who have an interest in defining as many conditions as possible as diseases. Disease mongering can be defined as 'the selling of sickness that widens the boundaries of illness and grows the markets for those who sell and deliver treatments' (Moynihan and Henry, 2006). Some argue that the current regulatory system is contributing to the 'creation' of new diseases (Healy, 2002).

6.5. Authenticity and personal identity

The argument that using enhancers might change one's authentic identity has been raised with respect to SSRI's (Elliott, 1998), but seems to be absent in the discussion on cognitive enhancement. Critics argue that enhancing mood, behaviour or character traits will lead to inauthenticity (to a personality that is not really one's own), normalization, and socially-enforced adaptation of behaviour and personality (Elliott, 1998, 2007). Some even fear dehumanization in the long run (The President's Council on Bioethics, 2003). Others, however, hold that psychopharmacological substances can help users to 'become who they really are' and thus strengthen their identity and authenticity (DeGrazia, 2005).

Studies on the efficacy of SSRI's, however, do not show a significant impact on mood and pro-social behavior. This may take the edge off the arguments of both proponents and critics of psychopharmacological enhancers; hope as well as fear seems to be overcharged. However, we still know too little about effects of both SSRI's and potential cognitive enhancers on the subjective and intersubjective perceptions of personal characteristics, behaviour, or individual identity (Singh, 2007). More research is needed here. The debate about authenticity and personal identity may therefore still be a relevant issue (Parens, 2005; Bolt, 2007).

6.6. Happiness and human flourishing

According to the influential President's Council on Bioethics, enhancement may threaten our sense of human dignity and of what is naturally human (The President's Council, 2003). We may forget what full flourishing or true human happiness really entails. Full human flourishing comprises more than mere happy feelings or optimal cognitive performance. For example, according to the President's Council on Bioethics, the use of memory blunters is morally problematic because it might cause a loss of empathy if we would habitually 'erase' our negative experiences, and because it would violate a duty to remember and to bear witness of crimes and atrocities. According to Fukuyama (2002), improving ourselves through technology instead of through practice and hard work is morally problematic. In contrast to this bioconservatist view, the so-called transhumanists highly value technologies to overcome humans' basic biological limits and to control our human condition (Bostrom, 2005). Some even claim there is a moral duty to enhance ourselves and see this as an ultimate form of human flourishing.

However, even proponents would have to acknowledge that the use of certain enhancers, such as oxytocine, raise moral questions: what is the meaning of trust and relationships if we are able to manipulate them? (Parens, 2005).

7. Conclusions: where are we now and what lies ahead?

In conclusion, a number of psychoactive drugs, acting on a variety of neurotransmitter systems, appear to be able to enhance:

- (a) cognition, specifically working memory, executive functioning (spatial planning ability), sustained attention and episodic memory;
- (b) mood, albeit to a lesser extent than cognition and only in the sense that SSRIs decrease negative affect, increase 'hassle tolerance' and induce a positive bias in information processing;
- (c) pro-social behavior, in the sense that oxytocin increases trust in a specific laboratory task, marginally enhances 'mind-reading' ability, and perhaps reduces social fear.

Moreover, it seems possible to interfere with both the consolidation and reconsolidation of traumatic memories by administering propranolol.

There are, however, a number of caveats: first, as cognition-enhancing drugs can simultaneously exert both linear and quadratic (U-shaped) effects, doses most effective in facilitating one behavior could at the same time exert null or even detrimental effects on other cognitive domains. Second, studies on dopamine augmentation provide some support for a *baseline dependency*: individuals with a 'low memory span' benefit from administration of dopamine agonists, whereas 'high span subjects' are 'overdosed' and show a deterioration of performance. And finally, there is evidence that a number of trade-offs are likely to occur: enhancement of LTM could impair working memory, enhancing the consolidation of LTM might disrupt the ability of new information to modify those memories, and increases of cognitive stability (which benefits working memory maintenance) come at the cost of a decreased capacity to flexibly alter behavior.

Of the future targets for enhancing cognition, the development of the ampakines appears to be furthest along. Even there, however, there has been a paucity of studies on human volunteers. Therefore, it remains to be seen whether these drugs really do prove to be any more effective than the currently available enhancers, and if they do not run into the same 'practical problems' and tradeoffs discussed above.

The short overview of ethical issues demonstrates that the concerns evoked by the use of cognition and mood enhancing drugs have been delineated quite thoroughly. But it also shows the tremendous variety in views and opinions regarding the subject. A challenging question is how to deal with this variety in views. Even if enhancers do not have a tremendous impact (yet), a growing demand of psychopharmacological substances in the grey area between treatment and enhancement is already taking place. How should physicians deal with a growing demand for psychopharmacological substances in adults and children? Sooner or later public policy should respond adequately to these developments, but it is not yet clear on what moral framework such policy should be based.

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