Medicine, Health Care and Philosophy (2007) 10:141–151
DOI 10.1007/s11019-007-9055-5

Scientific Contribution

Memory enhancing drugs and Alzheimer's Disease: Enhancing the self or preventing the loss of it?

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Abstract. In this paper we analyse some ethical and philosophical questions related to the development of memory enhancing drugs (MEDs) and anti-dementia drugs. The world of memory enhancement is coloured by utopian thinking and by the desire for quicker, sharper, and more reliable memories. Dementia is characterized by decline, fragility, vulnerability, a loss of the most important cognitive functions and even a loss of self. While MEDs are being developed for self-improvement, in Alzheimer's Disease (AD) the self is being lost. Despite this it is precisely those patients with AD and other forms of dementia that provide the subjects for scientific research on memory improvement. Biomedical research in the field of MEDs and anti-dementia drugs appears to provide a strong impetus for rethinking what we mean by 'memory', 'enhancement', 'therapy', and 'self'. We conclude (1) that the enhancement of memory is still in its infancy, (2) that current MEDs and anti-dementia drugs are at best partially and minimally effective under specific conditions, (3) that 'memory' and 'enhancement' are ambiguous terms, (4) that there is no clear-cut distinction between enhancement and therapy, and (5) that the research into MEDs and anti-dementia drugs encourages a reductionistic view of the human mind and of the self.

Key words: memory enhancing drugs, dementia, Alzheimer's Disease, the self, neuroethics

Introduction

For several centuries memory enhancement has been a theme for science fiction, but we are now emerging into a period of successful interventions based on an increasing understanding of the neurobiological basis of memory. Possibilities for drug development have stimulated the interest of biomedical researchers and pharmaceutical companies in both basic and translational research over the last two decades. Recognizing the desire for quicker, sharper, and more reliable memories, many researchers are explicitly pursuing drugs that might improve our capacity to remember (Farah et al., 2004). Based on our neurobiological and neuropsychological knowledge of memory function, huge research efforts are being directed to the development of memory enhancing drugs (MEDs).

Scanning the literature on MEDs reveals two crucial aspects. First, memory enhancement is coloured by utopian thinking (Gordijn, 2006). The development of MEDs falls into the class of self-improvements, where people are trying to improve all kinds of mental and bodily capacities, trying to work out ways of living longer, being more beautiful and more intelligent, being stronger, faster and better. Memory enhancement reminds us of the old utopias of an improved human life, aimed at ''ageless bodies, happy souls, better children, a more peaceful and cooperative society,'' in the words of Leon Kass, chairman of the U.S. President's Council on Bioethics (Kass, 2003, p. 11).[1] In the world of memory enhancement people speak in terms of ''cosmetic neurology'' (Chatterjee, 2004), ''smart drugs'', ''viagra for the brain'' (http://www.nootropics.com/smartdrugs/brainviagra.html) and even ''mind-enhancing drugs''.

The second crucial aspect of the literature is the connection between the development of MEDs and that of anti-dementia drugs. On the one hand, the

aim of developing MEDs can be called 'medical' and 'anti-dementia', on the other 'non-medical' and 'anti-aging'. There is an overlap between these two aims founded on the assumption that a decline in memory capacity is not confined to patients with dementia or other neurological diseases, but happens to all human beings as they age. This normal deterioration of memory is considered to be caused by a failure of the same biochemical mechanisms that break down in pathological conditions such as Alzheimer's Disease (AD). Although much of the MED research is aimed at finding treatments for dementia, there is reason to believe that some of the products under development may also enhance normal memory, particularly in middle and old age when many people have memory complaints and show a certain degree of memory decline. Similarly MEDs under development for people without dementia might also be helpful for people suffering from dementia.

In this paper we focus on this connection between the search for MEDs and for anti-dementia drugs. We will show that, although there is an overlap between these two fields of research, there is also a conflict of interests. While MEDs are being developed to improve oneself, in AD 'one loses one self'. Despite this it is precisely patients with AD and other forms of dementia that are the subjects of scientific research in the field of memory enhancement.

In the next section we describe the current research in the field of MEDs. After a short overview of various ethical and philosophical questions related to MEDs, we then concentrate on the following issues: (1) memory and its disturbances, particularly the ethical implications of the work on MEDs, (2) the distinction between therapy and enhancement, (3) various interpretations of the self related to research into memory and MEDs, and (4) the relationship between MEDs and anti-dementia drugs. We end up with some considerations about the further development of MEDs in relation to AD.

Research into MEDs

It is well known that memory can be improved by physical and social activities, by taking amphetamines, sugar, caffeine, or herbal drugs (Breithaupt and Weigmann, 2004). Simply walking sedately for half an hour three times a week is associated with better learning, concentration and abstract reasoning abilities. Elderly people who walk regularly perform better on memory tests than their sedentary peers (Heyn et al., 2004). Even dunking one's hand in freezing water may have a positive effect on the capacity to remember new information, at least in the short term. It appears from these examples that the complexity of the human body and especially the human brain makes it difficult to isolate the functions of memory from other neurophysiological processes such as perception, attention, and arousal. Many non-specific drugs or stimulants have a significant effect on memory and many 'memory drugs' have a significant effect on other bodily functions.

Memory enhancement research was primarily focused on neurodegenerative diseases such as AD, because one of the characteristic features of AD is a progressive loss of memory. Cholinergic mechanisms are involved in memory formation and cholinergic cells are amongst the first to die in AD patients. This has led to therapeutic interventions with a class of drugs called *anticholinesterase drugs* or acetylcholinesterase inhibitors such as tacrine, donepezil and rivastigmine. These agents block the enzyme that metabolizes acetylcholine, with the result that acetylcholine, once released, remains active in the synapse for a longer period of time. These drugs have had a real but limited effect on slowing down the decline of memory in some Alzheimer patients. They can slow down or moderate the effects of the disease, but they do not reverse the progressive degeneration of the brain itself (Breithaupt and Weismann, 2004; Marshall, 2004).

A new generation of memory enhancers is promising to be more specific and powerful (Russo, 2002). New drugs in the development pipeline act on other compounds in the biochemical pathway that encodes memory, for example drugs that modulate AMPA-receptors, the so-called *ampakines*. There is empirical evidence in animal studies that ampakines selectively enhance the encoding of both short- and long-term memory (Lynch, 2002), but – again – none of these drugs tackles the degeneration of the brain itself.

Recent research in animals has also improved our understanding of certain molecular and genetic "switches" that control memory. These discoveries have launched several new pharmaceutical companies formed specifically to develop potential drugs based on this research. In this category are drugs that increase cyclic AMP-responsive element binding protein (*CREB*), the activity of which is known to contribute to important neuronal functions, such as synaptic plasticity, learning and memory (Farah et al., 2004).

In magazines, books, newsletters, and on the internet, "smart drug enthusiasts" cite an impres-

sive list of scientific papers to support their claims, but the question is whether any of the substances advertised as so-called "smart drugs" really work? And what does 'work' then mean? Steven Rose (2002) has examined over 100 studies, some on animals, some on people with dementia, some on healthy people (Rose, 2002, 2005b). Rose rightly emphasizes that memory is not some mechanical process like recovering files from a computer disk, but involves active work on the part of the individual. Our wish for 'magic potions' to enhance our 'wisdom' is age old, he argues, but so far, drugs tested in humans have proved to be ineffective in enhancing learning and memory. We think that this statement is too strong. Although clinically relevant questions – such as can acetylcholinesterase inhibitors (AChIs) also be prescribed in case of a delirium or a Lewy Body Dementia? – remain insufficiently studied, the AChI donepezil has shown some efficacy in AD patients (Gerlai, 2003). However, several studies on the effect of donepezil on healthy elderly individuals did not show a significant improvement in cognitive performance compared to a placebo group. Sometimes even a transient mild worsening on some cognitive tests during donepezil administration was observed (Beglinger et al., 2004, 2005).[2]

In a time when the ideal of Evidence Based Medicine is paramount, we cannot pass over the need for an adequate scientific methodology. Most of the studies analysed by Rose appeared to be either misleadingly quoted by advocates of smart drugs or describe experiments that were poorly controlled or misinterpreted by researchers. Much of the evidence cited by smart drug enthusiasts comes from animal experiments that can only test a drug's effects on learning, not on memory. The animals are trained to perform highly specific tasks and the drugs are given within an hour or so of the training trials. On this basis, the best a smart drug could do is to increase the likelihood of the transfer of information from the short-term to long-term memory store. There is little evidence that any of these smart drugs can do even this much in humans. But there is more to this issue. Many studies of MEDs involve patients frequently diagnosed as suffering from AD. Effects on the patients are often evaluated using subjective criteria. Many of the trials are based on small samples of patients. According to Rose, a considerable number of the human studies comes from trials carried out in countries where the ethical controls and statistical procedures required in standard biomedical research are often lacking, or at least unspecified. The most dramatic claims often appear in conference proceedings that were not under peer review or in obscure journals.

All in all we cannot but conclude that memory enhancement is still in its infancy, that we have only partially effective drugs, and that it is not necessarily an unalloyed good. All of this work on MEDs – exciting though it may be for researchers, people with dementia, their caretakers and the general public – is very preliminary. Its significance for producing biotechnologies that might preserve or enhance human memory remains to be determined. So far, there seems to be no efficacious "magic bullet" for producing better memories.

Philosophical questions

The philosophical and ethical aspects of enhancement of cognition in general and of MEDs in particular have already been extensively discussed in the literature.[3] Ethical issues surrounding cognitive enhancement can be grouped into three general categories (Farah, 2005; Farah and Wolpe, 2004). The first is *safety*. Side effects and unintended consequences are a concern with all medications and medical procedures, but in comparison to other comparable elective treatments such as cosmetic surgery, neuroscience-based enhancement involves intervening in a far more complex system. We are therefore at greater risk of unanticipated problems when we try to change the function of the human brain. The second category is *social*: how will the lives of all individuals, including those who chose not to enhance themselves, be influenced by living in a society with widespread enhancement? Even in everyday work and school contexts, enhancement is likely to affect all of us. The freedom not to enhance may be difficult to maintain in a society where one competes by using enhancements. Conversely, barriers such as costs will prevent some people who would like to enhance from doing so. This could exacerbate the disadvantages already faced by people of low socioeconomic status in education and employment. The third category of ethical issues could be called *philosophical* in that it concerns our norms and values and our sense of self. We generally view self-improvement as a laudable goal. At the same time, improving our natural endowments for traits such as attention span runs the risk of making commodities of those traits. We generally encourage innovations that save time and

effort, because they enable us to be more productive and to direct our efforts toward potentially more worthy goals. However, when we improve our productivity by taking a pill, we may also undermine the value and dignity of hard work and medicalize human effort.

The focus of our paper is on what Farah (2005) calls "philosophical questions." More particularly, we will deal with a number of – what we would like to call – "questions of meaning and understanding." Memory research and the development of MEDs raise significant questions about human nature itself and human self-understanding. Some fine examples of these questions are mentioned in a staff working paper of the U.S. President's Commission on Bioethics (PCBE): "What does it mean to be the creature that remembers and forgets, that studies and wonders about memory, and that seeks to manipulate and control the way we remember? Is memory decline actually 'normal' for particular age groups? What would it mean to have a 'perfect' memory? Why do we so often remember what we would like to forget, and forget what we would like to remember?" (PCBE, 2005).

What is a better memory?

Any effort to understand human memory, let alone improve it, must confront the fact that memory is not a singular phenomenon. Neither is it mediated by a single neurobiological or neuropsychological system. There are many types of remembering and forgetting. We remember how to ride a bicycle, how to drive home from work, we remember phone numbers, the names of old classmates, the day we were married, and how to speak a foreign language. These are surely all acts of memory, but each of them involves different ways of remembering, and each of them has a different meaning.

Besides the well-known distinction between long-term and short-term memory, current psychological theory divides long-term memory into a so-called implicit and explicit memory, that is, in 'remembering how' and 'remembering that' (Ledoux, 2002, p. 98–103; Rose, 2005a). *Implicit* (or procedural, non-declarative) memories are reflected in the way we *act* more than in what we consciously *know*. Remembering how to ride a bicycle is implicit. Only the most severe of memory disorders such as those that show up in the advanced stages of AD affect implicit memory. People with memory disturbances can usually recall how to perform daily activities such as putting on clothes and cooking, even when they cannot subsequently describe what they have done. Remembering that a two-wheeled vehicle with a saddle and a handlebar is called a bicycle is explicit. The information gathered by our *explicit* (or declarative) memory is available for conscious recollection. Through explicit memory one can recall a phone number, the way someone looks, what one had for lunch yesterday, or what one did on one's last birthday. It is this memory that is first attacked in AD.[4]

All these models of memory are neither fixed nor mutually exclusive. Memory can fail in many different ways. A very rough distinction of memory problems is the one between intrusive and bad memories on the one hand and weak or lost memories on the other (PCBE, 2005). Some *bad memories* may be so traumatic that they destroy the lives of those who suffer from them. Many of us have felt a momentary desire to escape the sting of a shameful, embarrassing, or painful memory. The goal of many therapeutic interventions in psychiatry and psychology is to numb the emotional significance of certain bad memories. The memory enhancing drugs (MEDs) we focus on in this paper refer to weak or *lost memories*. AD is often considered the most blatant example of a declining personal memory that may progress to the total destruction of personal memories and the total loss of self-consciousness. Thus, in AD and other cases of age-related memory decline, the desire for a better memory involves the *restoration* of something that is being lost.

One such other category of age-related non-specific memory decline is called Mild Cognitive Impairment (MCI). MCI involves the slowing down that comes with human ageing, but more quickly or severely than normal. This decline often begins with a reduced ability to remember present names and facts by reducing the capacity to remember past experiences. MCI is defined as memory loss without any significant functional impairment (Petersen et al., 2001). The majority of MCI patients eventually develop AD. There are reasons to believe that MEDs might be effective treatment for MCI and for other kinds of age-related memory decline (Lynch, 2002), but attempts to improve the memory of these patients have not yet been very successful (Petersen et al., 2005).

Despite this, the commercial potential for memory enhancers is immense. Most drugs in development are designed to help people with AD and other brain disorders, but there is also a huge

potential market for the use of MEDs by people who simply want to enhance their powers of memory rather than treat memory loss. MEDs are not only "looking for diseases" (Vos, 1989), but are also being aimed at the milder, 'normal' memory based disturbances of daily life.

The crucial problem is that it is difficult to design experiments that test the effects of MEDs, when there are so many indirect influences on mental performance. Elderly people, living in institutions, who cannot remember what they had for breakfast that morning may be able to recall childhood episodes with great clarity. Have they lost memory, or have they lost interest in institutional food, where one breakfast may be just like another? In addition to suffering memory loss, elderly patients in hospital, especially those with dementia, are often angry, suspicious, anxious or depressed. A drug that reduced such feelings could easily result in an apparent improvement in memory, while having no effect on the actual mechanisms of memory (Rose, 2002).

Another problem to be sorted out is what advocates of smart drugs really mean by "improving memory" or "enhancing cognition." Memory enhancement as discussed in this paper has more to do with our neurobiological capacity to store certain experiences and to remember things (or not to forget things), than with enhancing the *content* of our memories.

If we broaden the scope a bit in order to try to understand the meaning of our memory, one of the more crucial questions about meaning and understanding is about what is meant by a "better memory." To speak about "better memories" is to imply some notion of "best" or "perfect" memory. Unfortunately it is not easy to specify what having a "perfect" memory would mean. The U.S. President's Council on Bioethics (PCBE) specified three interpretations in a Staff working paper (PCBE, 2005).

One interpretation is that an individual with a perfect memory would *never forget anything*. He would remember every fact, every face, every encounter, every piece of information. It does not take much reflection to see that such indiscriminate and perfect recall would be not a blessing but a curse. Second, a perfect memory might mean *remembering only what we desire*, or what we find desirable when we experience it. This interpretation is problematic too. For much that is most worth remembering is not by nature desirable and much that seems undesirable when we first experience it, only reveals its true significance, meaning, or value in our lives much later. Third, a perfect memory might mean *remembering things as they really are* or *as they actually happened*. This seems better, though giving an account of what this might actually mean is rather difficult. It does have its own imperfections. To remember things as they are offers no guidance about what is worth remembering. It provides no insight into the difference between simply cataloguing events (the brain as camera) and discerning their meaning (the mind as photographer and editor).

We fully agree with the conclusion of the PCBE that there is no such a thing as a 'perfect' memory, just as there is no such a thing as a perfect human life.[5] To be an imperfect being means, among other things, having a memory that imperfectly renders many imperfect things. To be creatures of space and time means having a memory that is by nature incomplete. And to be mortal beings means having a memory that must ultimately fail. What we seek, in other words, is not a perfect memory but a *good* or *excellent* memory. But then the question reads: what is a good or excellent memory? And what does enhancement of our memory actually mean? What difference would therapy make?

Therapy versus enhancement?

The PCBE's report *Beyond Therapy: Biotechnology and the Pursuit of Happiness* (PCBE, 2003) contains some interesting thoughts on the distinction between therapy and enhancement. *Therapy* is described as the use of biotechnical power to treat individuals with known diseases, disabilities, or impairments, in an attempt to restore them to a normal state of health and fitness. *Enhancement*, by contrast, is the use of biotechnical power to alter, by direct intervention, not disease processes but the 'normal' workings of the human body and psyche, to augment or improve their native capacities and performances. With this distinction between therapy and enhancement it was hoped that we would be able to distinguish between acceptable and dubious or unacceptable uses of biomedical technology.

At first glance, the distinction between therapy and enhancement seems a useful way to distinguish between the central task of medicine and its marginal activities in enhancing 'normal' bodily and mental capabilities. However, the distinction between therapy and enhancement is ultimately inadequate for the moral analysis of the use of memory enhancing techniques (Kass, 2003). As is

well explained in *Beyond Therapy*, the term enhancement itself is highly problematic. In its most ordinary meaning, it is abstract and imprecise. Moreover, 'therapy' and 'enhancement' are overlapping categories: all successful therapies are enhancing, even if not all enhancements enhance by being therapeutic. Even if we take 'enhancement' to mean 'non-therapeutic enhancement,' the term is still ambiguous (Parens, 1998a, b; Juengst, 1998). When referring to a human function, does enhancement mean making more of it, or making it better? Does it refer to bringing something out more fully, or to altering it qualitatively?

Beyond these conceptual ambiguities, there are difficulties deriving from the fact that the notions of both 'enhancement' and 'therapy' are dependent on the complicated notions of health and normality. For the purpose of this paper it may suffice to recall that there is no clear-cut distinction between health and disease (or illness) and between normal and abnormal. Most human capacities fall along a continuum – often a normal distribution curve. Let us again consider the categories AD, MCI, 'benign age associated memory impairment', and the group of elderly people with 'normal' memory. This series represents a continuum in the level of cognitive functioning retained by different people with increasing age. Where precisely do we have to draw the line between normal and abnormal? For AD patients it is statistically normal and inherent to their disease to have memory problems. Yet it is called therapy when this weakened memory is enhanced. The syndromes MCI and 'benign age associated memory impairment' are medical constructions and far from being clearly definable disorders. As a consequence, drawing a precise line between patients exhibiting these syndromes and elderly people with a 'normal' memory is a rather arbitrary exercise.

We thus agree with the PCBE that relying on the distinction between therapy and enhancement in order to decide on the moral acceptability of a particular intervention in the brain will not succeed. Arguments about whether or not something is an 'enhancement' can often get in the way of the proper ethical questions: What are the good and bad uses of biotechnical power? What makes a use 'good,' or 'acceptable'? For example, it does not necessarily follow from the fact that a drug is being taken solely to increase 'normal' concentration, that its use is objectionable. Conversely, certain interventions to restore functioning wholeness might well be a dubious use of biotechnical power. The meaning and moral assessment of the use of a medical technique such as memory enhancement must be tackled via other means than the distinction between therapy and enhancement. Might the extent to which MEDs affect the self be a criterion?

Memory and the self

In what way do drugs, which affect mood, cognition and memory, also enhance the self? And what does it mean to 'enhance the self'? Should this be thought about in terms of doing something different from curing a mental or biological disorder? Questions like these were the starting-point for this thematic section of *Medicine, Health Care and Philosophy* on 'Psychopharmacology and the Self'. Rephrased and focused on the subject of this paper, the crucial problem can be stated as follows. The term 'memory enhancing drugs' suggests that these drugs do indeed enhance memory. Apart from the problem what 'memory' and 'enhancement' then mean, the question is whether MEDs also enhance the self? We suggest that this question must be answered in the negative. Apart from the problematic distinction between therapy and enhancement it must be recalled that MEDs are only partially and minimally effective and under very specific conditions. They certainly improve certain learning processes, but do they improve memory? And even given the fact that MEDs – be it in a minimal way – positively affect learning processes and memory building, it is still 'a long way' to the self: the enhancement of memory is not necessarily identical to enhancing the self.

We realize that this statement presupposes a specific view of the self. We confine our selves in this paper to two conclusions. First, debates on the meaning of 'the self' are more appropriate in relation to the development and use of a certain class of antidepressants, the selective serotonin-reuptake inhibitors (SSRIs) of which fluoxetine (Prozac) is the best known (DeGrazia, 2000; Svenaeus, 2007), than in the context of MEDs. The simple reason is that – given the present state of development – SSRIs are more effective in improving our mood than MEDs are in improving our memory. The question of how the self is influenced by the use of MEDs might possibly become a philosophical challenge in the future, but is now relatively unimportant. Second, central in the debate about neuro-enhancement is the fear that neuroscience gives room to all kinds of reductionistic and deterministic views of the

human mind and the self. In our view, current biomedical memory research and research into MEDs might indeed lead to a reductionistic view of human memory and the self. An example is Ledoux's book *Synaptic Self* (Ledoux, 2002).

In modern psychology, the notion of the self is closely tied in with consciousness, in the sense of being self-aware, possessing conscious control, having self-knowledge and self-esteem. Ledoux has a broader view of the self in which elements from the unconscious aspects of the self also play a role. He describes a way of thinking about the self that is compatible with current understanding of brain functions. According to Ledoux, most of what the brain does is accomplished by synaptic transmission between neurons. He calls memory the ''synaptic result'' of learning (Ledoux, 2002, p. 9). Given the crucial role of synaptic transmissions in functions of the brain and based on the view that the self is in part made and maintained by memory, he arrives at the conclusion that ''your 'self', the essence of who you are, reflects patterns of interconnectivity between neurons in your brain'' (Ledoux, 2002, p. 2). The central question of *Synaptic Self* is therefore not how consciousness comes out of the brain, but rather how does our brain make us who we are? (ib., p. 10). In a later article Ledoux (2003, p. 298) writes: ''Because you are a unique individual, the particular multifaceted aspects of the self that define 'you' are present in your brain alone. And in order for you to remain who you are from minute to minute, day to day, and year to year, your brain must somehow retain the essence of who you are over time. In the end, then, the self is essentially a memory, or more accurately, a set of memories.''

Realizing that this short description does not fully do justice to Ledoux's position,[6] we draw two conclusions from it. First, this approach to memory and the self is based on the fundamental role synapses play, which makes it easy to understand the neurobiological basis of memory loss in AD. Research over many decades has produced extensive knowledge of the molecular cascade occurring during memory formation. However, the whole of these molecular processes does not explain memory itself. It merely describes the brain events involved in making it (Rose, 2004).

Second, we call Ledoux's view of the self 'one-sided' compared with holistic, in particular narrative, interpretations of the self. The difference is not that a reductionistic view is static and a narrative view dynamic. Ledoux emphasizes, for example, the dynamic aspects of the self, be it that the dynamics of the self in his view are based on a continuous change of synaptic interactions. The difference is that narrative interpretations of the self take their point of departure at the mental side of human existence. Numerous authors have argued that the narrative view adds a fundamental way of attributing meaning in our lives and that constructing stories about the self is linked to the construction of our selves. In addition to the individual's role in constructing his or her self through narrative configuration, elements of dialogue are also important (Kinsella, 2005). A narrative configuration of the self involves not only a reflexive relationship of self to self, but also a relationship of self to others (Ricoeur, 1992). We think that this dialectic and relational dimension of the self is crucial in understanding patients with AD and may inspire a more holistic view of the self in AD compared with a reductionistic 'synaptic' position.

Alzheimer's Disease and MEDs

The current literature describes AD as a syndrome combining a set of clinical features with specific neuropathological characteristics. Genetic factors play a role as well (Dekkers and Olde Rikkert, 2006). Memory dysfunction is generally the first and most severe cognitive impairment in AD.[7] The progressive mental decline, which is caused by AD is feared by many people. Lay people as well as caregivers consider dementia as a degrading state accompanied by unbearable suffering due to the loss of independence and personality.[8] In the concluding chapter of a reader on the biological, clinical and cultural perspectives of AD, Peter Whitehouse writes: ''Alzheimer disease (AD) is a malignant threat to the quality of life of affected individuals as well as to the quality of life of the human race in the future. Our ability to recognize the challenges and dangers that lie ahead will be critical in determining whether we can make appropriate personal and social responses to this condition'' (Whitehouse, 2000, p. 291). In the last lines of the same chapter he writes: ''However the concept of AD changes, the disease will likely play an important role in the future of our world and our conceptions of human personhood. Loss of intellect is perhaps the greatest challenge to the post-Enlightenment person who (over)values cognition. Neuroscience will play a critical, but not the dominant role in addressing the threat of dementia'' (Whitehouse, 2000, p. 304).

These quotations illustrate the negative perception of AD in our modern ''hypercognitive'' society as a ''malignant'' disease and the need of a personal and social response to AD. This negative perception of AD seems to go hand in hand with an awareness of a challenge for the future in which much room is being reserved for the neurosciences. The need for further research on the enhancement of cognition and memory is partly grounded in an awareness of the severe cognitive failures in AD. This might explain why AD is mentioned in the majority of state of the art articles about MEDs (Whitehouse et al., 1997; Farah et al., 2004; Kandel, 2005). ''The war on Alzheimer's disease and other cognitive ravages of aging is stimulating an intensive effort to develop drugs to improve cognitive function,'' Mehlman (2004, p. 483) writes.[9] This approach might also explain why people with dementia are the subjects of many drug trials (Simard and Van Reekum, 1999).

Regulatory authorities both in the US and in Europe have licensed anti-dementia drugs when such a treatment proved to be significantly superior compared to placebo treatment in two of the three following domains: cognition, activities of daily living, and clinical global impression. These outcomes (of which only cognition is obligatory) clearly connect research in anti-dementia drugs to MEDs. However, recently many authors and licensing authorities have argued that cognitive endpoints are an insufficient assessment for anti-dementia drugs. Additional criteria such as time to nursing home admission and cost-efficiency calculations have been regarded as at least equally meaningful. In addition, many researchers feel that other clinical questions should be answered before the next generation anti-dementia drugs deserves to be registered. What effects do these drugs have on mood, functional status, quality of life, caregiver burden, and dementia progression? It is argued that we should try to define outcome measures in real life studies on dementia drug treatment that are more closely linked to the patients' and caregivers' preferences. Thus, the similarity between MEDs and anti-dementia drugs is their focus on the cognitive dimension. The difference between the two is that the effect of anti-dementia drugs should be measured in the ward, rather than against purely cognitive parameters.

Finally, a current objection to all kinds of new medical technologies is the danger of an unequal access to these techniques and unfairness in the distribution of resources (Bailey, 2003). The distribution of MEDs on a free market would have anti-egalitarian consequences. The rich and healthy would get access to brain enhancements first, and would thus acquire a greater competitive advantage over the poor and people already suffering from cognitive disorders. In our view, this is a serious criticism of the use of MEDs, even though it is not specific to MEDs, because it is an objection to any kind of biomedical intervention. Others, however, hold that MEDs and other neuropharmacological drugs are likely to be more equitably distributed than, for example, genetic enhancements, and as a result might increase social equality. It has even been argued – as Mehlman (2004) does – that competent adults should be free to decide whether or not to use cognition enhancing drugs and that, if these drugs are sufficiently safe and effective, the government should subsidize access to them. Our fear is that – in the best case – people with dementia and other forms of cognitive decline will bear the burden of the development of effective MEDs and people with a 'normal memory' will share the benefits. The first group will contribute much to the development of MEDs, but will benefit less from the results. In the race for new and more effective MEDs the implications of the research and subsequent implementation of these drugs for AD patients deserves more attention.

Conclusion

In this paper we focused on some philosophical questions related to the development of MEDs and anti-dementia drugs. Biomedical research in these fields appears to be a strong impetus for rethinking what we mean by 'memory', 'enhancement', 'therapy', and 'self'. We conclude (1) that the enhancement of memory is still in its infancy, (2) that current MEDs and anti-dementia drugs are only partially and minimally effective under specific conditions, (3) that 'memory' and 'enhancement' are ambiguous terms, (4) that there is no clear cut distinction between enhancement and therapy, and (5) that research into MEDs and anti-dementia drugs increases the tendency to take a reductionistic view of the human mind and of the self.

It is not our intention to stimulate a pessimistic view of dementia by putting so much emphasis on the vulnerability of persons with dementia and on the alleged 'loss of self'. However, even if one describes dementia and the ways one can treat it in more optimistic terms, there still exists a strong

contrast with the world of MEDs. MEDs aim at "doing better", anti-dementia drugs aim at "doing less worse". The world of MEDs is coloured by utopian thinking and a belief in the human capacity to overcome all kinds of bodily and mental limitations in human existence. The world of MEDs is a world of hopes for better bodies, better souls and better lives, in sum the world of *hybris*. What seems to be undervalued or denied in the world of MEDs is precisely that which characterizes the world of dementia: the steady mental decline, severe memory problems, all kinds of vulnerabilities and a gradual loss of self.

Despite the difference between these two worlds, they are intrinsically linked. In the search for MEDs it is often people with AD who are the subjects of clinical trials. MEDs are aimed at improving memory, which is the crucial cognitive function that is affected in persons with AD. Finally – and more importantly – it is the confrontation with human (cognitive) vulnerability, so characteristic of people with dementia, which is the basis for the utopian thinking and the drive to search for MEDs.

Notes

1. See also, for example, the mission statement of the World Transhumanist Association: "The World Transhumanist Association is an international non-profit membership organization which advocates the ethical use of technology to expand human capacities. We support the development of and access to new technologies that enable everyone to enjoy better minds, better bodies and better lives. In other words, we want people to be better than well" (http://www.transhumanism.org/index.php/WTA/index/ accessed on april 14, 2006). Also the website of the Center for Cognitive Liberty and Ethics (CCLE) with its focus on the ethical aspects of the individual's right to control her own brain is illustrative (http://www.cognitiveliberty.org). See also book titles such as *The Memory Bible* (Small, 2002) and *The Memory Workbook* (Mason et al., 2001).
2. In a recent survey 666 out of 671 articles on the effect of cognitive enhancers in healthy individuals showed no effect or even a slight worsening (A.R. Cools, personal communication).
3. The following list of statements and objections to MEDs (Baily, 2003) might serve as a philosophical agenda: Neurological enhancements (1) permanently change the brain, (2) are anti-egalitarian, (3) are self-defeating, (4) are difficult to refuse, (5) undermine good character, (6) undermine personal responsibility, (7) enforce dubious norms, (8) make us inauthentic.
4. Explicit memory can be split into 'semantic' and 'episodic' memory. Remembering that the first of January is New Year's Day is semantic. Remembering the New Year party you went to last year is episodic. The most vulnerable form of memory is episodic.
5. It is mostly in relation to the imperfections of memory that interesting questions arise with respect to neuroethics. Much cited in this context is Schacter's list of seven fundamental categories, seven ways memory fails, called by him "seven sins of memory" (Schacter 2001): (1) transience: decreasing accessibility over time; (2) absent-mindedness: lapses of attention, forgetting to do things; (3) blocking: temporary inaccessibility of stored information; (4) misattribution: attributing memories to an incorrect source, false recognition; (5) suggestibility: implanted memories; (6) bias: retrospective distortions produced by current knowledge and beliefs; (7) persistence: unwanted recollections that people cannot forget
6. If Ledoux asserts that synapses are the basis of our personality, he does not assume that our personality is totally determined by synapses. It is rather the other way around. Synapses are simply the brain's way of receiving, storing, and retrieving our personalities, as determined by all the psychological, cultural and other factors (Ledoux, 2003). Finally, he does not commit himself to a straight materialist position, that is that the mind is a product of the brain: "Although I believe that my mind (and yours) is the product of a physical system, I don't outright reject other ways of thinking about the mind. Reductionism is a good approach to brain research, but isn't necessarily a good principle for guiding us through daily life ..." (Ledoux, 2002, p. 327).
7. The definition of *Alzheimer Europe*, for example, reads: "Alzheimer's disease [is] a degenerative disease, which slowly and progressively destroys brain cells. It is named after Aloïs Alzheimer, a German neurologist, who in 1907 first described the symptoms as well as the neuropathological features of Alzheimer's disease such as plaques and tangles in the brain. The disease affects memory and mental functioning (e.g. thinking and speaking, etc.), but can also lead to other problems such as confusion, changes of mood and disorientation in time and space" (http://www.alzheimer-europe.org, accessed on November 21, 2005).
8. Dementia is generally characterized by decline, vulnerability, loss of the most important cognitive functions and even a loss of self. It is often thought that dementia is characterized by a gradual disappearance of that which makes a being a *human* being. In the literature the emphasis is often on what is gone. However, one can also ask what remains. The question, then, is not what kinds of capacities are absent, but what capacities are still intact. It is beyond doubt that persons with (severe) dementia are incompetent to make rational, explicit and deliberate decision, but this lack of explicit decision-making capacity does not

automatically imply that no remains of the self are left (Dekkers, 2004).

9. Donepezil, rivastigmine, galantamine, memantine, and modafinil are examples of these drugs.

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