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Neuroethics of Cognitive Enhancement

Danielle C. Turner* and Barbara J. Sahakian

Department of Psychiatry, University of Cambridge, School of Clinical Medicine, Box 189, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

E-mail: dct23@cam.ac.uk

Abstract

The prospect of being able to take safe and effective drugs to improve mental functioning is becoming a reality. With the potential for widespread use of cognitive enhancers by large sectors of the population, this article discusses the rationale behind the development of these drugs and how society might benefit from them. Important ethical questions and scenarios are also raised. Scientists are urged to explore the implications of their work and engage in active debate with a wide range of interested stakeholders about the ethical and moral consequences of these new technologies to ensure maximal benefit with minimal harm.

Keywords Cognitive Enhancement, Ethics, Human, Neuroethics, Smart Drugs

The social implications of pharmacologically improving the brain functioning of healthy, normal individuals are numerous. Neuroethics is a new and expanding area concerned with the benefits and dangers of modern research on the brain. In 2002, the Dana Foundation defined neuroethics as 'the study of the ethical, legal and social questions that arise when scientific findings about the brain are carried into medical practice, legal interpretations and health and social policy' (Marcus, 2002). Recent advances and trends in neuroscience raise some important ethical questions that are demanding the attention of scientists, ethicists, policy-makers and the public. In particular, this article will focus on developments in the pharmacological enhancement of cognition. One framework in which to discuss the ethical implications of cognitive enhancement is by commencing at a relatively tangible starting point, namely by describing the scientific basis of these discoveries, their potential and the motivations behind their development.

The need for cognitive enhancers

Major psychiatric illnesses are extremely common and their effects on behaviour, perception, emotion and cognition constitute an enormous contribution to worldwide

Danielle C. Turner is a postdoctoral researcher in the Department of Psychiatry, University of Cambridge and a Fellow of the Center for Cognitive Liberty (CCLE), USA. Her core research interest is in the enhancement of cognition, and she recently completed a PhD entitled 'Psychopharmacology of cognitive enhancement' at the University of Cambridge.

Barbara J. Sahakian is Professor of Clinical Neuropsychology at the University of Cambridge, UK. She currently holds the F.C. Donders Chair in Psychopharmacology at Utrecht University. Her research interests include neuropsychology, neuropsychiatry, neuroimaging and cognitive psychopharmacology, and she has over 200 publications in scientific journals, including *Nature*, *Science*, *The Lancet*, *British Medical Journal*, *Brain*, *Archives of General Psychiatry*, *Biological Psychiatry* and *Psychological Medicine*.

*Corresponding author.

disability (see www.who.int). Numerous neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), schizophrenia, frontal dementia, Alzheimer's disease, Huntington's disease and Parkinson's disease are characterized by cognitive impairments. Patients frequently struggle with many everyday activities requiring concentration, memory, problem-solving and planning. The potential public health benefit of improving current treatments for cognitive disabilities in patients is largely undisputed (Meltzer, 2003).

The disorder of schizophrenia provides a particularly good illustration of the potential benefits to be had from exploring new options for the treatment of cognitive dysfunction. It is estimated that 24 million people worldwide suffer from schizophrenia, with schizophrenia ranking third in terms of the global burden of neuropsychiatric conditions, following depression and alcohol dependence (Murray and Lopez, 1996). The economic impact alone of the disorder is enormous: in the United States the direct and indirect costs of schizophrenia were estimated to have been as much as $40 billion in the year 2000 (Fuller Torrey, 2001). In many patients with schizophrenia, cognitive difficulties are the main factor limiting full rehabilitation (such as returning to work) and quality of life, particularly after the clinical symptoms have remitted (Goldberg *et al*., 1993; Mitchell *et al*., 2001). Indeed, it has been proposed that in certain patients with schizophrenia even small improvements in cognitive functions, such as enhancing the ability to adapt efficiently to new situations and to plan effectively, could help patients make the transition to independent living outside a psychiatric institution (Davidson and Keefe, 1995). The relatively recent shift in clinical emphasis, away from a restricted targeting of the more overt psychotic symptoms of this disorder, serves to emphasize the debilitating long-term effects that cognitive impairments can have, and the need to identify effective treatments.

The pharmacological enhancement of cognition

Cognitive enhancement is commonly considered in terms of improving memory and attention, largely through the use of pharmacological agents (Stahl, 2000). Effective cognitive functioning typically involves numerous neuronal pathways and neurotransmitter systems, with several distinct neurotransmitters being implicated in the enhancement of cognitive function (Robbins *et al*., 1997). In particular executive functions, such as attention, planning, problem-solving and adapting behaviour, are crucial for the successful performance of many everyday procedures like prioritizing tasks and remembering important information for completion of a task while engaging in other necessary task activities (Stuss and Levine, 2002). Frontal neural networks in the brain have been shown to subserve many of these crucial functions and to be modulated by neurochemicals such as the catecholamines dopamine and noradrenaline (Solanto *et al*., 2001).

It is now known that many of these functions are susceptible to intervention with pharmacological agents. Agents that target these catecholamine neural projections include conventional stimulants such as amphetamine and methylphenidate (Ritalin™), both of which have been shown to have cognitive enhancing properties (Elliott *et al*., 1997; Halliday *et al*., 1994; McKetin *et al*., 1999), and also more novel compounds such as modafinil (Provigil™) (Turner *et al*., 2003) and the ampakines (Ingvar *et al*., 1997; Lynch, 2002).

Work in our own laboratory has shown that a single dose of modafinil, a drug originally licensed for the treatment of narcolepsy, consistently improves short-term memory and planning abilities in healthy, young volunteers, adults with ADHD and patients with schizophrenia (Turner *et al.*, 2003, 2004a, 2004b).

The neural mechanisms by which many of these drugs exert their effects are also becoming clearer. For example, neuroimaging in healthy volunteers has shown that methylphenidate (a drug primarily used to treat ADHD) enhances efficacy within certain neural networks in the brains of young, healthy volunteers, including the important frontal areas that are implicated in many executive functions (Mehta *et al.*, 2000b). Much work of this type has helped define the neural pathways and neurotransmitters that are closely associated with the different psychiatric disorders.

Through an increased understanding of neurochemical mechanisms, it is becoming increasingly possible to identify drugs that are intended to help patients lead lives unhindered by cognitive impairments. Short-term administration of pharmacological agents can improve certain aspects of cognition in ADHD (Aron *et al.*, 2003; Mehta *et al.*, 2000a; Turner *et al.*, 2004a, 2005), schizophrenia (Turner *et al.*, 2004b) and frontotemporal dementia (Rahman, 2001), as well as in patients with cognitive impairments resulting from traumatic brain injury (Cardenas *et al.*, 1994; McDowell *et al.*, 1998). The long-term effects that these drugs have on cognition, and the extent to which changes in laboratory measures of functioning will translate into improvements in everyday performance, are currently being explored. It is important that work of this kind continues if we are to help improve the suffering of thousands of patients and their families, as well as to reduce the financial burden of these disorders on society.

Much of this research work necessarily involves studies using healthy volunteers. Indeed, many of the advances in understanding cognition would not have reached the current state without research in healthy adults. Volunteer studies enable a comprehensive understanding of the effects of pharmacological cognitive enhancement, relatively free from the problems of interpretation posed by underlying pathology. This work is vital in furthering our understanding of cognition and deepening our knowledge of underlying brain mechanisms. It is also the most contentious because of the ethical issues inherent in enhancing the healthy brain. Until recently, psychotropic medications had significant risks and side effects that made them attractive only as an alternative to disorder or illness. However, the body of evidence demonstrating that it is possible to pharmacologically enhance cognition with minimal side effects in healthy volunteers is growing (Elliott *et al.*, 1997; Ingvar *et al.*, 1997; Turner *et al.*, 2003). Executive functions and memory seem particularly susceptible to improvement. As a result, many drugs are increasingly being used off-label (Farah *et al.*, 2004).

Thousands of normal, healthy adults and children have on their own discovered the benefits of cognitive enhancement (Farah, 2002) with many people already self-medicating, using over-the-counter remedies such as herbal stimulants, tonics and caffeine, to improve performance at work, school and leisure. Increasingly, people are turning to pharmaceutical cognitive enhancers. Cognitive enhancement is thus no longer just a theoretical possibility (Farah, 2002). Many agents, such as methylphenidate and modafinil, are

readily available though the Internet. With their worldwide availability, ethical discussions need to consider the effects of these drugs on all sectors of society.

Ethical considerations of cognitive enhancement

The brain, with its higher cognitive processes, demands unique ethical consideration. One of the reasons why ethical dilemmas regarding enhancement of the brain are so much more complex than, for example, enhancement of one's appearance, is that we primarily define and distinguish ourselves as individuals by our behaviour and personality. There are two main discussion points regarding the use of cognitive enhancers in healthy people. The first is the definition of what is considered a 'normal' healthy brain (and the distinction between treatment and enhancement) and the second relates to the consequences that widespread use of 'smart drugs' could have.

Defining normal

It is generally accepted that, because of natural human diversity, 'normal' encompasses a distribution of abilities. In psychiatric terms, 'normal' implies an absence of any psychiatric diagnosis. However, it can often be difficult to categorically determine whether an individual is 'normal' or suffering from a psychiatric condition requiring treatment, with many psychiatric diagnoses presenting as spectrum disorders. For instance, despite attempts at standardizing criteria using tools such as the *Diagnostic and statistical manual* (American Psychiatric Association, 1994) and the *International classification of diseases* (World Health Organization, 2004), cross-cultural studies on the rating of symptoms of ADHD show major, significant differences in the diagnosis of childhood ADHD amongst raters from different countries (Mann *et al*., 1992), in the diagnosis of children from different cultures (Sonuga-Barke *et al*., 1993), and even in the diagnosis of children from within the same culture (Rappley *et al*., 1995). As an illustration, in the United States, ADHD is conservatively estimated to occur in 3.0–7.5% of school-age children, although some estimates are as high as 17%, and up to 20% of boys in some private schools have been found to be receiving psychostimulant treatment (reviewed by Castellanos and Tannock, 2002). Sociological factors can thus play a highly prominent role in clinical deliberations when considering treatment.

In order to overcome discrepancies due to the lack of objective diagnostic tools, often a patient's symptoms must be seen to significantly impair everyday functioning before a diagnosis is made (American Psychiatric Association, 1994). Yet impaired cognition and alertness also chronically affect millions of otherwise healthy people, frequently as a result of jet lag, shift work, sleep deprivation or even old age. Cognitive performance and alertness deficits that result from monotonous activities or sleep loss are recognized as a considerable threat to productivity and safety in both industrial and military settings (Wesensten *et al*., 2002). Furthermore, a disadvantaged educational background might put a person on the lower end of the 'normal' distribution curve, while low cognitive reserve is known to be a risk factor for the adverse effects of stressors such as head injury, dementia and psychiatric disorder (Orrell and Sahakian, 1995; Salmond *et al*., in submission; Stern, 2002). Could these be justifications for enhancement? It might seem easier to justify the use of pharmaco-

logical cognitive enhancement to enable someone to enter employment for the first time, than to help an ambitious student overcome weeks of sleep deprivation. Is there a moral distinction between self-induced and inherent deficits, when deciding whether it is appropriate to offer treatment? However, if everybody has the right to fulfil their potential, this surely must also include 'already-clever' people who choose to enhance. The medical profession has a duty to service those in need. But it is not inconceivable that limited healthcare resources could mean that, in the future in the UK, certain people would be able to receive cognitive enhancement on the National Health Service while others would be urged to 'go private'.

If we are going to posit differences between treatment and enhancement, we need a clear conceptualization of the point at which treatment becomes enhancement. As mentioned previously, this hinges on the definition of normal. 'Normal' is traditionally defined as typical, or not deviating from the standard (*The Chambers dictionary*, 1993). However, diversities in culture, wealth and economic status make it difficult to envisage an ideal 'standard' for human cognition in a global environment. Besides, no human can perform 'typically' (or indeed, optimally) all the time—are we therefore all entitled to occasional 'treatment'? There are countless examples of lifestyle habits that result in less-than-ideal performance (such as excessive alcohol consumption or a lack of sleep). Drugs such as caffeine are already used widely to target temporary deficits in performance in 'normal' individuals. Indeed, there might be situations in which clinicians might wish to use cognitive enhancement for rehabilitation purposes, such as in the case of substance abuse (Duka *et al.*, 2005). However, even if it is difficult to categorically define treatment and enhancement, many are still concerned about the potential harms that could accompany widespread use of cognitive enhancers.

Concerns and limitations

Ethicists have already begun grappling with some of the potential effects on society of the use of these technologies. For example, some people are concerned about what would happen if the level of 'normal' cognitive performance was increased, while at the same time only the wealthy had the means of attaining this new level (Caplan, 2002). Others, however, point out that unequal distribution is not a reason to reject neurocognitive enhancement outright, as there are countless examples in our society of the unfair distribution of education, wealth and resources that are accepted as inevitable (Farah, 2002). Indeed, an alternative fear is that the opposite might become true, where the widespread use of cognitive enhancers leads to the creation of population homogeneity and loss of diversity (Butcher, 2003). Along a similar vein, some are concerned that if we substantially improve our overall cognitive functioning, we may alter fundamental aspects of our identity by eliminating the need to strive for success (Parens, 2002). Is it likely that virtues such as motivation, applying oneself and working hard could potentially become outdated as society becomes more productive, fuelled by the ability to perform optimally for extended periods?

Many of these predictions and fears rely on the assumption that a range of 'ideal' psychotropic drugs will be developed with robust and predictable effects. We are already considerably nearer this goal and it is conceivable that, in the future, we will have a suffi-

cient understanding of the interactions between the neural, pharmacological, genetic and environmental effects on our psyche, in order to develop the 'perfect' cognitive enhancer. Thus, these fears should not be summarily dismissed. It is worth considering whether we are capable of creating a homogeneous society in which members lose all personal and individual identity, and diversity disappears. For this to happen we would have to attend to all facets of human psyche. Some people will always work harder, whether enhanced or not. Thus, for the moment, these technologies are neither so advanced, nor so predictable, that we are in danger of an Orwellian existence.

Perhaps more pressing is the need to concern ourselves with the *current* acceptability of drug use for cognition. One of the predominant concerns of widespread cognitive enhancement is safety (Butcher, 2003). Patients with severely debilitating symptoms will often tolerate the side effects of drug treatment because improvements in symptoms outweigh the negative aspects. It is very difficult to be certain about the potential for subtle, rare or long-term side effects, particularly in relatively new pharmaceuticals, and thus a full exploration of the long-term implications of any treatment that might be used by the healthy population is imperative. Children, especially, are at risk if drugs are discovered to adversely affect brain development. It would be devastating to learn that a dazzling youth of successful cognitive enhancement meant a middle age of premature memory loss and cognitive decline (Farah, 2002). Scientists, pharmaceutical companies and the government must commit resources to the development of robust predictive and long-term detection methods. Research and development organizations should be encouraged to improve on preclinical screening methods for drugs.

Another concern is the extent to which purported beneficial effects of certain drugs are neither predictable nor guaranteed. Our understanding of pharmacogenomics, whilst growing (Roiser *et al*., 2005), is not yet fully developed. At the moment, our knowledge of the effects of cognitive enhancers is largely based on small-scale proof-of-concept studies and more work is required before we can understand the full effects of these drugs. For example, when healthy adults are given methylphenidate, improvements are typically seen in performance on novel cognitive tasks and impairments seen when a task is familiar (Elliott *et al*., 1997). It is possible that inverted U-shaped functions that illustrate the Yerkes–Dodson principle of optimal levels of arousal for effective performance (Yerkes and Dodson, 1908) are implicated in these different effects. Similarly, baseline levels of performance, particularly on working memory tasks, may have some predictive value in determining the cognitive enhancing effects of certain drugs. Mehta *et al*. (2000b) showed that the beneficial effects of methylphenidate on working memory in normal adult volunteers were greatest in those subjects with a lower baseline working memory capacity. However, the opposite effect was observed in children with ADHD, where this time it was those with the highest baseline digit span scores who demonstrated the greatest improvement in spatial working memory following methylphenidate (Mehta *et al*., 2004).

Given the enthusiasm with which society tends to embrace new technologies, some might argue that it is advantageous to encourage paternalism within appropriate authorities in order to minimize harm. Pharmaceutical companies, scientists and the media must avoid unwarranted claims of efficacy, and perhaps government regulators should restrict availability of drugs until their full effects are understood. We only need to look at the explosion

in the use of botulinum toxin type A (Botox™) for beauty enhancement, or sildenafil (Viagra™) for sexual performance, to realize that many people are not hindered by the potential for long-term risks if there is immediate, tangible benefit (Boshier *et al*., 2004; Vartanian and Dayan, 2004).

However, many would argue against such restrictions. Sententia (2004), for example, points out that public policy decisions about cognitive enhancement should be guided by the democratic right to what she terms 'cognitive liberty' and the principle of safeguarding one's own thought processes, rather than by moralism or paternalism. Moral and safety precautions will inevitably have a place in determining appropriate uses of drugs, but she argues that what is paramount is that each individual should have access to the information necessary in order to determine for him or herself what is an acceptable personal risk.

This idealistic libertarianism assumes that all people exposed to such developments live in democratic societies with access to education and the freedom of information. It also supposes that people will be educated to a high enough standard to be able to make informed personal decisions. If we adopt this libertarian approach, we have to consider that many of the freedoms enjoyed in our society are not universal, and that many of these drug developments will impact on people living in less democratic or in less educated societies, and in poorer situations. Furthermore, the majority of safety-orientated drug trials are funded by the pharmaceutical industry and access to the full results by individuals and independent scientists is often not possible (Lexchin, 2004, 2005). This has already been tackled to some extent, with a recent European Union directive (Clinical Trials Directive 2001/20/EC) intended to ensure greater access to information about clinical trials. Similar measures are also encouraged by the Food and Drug Administration (FDA) in the United States, with the FDA Modernization Act of 1997. In addition, independent government-funded trials with widespread dissemination of the results should be encouraged. To ensure this information is utilized effectively, healthcare professionals should be encouraged to acquire the skills to analyse scenarios on a case-by-case basis, bringing together an understanding of science and public policy in collaboration with social scientists, legislators, insurance companies, employers and educational authorities. Due to the increase in information sources and the Internet, patients are already considerably more educated about treatment options than during the last century (Porter, 1997), and it is likely that this trend will continue. The media is essential in the dissemination of ideas and we should not underestimate people's ability to make informed decisions.

Even if we are able to embrace the above principles so that the majority of individuals can make fully informed decisions, widespread availability of cognitive enhancers could bring with it the more sinister prospect of compulsory or forced drug administration to individuals unable to give informed consent. Forced drug administration is already a part of our healthcare system. At present, in extreme circumstances, individuals whose behaviour is considered to be dangerous to themselves or to others can be treated with psychotropic medication under the UK Mental Health Act 1983 (Dale *et al*., 2001). In the United States authorities are increasingly attempting to order individuals in criminal proceedings to take psychotropic medication to improve their competence to stand trial (Boire and Ruiz-Sierra, 2003) or even to be executed (Randall, 2004). Children, in particular, are also very vulnerable to overzealous drug administration. As described earlier, the diagnosis

of many disorders such as ADHD still involves some degree of subjectivity, which can make it very difficult to ensure that children are not being unnecessarily medicated as a result of misleading accounts by enthusiastic parents who want to give their child the edge at school, or frustrated teachers who desire a better-behaved classroom (Farah, 2002). Even relatively poorly defined forces, such as social pressures, could be driving the unnecessary increase in the use of cognitive enhancers. The pressure to take a cognitive enhancer, when all of one's peers are pharmacologically enhanced, is great. Perhaps we should be asking how many of these ethical quandaries would still exist, if expectations of ourselves and others were more reasonable.

Future decisions

We need to decide if it is the practicalities of cognitive enhancement that worry us—the risks and harms—or the outcomes. History has shown that many of the concerns that people have had in the past about new technologies, such as heart transplants and *in vitro* fertilization, no longer worry the vast majority of citizens as these technologies are perfected. Concerns may always remain topical when human brain function and performance is under consideration. However, if we imagine the perfect cognitive enhancer and ask ourselves how we would proceed, will this provide us with a clearer moral picture? We could then examine what aspects of the current limitations might affect our opinion and whether these can be reconciled or overcome. Alternatively, we could approach these questions in the context of currently available drugs, with the assumption that we may never develop the 'perfect' cognitive enhancer and thus there is no point in considering the 'perfect' situation.

There are many reasons to strive to identify the ideal cognitive enhancer. Already countless patients have benefited from advances in neuropsychopharmacology. We must not shy away from new developments on the grounds of conservatively fearing change. However, scientists should be encouraged to take moral responsibility for their research and to monitor and foresee, as far as possible, the consequences of their work. It can be very difficult for scientists to anticipate the implications of their work, particularly at the discovery stage. Nevertheless, consideration for the ethical implications of research could be further encouraged by funding bodies, in the same way that scientists have been urged to engage in the public dissemination of their results. Funding bodies will often be the main determinants of the type of research carried out, and are certainly in a position to encourage much greater collaboration between scientists, social scientists, philosophers and ethicists. Furthermore, many scientists, due to the international, collaborative nature of their research work, are in a position, through these networks, to monitor and assess the consequences of their work in many different social groups.

Only time will determine the true impact of these enhancing technologies. Ultimately, however, many people believe (e.g. Sententia, 2004) that, as long as a person's behaviour does not harm others, they should be free to take any substances they wish to, and equally, as long as a person's behaviour does not endanger others, individuals should not be compelled against their will to use technologies that will affect their cognitive liberty. Clearly, these developments in cognitive neuroscience will improve the quality of life for

patients and their families and reduce the economic burden on society. We must, therefore, rationally consider and debate the implications of these new developments so that strategies can be put in place to ensure these advances support maximal benefit to the individual person and society, with minimal harm.

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