Available online at www.sciencedirect.com
SCIENCE DIRECT®
ACADEMIC PRESS
Brain and Cognition 50 (2002) 387–395
Brain and Cognition
www.academicpress.com

Treatment, enhancement, and the ethics of neurotherapeutics

Paul Root Wolpe

Department of Psychiatry, Department of Medical Ethics, Department of Sociology, and Center for Bioethics, University of Pennsylvania, Philadelphia, PA 19104, USA

Accepted 5 August 2002

Abstract

Emerging neurotechnologies, including psychopharmaceuticals, brain stimulation, implantable brain chips, transcranial magnetic stimulation, and brain imaging raise a number of ethical questions. One of the most contentious is the proper role of these technologies in improving or increasing mental and neurological traits and skills in those with no identifiable pathology. The ''enhancement'' debate centers around a number of concerns and philosophical approaches to the proper role of medicine, therapeutics, and desirable human qualities. Arguements for and against neurological enhancement are reviewed, and historical and social perspectives are offered.

1. Introduction

The study of the brain has always promised more than just the cure of disease. Franz Joseph Gall's phrenology, which identified 27 faculties in the brain (such as valor, cunning, pride, ability to learn, ambition, and metaphysical perspicuity), was intended to detect the morally infirm and differentiate ''higher'' from ''lower'' races. Cesare Lombroso, the 19th Century ''Father of Modern Criminology,'' argued that criminals were evolutionary throwbacks with ''atavistic'' brains and morphological features characteristic of lower races. Craniometry, the science of correlating brain size with intelligence, was used primarily to create intelligence hierarchies within and between races. Nobel Prize winning psychiatrist Antonio Egas Moniz advanced lobotomy in the late 1930s and 1940s as a means of controlling aggressive or violent behavior. These efforts, and most that came after them, were suffused with moral assumptions and visions of desirable and undesirable human characteristics, but were believed by their proponents to represent the dispassionate pursuit of objective science.

Neuroscience today is also built on a series of fundamental assumptions about human nature and worth. It is not possible, and perhaps not desirable, to purge neuroscience of moral presuppositions, dealing as it does with fundamental aspects of identity, personality, free will, and other value-wrought concepts. As in the 19th

E-mail address: wolpep@mail.med.upenn.edu

0278-2626/02/$ - see front matter © 2002 Elsevier Science (USA). All rights reserved.
PII: S0278-2626(02)00534-1

and early 20th centuries, our scientific inquiry is guided by culturally determined standards of what traits we think are valuable to explore and what behaviors we think are desirable to control or eradicate. For example, imaging studies that look for morphological or functional differences in the orbitrofrontal cortex or the amygdala of "psychopaths" (usually defined as violent criminals with antisocial personality disorder) raise many of the same ethical and philosophical questions (if in much more sophisticated scientific packaging) as the science of earlier in the century (Abbott, 2001; Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). The attempt to localize criminality and explain it as the function of a specific pathologized section of the brain is itself an agenda of a particular cultural and historical moment, and one with significant moral implications.

Perhaps the most significant moral discussion in modern neuroscience has been directed at the use of pharmaceuticals to alter the fundamental cognitive and affective functions of the brain. The human desire to induce mental states through ingestion is, of course, as old as the discovery of fermentation (if not older, with the discovery of natural hallucinogens or stimulants), and so is moral debate about it. Nineteenth century America was particularly enamored of developing nutritional philosophies of health with a moral tinge, from the botanical medicine of Samuel Thompson to the non-stimulating diets developed by Will Kellogg (corn flakes were invented as a bland breakfast to avoid stirring up the passions in the morning) or Sylvester Graham (whose now-famous cracker was designed towards the same ends as corn flakes). For centuries, lay, folk, and professional movements in both Western and Eastern medicine have prescribed foods, herbs, and potions to induce proper physical and mental functioning. We still try to "eat right" to improve mood and general mental functioning, and use stimulants (caffiene), sedatives (alcohol), and mood enhancers (chocolate), and have built nutraceuticals (St. John's Wort, Kava, *Ginkgo biloba*) into a multi-billion dollar market. Yet, the debates about the proper use of these substances show no signs of abating.

The ability of the new range of pharmaceuticals to alter or target mood states, levels of cognition, or cognitive skills such as memory is one of the most promising and challenging developments of the 21st century. Drugs developed for some of our most intractable diseases now promise us the power not only to treat pathology, but to improve or augment otherwise average or typical functioning; not only to arrest the cognitive deterioration of Alzheimer's, for example, but to improve cognitive functioning in the healthy. Drugs developed for narcolepsy entice us with amphetamine-free wakefulness (Bastuji & Jouvet, 1988); drugs developed for depression promise to elevate our spirits in general (Kramer, 1993); and drugs developed for erectile dysfunction are sold freely on the web with only a nod to medical necessity (Armstrong, Schwartz, & Asch, 1999). If history is any precedent, we will enthusiastically embrace these technologies, even as we agonize over whether or not we should do so.

Debate has already begun as to the implications of these technologies for defining the difference between treatment and enhancement. There are two fundamental questions that confront us. The first, more philosophical question of enhancement is about categorization: what do terms such as "average" or "normal" functioning, or even "disease" and "enhancement" mean when we can improve functioning across the entire range of human capability? Is the typical, occasional erectile dysfunction that most men experience a "disease" (or at least a condition worthy of medical attention) now that we have a treatment for it? If Prozac can lift everyone's mood, what then becomes "normal" or "typical" affect, and will grouchiness or sadness or inner struggle then be pathologized? And if we can all be happy and well-adjusted through Prozac, should insurance pay for everyone to reach that state of bliss? The second, related question addresses a broader social concern: should we encourage or discourage people to ingest pharmaceuticals to enhance behaviors, skills, and traits?

What are the social (and economic, religious, psychological,. . .) implications of using drugs or other neurotechnologies to micromanage mood, improve memory, to maintain attentiveness or improve sexuality?

2. Defining enhancement

The answers to these two questions are, in large measure, dependent on how we define enhancement itself. But the more closely we examine the concept, the slipperier it appears. As enhancement is a concept that defines the boundary condition between what we consider disease intervention and what we do not, by definition the term will conform to what the culture, or medical professionals, see as the proper objects of medical intervention. In other words, what medicine chooses to treat is defined as disease, while altering what it does not treat is enhancement.

The difficulty of creating a meaningful enhancement standard to use to allocate medical care or create guidelines for clinical treatment can be illustrated by looking at one proposal. The bioethicist Norm Daniels asks what kind of medical care should be covered for all citizens in a just society, and in doing so has developed probably the most detailed discussion of the enhancement issue (Daniels, 1985; Daniels, 2000; Sabin & Daniels, 1994).

Daniels is interested in determining what should be considered obligatory vs. non-obligatory provision of care in a just society. He begins by arguing *against* trying to demarcate a treatment/enhancement distinction to solve that dilemma. First, he suggests, even if we could clearly define the two, we cannot draw a clear moral line that justifies considering one the legitimate object of medical attention and not the other. Secondly, there is something ultimately arbitrary about how we draw many of our disease/non-disease distinctions. Finally, there are treatments or conditions (such as abortion or shyness) that are clearly outside disease definitions, yet that we may want to provide in our standard medical offerings.

Daniels illustrates his point by offering the following example: imagine two boys, both of whom are of short stature and are projected to grow into short stature adults of about 5 ft 3 in. (which is at the low end of the normal growth distribution for males). One is short because he has growth hormone (GH) deficiency from a brain tumor, while the other is short because, though he has normal GH secretions, he has very short parents.

Both ''suffer'' from the same condition, and in both the causes are fundamentally biological. Yet only one is ''sick''; any intervention we design on behalf of the second is likely to be labeled ''enhancement.'' Daniels pushes it even further: what if we find the gene(s) that cause short stature in the boy without the tumor, and discover he is short because his cells do not respond readily to GH, or because his GH levels level off faster, or because he has fewer receptors? Is he *then* ''sick?'' And what if the other boy has a gene that predisposes him to the tumor? Now both causes can be considered genetic, yet one boy is granted full economic and social access to medical resources, while the other may not be.

Daniels' concern is about obligatory vs. non-obligatory medical services, and its implications for social justice; what services must be provided to all citizens in a society that sees provision of basic care an inalienable right? What standards of ''medical care'' do we use when we desire to distribute medical care fairly and equitably in society? Why is the society ready to help the boy with the tumor reach greater stature, and not the other, and is the reasoning justified?

Daniels suggests that instead of using definitions of disease as our standard, which may lead us to treat one boy and not the other, we should instead determine for each trait, state, or behavior what he calls ''species-typical functioning.'' The concept implies not just a statistical accumulation of some average level of functioning in a

particular realm of human activity, but rather an examination of the design of the organism to determine the "natural functional organization" of its members. The "normal function model" serves as the standard of functioning that a society has an obligation to try to achieve for all its members. While a society has no obligation to provide services that raise any citizen's function above the typical level for the species as a whole, it does have an obligation to provide services that, to the degree possible, raise the level of functioning of any citizen with deficits to the species-typical level. In such a case, if short stature can be shown to cause difficulties in the lives of males of such stature (as it can, in such things as employment discrimination and mate selection), society has an obligation to try to ameliorate that departure from normal function (i.e., male-typical height) no matter what the cause. Daniels goes on to suggest that normal functioning is important as a baseline not because it is "natural" (a thorny concept philosophically) and so inviolable, but because it is a convenient baseline to determine what society should owe to its members. In addition, the approach resists the trend towards medicalizing problems, and sets stronger boundaries around what medicine should attend to. Pursuing some ideal of total physical, mental, and social well-being is beyond medicine's proper domain (Parens, 1998).

There are a number of problems with Daniels' argument. His model has been criticized as to the difficulty in determining species-typical functioning for a host of traits (e.g., what is "species-typical" happiness, or shyness, or cognition, or even erectile function?). Remember that we need to determine this not by some statistical average, but rather by a "theoretical account of the design of the organism." How happy were we, in fact, designed to be? Other critics have pointed out the model's assumption of the innateness and immutability of talents and traits; the presumption that maximization of potential is only owed the low-functioning; and the culturally and ideologically bound determination in many traits of what should be considered "typical" or "normal" (e.g., Juengst, 1998; Lachs, 2000; Silvers, 1998). Daniels' effort well illustrates the fundamental problem of drawing the lines between the kinds of physiological interventions that we conceptualize as curative or normalizing, and those we consider extraordinary or enhancing.

Other models have been proposed as well (see Juengst, 1998, for a review). Yet, ultimately, any exclusive enhancement definition must fail, in part because concepts such as disease, normalcy, and health are significantly culturally and historically bound, and thus the result of negotiated values. The provision of services under the rubric of medicine is, ultimately, somewhat arbitrary, the product of social negotiation and historical precedent. Decisions about what to fund through insurance reimbursement, what to restrict by regulating access (through physicians, for example), and how society as a whole should regard the use of "enhancing" pharmaceuticals and other technologies will be the product of a long series of conversations in the professional literature and in public fora as these technologies develop.

The enhancement/treatment conundrum can therefore be summarized as addressing three levels of inquiry:

1. *Medicine and reimbursement*: what should be the proper role of enhancement technologies in medicine and those who fund it? Can a distinction be made between therapy and enhancement that is meaningful and operationalizable? Can we defend the proposition that medicine should concern itself with, or that third party payers should only fund, "treatment" and not "enhancement?"
2. *Public policy*: in what spheres of public policy should a distinction between disease and enhancement be maintained? Should there be rules against using certain enhancement technologies in sports, for example, or among children? And conversely, should public policy encourage use of enhancement technologies among those for whom it might aid in safeguarding the public good?

3. *Normative behavior*: is there a normative recommendation for how we should think about enhancement in general? Should society promote or resist biotechnological enhancement? And whatever the normative decision, why does there seem to be such initial resistance to its uses?

3. Neurotechnologies and the enhancement question

The questions posed above are particularly trenchant when applied to emerging neurotechnologies. On one hand, human beings have always developed strategies and technologies to enhance their cognitive and affective functioning. We send our children to school, memorize poetry, develop training programs, meditate, enrich our word power, read novels, go to therapy, try to get a good night's sleep before exams, eat "brain food" such as fish, shut the door and turn off the music to study—all actions that, to one degree or another, are intended to create environments, inner states, or improved functioning that will encourage or support a desired level of neurological performance. We bang our heads, rub our temples, snap our fingers, and try to stop thinking directly about a topic to recall it to memory. In addition, we drink alcohol and caffeine, take Ritalin and Prozac, inhale nicotine, smoke marijuana, and use other pharmacological means to induce our brains to act in ways that we desire—to increase memory, stabilize mood, encourage creativity, or promote attentiveness.

The enhancement question, however, arises primarily in technologies that attempt to *directly* moderate the neurochemical, structural, or electrical components of the brain. The manipulation of brain function through learning, meditating, behavioral reinforcement, biofeedback, temple rubbing, or any other mechanism that either draws on the body's own resources, or manipulates the external environment to induce change do not raise the same ethical challenges. What characterizes the particular ethical currency of the enhancement debate today is the ability to bypass these types of activities and to change the brain directly.

Let us leaven our discussion with an example of a drug with the ability to enhance normal functioning: modafinil. Modafinil (2-(diphenylmethyl)-sulfinylacetamide) is a eugeroic (literally, "good arousal") drug that creates a wakeful, alert state in those who take it. Early reports suggest that, unlike amphetamines, modafinil does not create a "buzz," does not cycle high and low, does not increase heart rate and blood pressure, and is non-addictive (Bastuji & Jouvet, 1988; US Modafinil in Narcolepsy Multicenter Study Group, 2000). Amphetamines create a dose-dependent impairment of the sleep cycle, so that one needs more and more amphetamines to stay awake, and is ultimately more fatigued. Modafinil not only does not disturb sleep, it only seems to cause wakefulness under conditions where vigilance is sought by the person who has taken it (Legarde, Batejat, van Beers, Sarafian, & Pradella, 1995). Modafinil is generally prescribed for sleep disorders, such as narcolepsy and hypersomnia, and may be effective in the sleepiness that can accompany diseases such as Parkinson's.

Modafinil, marketed under the brand name Provigil, may eventually challenge Viagra in its appeal to off-label and black market usage. Also like Viagra, new sources have begun to tout the benefits of modafinil. A CBS News report trumpeted, "A Dream Come True? New Drug Tricks Brain To Be Awake" (CBS News, 2002). The New York Times ran an article emphasizing the drug's potential in "a chronically sleep-deprived nation" (Goode, 1998), and The New Yorker magazine ran a glowing piece asking whether "science can make regular sleep unnecessary" (Groopman, 2001). Cepahlon, the manufacturer, has done little to discourage the hype; in fact, the PDA recently cautioned Cephalon to be more careful in its claims about Provigil in its direct-to-consumer advertising (Los Angeles Times, 2002).

Additionally, the potential of modafinil to be used for non-therapeutic purposes has been promoted in reports citing the armed services' interest in the drug for use in pilots. One study that came out of the United States Army Aeromedical Research Laboratory examined helicopter pilots who were exposed to two 40-h periods of continuous wakefulness separated by only one night of recovery sleep. When receiving modafinil, the pilots scored higher on tests of performance and physiological arousal than they did while on placebo, and also had improved self-ratings of vigor, energy, alertness, talkativeness, and confidence (Caldwell, Caldwell, Smythe, & Hall, 2000). It is not therefore surprising that the United States army, as well as a number of European armed forces, are already using monafidil; up until now, the standard issue wakefulness drug was Dexedrine, which cause all the side effects of amphetamines. The Department of Defense Advanced Research Projects Agency (DARPA), which is funding research into modafinil, justified the research by claiming:

> As combat systems become more and more sophisticated and reliable, the major limiting factor for operational dominance in a conflict is the warfighter. Eliminating the need for sleep while maintaining the high level of both cognitive and physical performance of the individual will create a fundamental change in warfighting and force employment, (quoted in Groopman, 2001, p. 55).

The armed services are not employing the drug without at least some ethical reflection on the appropriate uses of pharmaceuticals as enhancement agents; as a United States Air Force report puts it: "The development of modafinil brings to light a crucial social question. What would be the impediment for its use, if a compound such as modafinil is more like caffeine than amphetamine in terms of safety, and yet, as effective as the amphetamines?" (Lyons & French, 1991).

The "crucial social question" of Lyons and French already confronts us. The use of Viagra, for example, is common among men who would not qualify for a diagnosis of erectile dysfunction (Armstrong et al., 1999). Ritalin sales in certain school districts exceeds any reasonable estimate of children with ADHD that meets DSM-IV criteria (Diller, 1996; Miller, Lalonde, McGrail, & Armstrong, 2001a,b). Kramer (1993) suggested that Prozac makes some patients "better than well," and prescriptions soared. Clearly, some of the top selling drugs in the world today are being used by patients who fit no traditional definition of pathology, yet still see in their own functioning a deficit that these drugs address.

Modafinil will likely follow the patterns of Viagra and Prozac, with areas of overprescribing, significant off-label usage, websites with cursory medical examination, and significant non-prescription sales. Still (or perhaps therefore?) policies need to be made, and so the enhancement question must be addressed. Should modafinil be prescribed solely as a medical drug, properly used only for those suffering from sleep pathology? If so third party payers, including government programs, should cover it. Or, should it be classified as an over-the-counter drug, available to anyone who wants it? Or, should we create a class of drugs available only to those who can show legitimate social need, those whose fatigue might put others at risk, such as airline pilots, or truck drivers? If so, we might see modafinil use as akin to reconstructive surgery, where payment is determined on perceived necessity. For those with severe injury or disfiguring birth defects, reconstructive surgery is medically justifiable and covered. For those electing to have surgery for cosmetic purposes, physicians are still free to offer it (or not), but no one is under a moral obligation to fund it. Finally, as a general social policy question, should we restrict modafinil's use in certain defined social settings, such as sports competitions (where those who use it will have an advantage), or in pediatric use (where students should be learning non-pharmaceutical attention skills), or in people in particularly high-stress jobs, such as airport traffic controllers (who might be tempted to abuse it)?

4. The problems of neurological enhancement

The difficulty in deciding the questions of the correct use of neurological enhancers is, in part, a recognition that since we do not really understand the implications of enhancing neurological function, our strategies may backfire. The idea that attention is good, so increased attention is better, or that cognition is good, so increased cognition is better, may turn out to have unexpected consequences. Let us take as an example the effort to develop drugs targeted to improving memory in human beings (e.g., Furey, Pietrini, Alexander, Schapiro, & Horwitz, 2000). The improvement of memory sounds attractive in the abstract, and certainly is desirable for those suffering from Alzheimer's or other conditions that affect memory functions. But there are many unknowns in the use of such drugs in the cognitively intact. The assumption is that memory drugs will simply increase the amount of memory we have available, leaving all other cognitive and affective processes unaffected. But in fact, memory is a selective, delicate process. There are experiences and data that our brains filters out. Our cognitive processes retain specific kinds of data, under specific circumstances, while other input is neglected. Who needs to remember the hours waiting in the Department of Motor Vehicles staring at the ceiling tiles, or to recall the transient amnesia following a personal trauma? Yet, we do not know whether memory enhancement drugs might impair our selectivity process. Might they improve our retention of all memories, even the traumatic or trivial memories that the brain tends to repress? Might we end up awash in memories that are troubling to us, unable to forget a painful past? And how might a memory drug affect associated mental processes—mood (which is closely connected to memory), or attentiveness (daydreaming is often fueled by a sudden recollection)? Perhaps evolution has stabilized at a particular level of memory capacity because more sacrifices a certain cognitive flexibility; a plastic brain may have advantages over one crammed with memory.

The concern is not only speculative. In 1999, scientists reported in *Nature* that they had genetically engineered mice with increased ability to perform learning tasks (Tang et al., 1999). The scientists inserted a gene in mouse zygotes that increased the production of the protein subunit NR2B, part of the NMDA receptor. The mice also displayed physiological changes in the hippocampus (associated with learning) when compared to non-transgenic mice. However, subsequent research seemed to indicate that the mice with enhanced NR2B seemed to have a greater sensitivity to pain (Wei et al., 2001). Though it may be that the mice do not feel the pain more acutely, just learn about pain more readily and thus seem to react to it more strongly (Tang, Shimizu, & Tsien, 2001), it is troubling that even the most preliminary research on memory enhancement has already raised the question of unexpected collateral effects. Perhaps there is a link we do not understand between memory and pain, either at the structural or behavioral level. What other unexpected linkages might be discovered in attempts to change cognitive functions through induced physiological modification?

While most of the "cognitive enhancement" discussed in the literature focuses on memory or attentiveness, the range of cognitive abilities, of course, exceeds just these two traits. Learning, language, skilled motor behaviors, and "executive functions" (such as decision making, goal setting, planning, and judgment) are all part of general cognition, and a drug that managed to enhance a greater range of function (especially executive function) may be more desirable than one that narrowly enhanced memory alone (Whitehouse, Juengst, Mehlman, & Murray, 1997). But if memory drugs alone have collateral affects, how much more so might a drug that influences a greater range of cognitive functioning?

It is not only the collateral effects of neurological enhancement that are troublesome, but also the nature of the change itself. For example, the progressive loss of cognitive function that characterizes Alzheimer's is usually described as constituting

the "loss of personality" of the person with the disease. "Dad isn't Dad anymore" because his cognitive faculties as experienced by his loved ones are considered fundamental to who he is; loss of those functions are seen as loss of his essence. A general cognitive enhancement may have the same effect. Significantly improving our overall cognitive functioning may also alter aspects of our identity that are seen as fundamental to who we are. As Whitehouse et al. (1997, p. 16) write:

> Increased memory, new insights, and better reasoning could all lead to new values, new perspectives on one's relationships, and new sources of pleasure and irritation. That does not mean that the enhanced literally will lose their identities and become different people, any more than someone with Alzheimer's does. But in the figurative sense intended by caregivers of people with the disease, it may be that after some point the cognitively enhanced will no longer be recognizable by those who knew them before their enhancement.

Research on patients with frontotemporal dementia, who demonstrate often dramatic changes in well-established patterns or religion, dress, style, and political philosophy, seems to indicate that some aspects of the self are functions of the frontal lobes (Miller et al., 2001a, b). Lauren Slater, author of the memoir "Prozac Diary," writes that though Prozac relieved her of her symptoms, she no longer felt any desire to read the angst-ridden psychology and philosophy books that lined her bookshelf (Slater, 1998). Slater wonders what the loss of these books, that had once been sources of wisdom for her, meant for her sense of self: "who was I? Where was I? Everything seemed less relevant—my sacred menus, my gustatory habits, the narrative that had had so much meaning for me. Diminished." Even when she rediscovers her spiritual side later in the memoir, she now wonders if her calmer, more contemplative spirituality comes not from God, but from Prozac.

Neurological biotechnologies differ from others in that they ask us to explicitly consider the kind of "self" we want to have; or, to put it less dualistically, perhaps, the kind of self we want to be. For some, our astounding ability to manipulate our own biology is an integral part of who we are as human animals. For others, it is an affront to our humanity. This is an argument for which there are no right or wrong answers, emerging as it does from two philosophically different visions of human life. Yet therein lies the tension of the enhancement debate, and there is little doubt that the battlefield on which the debate will be waged next will be our ancient desire to control the workings of our own minds.

References

Abbott, A. (2001). Into the mind of a killer. *Nature*, **410,** 296–298.

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrental cortex. *Nature Neuroscience*, **2**(11)**,** 1032–1037.

Armstrong, K., Schwartz, J. S., & Asch, D. A. (1999). Direct sale of sildenafil (Viagra) to consumers over the internet. *New England Journal of Medicine*, **341**(18)**,** 1389–1392.

Bastuji, H., & Jouvet, M. (1988). Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Progress in Neuro psychopharmacology & Biological Psychiatry*, **12**(5)**,** 695–700.

Caldwell, J. A., Caldwell, J. L., Smythe, N. K., & Hall, K. K. (2000). A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: A helicopter simulator study. *Psychopharmacologia*, **150**(3)**,** 272–282.

CBS News, A dream come true? New drug tricks brain to be awake; Military Is Interested. January 14, 2002. (http://www.cbsnews.com/now/story/0,1597,324299-412,00.shtml).

Daniels, N. (2000). Normal functioning and the treatment-enhancement distinction. *Cambridge Quarterly*, **9**(3)**,** 309–322.

Daniels, N. (1985). *Just health care*. New York: Cambridge University Press.

Diller, L. H. (1996). The run on Ritalin: Attention deficit disorder and stimpulant treatment in the 1990s. *Hastings Center Report*, **26**(2)**,** 12–14.

Furey, M. L., Pietrini, P., Alexander, G. E., Schapiro, M. B., & Horwitz, B. (2000). Cholinergic enhancement improves performance on working memory by modulating the functional activity in

distinct brain regions: A positron emission tomography regional cerebral blood flow study in healthy humans. *Brain Research Bulletin*, **51**(3), 213–218.

Goode, E. (1998). New hope for losers in the battle to stay awake. *New York Times*, November 3, F1.

Groopman, J. (2001). Eyes wide open. *The New Yorker*, December 3, 52–57.

Juengst, E. (1998). What does enhancement mean?. In E. Parens (Ed.), *Enhancing human traits* (pp. 29–47). Washington, DC: Georgetown University Press.

Kramer, P. O. (1993). *Listening to Prozac*. New York: Penguin books.

Lachs, J. (2000). Grand dreams of perfect people. *Cambridge Quarterly*, **9**(3), 323–329.

Los Angeles Times (2002). EDA reprimands 4 drug makers for misleading promotions. January 16. (http://www.latimes.com/business/la-000004018janl 6.story?col = la-headlines-business).

Legarde, D., Batejat, D., van Beers, P., Sarafian, D., & Pradella, S. (1995). Interest of modafinil, a new psychostimulant during a sixty hour sleep deprivation experiment. *Fundamental & Clinical Pharmacology*, **9**(3), 271–279.

Lyons, T. J., & French, J. (1991). Modafinil the unique properties of a new stimulant. *USAF School of Aerospace, Brooks TX Science News Note*, **62,** 432–435.

Miller, A. R., Lalonde, C. E., McGrail, K. M., & Armstrong, R. W. (2001a). Prescription of methylphenidate to children and youth, 1990–1996. *CMAJ, Canadian Medical Association Journal*, **165**(11), 1489–1494.

Miller, M. D., Seeley, W. W., Mychack, P., Rosen, M. D., Mena, I., & Boone, K. (2001b). Neuroanatomy of the self. *Neurology*, **57,** 817–821.

Parens, E. (1998). Is better always good? The enhancement project. *Hastings Center Report*, **28**(1), S1–S15.

Sabin, J. E., & Daniels, N. (1994). Determining 'medical necessity' in mental health practice. *Hastings Center Report*, **24**(6), 5–13.

Silvers, A. (1998). A fatal attraction to normalizing, treating disabilities as deviations from "species-typical" functioning. In E. Parens (Ed.), *Enhancing human traits* (pp. 95–123). Washington, DC: Georgetown University Press.

Slater, L. (1998). *Prozac diary*. New York: Random House.

Tang, Y. P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., Zhuo, M., Liu, G., & Tsien, J. Z. (1999). Genetic enhancement of learning and memory in mice. *Nature*, **401**(6748), 63–69.

Tang, Y., Shimizu, E., & Tsien, J. Z. (2001). Do 'smart' mice feel more pain, or are they just better learners? *Nature Neuroscience*, **4**(5), 453–454.

US Modafinil in Narcolepsy Multicenter Study Group (2000). Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* **54**(5), 1166–1175.

Wei, F., Wang, G. D., Kerchner, G. A., Kim, S. J., Xu, H. M., Chen, Z. F., & Zhuo, M. (2001). Genetic enhancement of inflammatory pain by forebrain NR2B overexpression. *Nature Neuroscience*, **4**(2), 164–169.

Whitehouse, P. J., Juengst, E., Mehlman, M., & Murray, T. H. (1997). Enhancing cognition in the intellectually intact. *Hastings Center Report*, May–June, 14–22.