Neural Enhancement: A Slippery Slope for Neurologists

By Ricki Lewis, PhD [2]

cognitive enhancement, cosmetic neurology

Boosting brainpower is popular in fiction—from the sudden smarts of the scarecrow in the Wizard of Oz to variations on the theme in which a character emerges from a mental fog only to then lose the clarity. The idea of neural enhancement is growing in popularity, echoing the use of steroids to enhance athletic performance. In the coming years, it will probably be commonplace for a healthy patient to approach a neurologist for help in honing cognition or improving memory. Helping the healthy isn't new, said Martha Farah, PhD, director of the Center for Cognitive Neuroscience at the University of Pennsylvania. "Other branches of medicine have gone down this road. Consider plastic surgery or a 40-year-old woman wanting a child. In both cases, a physician has the option to make life better by pushing the limits a little bit." Focus on the brain is not novel either. The fuzzy line between prescribing medication for attention deficit hyperactivity disorder (ADHD) and the illicit use of ADHD drugs by students seeking to increase their powers of concentration come exam time vividly illustrates the slippery slope underlying neural enhancement. And the practice is already pervasive. Richard Kadison, MD, chief of mental health at University Health Services at Harvard University, described one student who took his roommate's methylphenidate to pack in more study hours and another student who used antidepressants so that he would have less anxiety when participating in class.1 Such reliance on pharmaceuticals continues after college. The New York Times recently profiled2 stressed 25-somethings who regularly exchanged alprazolam (Xanax, Pfizer) and zolpidem tartrate (Ambien, Sanofi Aventis), lorazepam (Ativan, Biovail) and fluoxetine (Prozac, Eli Lilly). At the other end of the life cycle, seniors seek ways to prolong mental acuity. The quest for brain enhancement may be inexorably knit into our social structure. Thomas Murray, PhD, president of the Hastings Institute in Garrison, NY, began his 8 am lecture on the phenomenon at the Society for Neuroscience annual meeting in November 2005 with "How many of you have indulged in a cognitively enhancing drug this morning?" Many hands shot up. For a generation brought up with drug solutions to learning disabilities and mood disorders and a constant barrage of pharmaceutical ads—and with the relative ease of obtaining prescriptions for psychoactive drugs by parroting symptoms gleaned from Internet-based research-investigations are hardly necessary to track the trend of "head-med" abuse. One need only talk to a high school or college student around SAT time or finals. But what isn't known is how the medical profession should respond. "There are no guidelines, nor much tradition to guide physicians. My sense is that physicians react individually to these situations. We don't have a clue what neurologists, psychiatrists, and primary care physicians are doing. Ultimately, organizations such as the American Academy of Neurology will have to produce practice parameters just as they do for various diseases to establish a standard of care," said Anjan Chatterjee, MD, associate professor of neurology at the University of Pennsylvania. He coined the term "cosmetic neurology."3 Modafinil: A Case Study for Neural Enhancement Modafinil, marketed in the United States by Cephalon as Provigil and in Canada by Draxis Health as Alertec, offers a prime example of a drug with established medical use that could benefit the healthy. Developed in the late 1970s in France, modafinil was approved by the FDA to treat daytime sleepiness from narcolepsy in 1998 and to treat ADHD in 2005. It is an investigational drug for a long list of other indications, including Alzheimer-related depression, myotonic dystrophy, age-related memory decline, obstructive sleep apnea, and shift work sleep disorder. Several factors are converging that may push modafinil into the company of "lifestyle" drugs: - Cephalon applied in 2005 for over-the-counter status. - The World Anti-Doping Agency added modafinil to its list of banned drugs just before the 2004 Summer Olympics. - The drug will become generic this year. Cephalon has filed a new drug application for Nuvigil, a single-isomer formulation. Modafinil affects orexin-producing neurons in the hypothalamus that project to regions that promote wakefulness. Stimulation of these neurons increases availability of dopamine and norepinephrine; modafinil boosts dopamine levels by inhibiting reuptake. The drug maintains wakefulness for up to 88 hours, without the jitteriness, cardiac effects, or dependency of amphetamines. Complete recovery is achieved following an 8-hour slumber. Half-life is 12 to 15 hours; effects peak between 24 and 32 hours. The
military has great interest in modafinil because it promotes vigilance—the ability to think clearly and remain on task. A much-quoted study published in Psychopharmacology in 2000 that looked at 6 pilots in a helicopter simulator demonstrated that the drug is indeed a "memory-improving . . . mood-brightening psychostimulant," but it has side effects, including vertigo, nausea, and dizziness. These findings gained renewed importance in 2002, after 2 sleep-deprived US Air Force pilots killed 4 Canadian pilots on a training mission in Afghanistan. Defense counsel blamed the pilots' reliance on dextroamphetamine sulfate (Dexedrine, GlaxoSmithKline) to stay awake, although 3 physician-officers at Fort Rucker, AL, pointed out that the link to the drug had never been reported. Another study further built modafinil's case. Ten pilots using helicopter simulators were given 100-mg doses of the drug or placebo. Ability to maintain flight accuracy was within 15% to 30% of baseline for the treated pilots, compared with a deficit of 60% to 100% for patients receiving placebo. Participants reported that when they took the drug but were sleep-deprived, they tended to feel less angry and depressed than they would have felt had they not been medicated and that, while medicated, they experienced increased vigor, alertness, and confidence. While the military continues to investigate use of modafinil in war zones—such as in exhausted soldiers who fall asleep at the wheel—others see the drug sliding down a slippery slope. Murray imagined modafinil in the legal arena: "It will allow more billable hours." RUL CHANGES Neural enhancement requires a re-examination of risks and benefits, and perhaps also requires adaptations in the drug-approval process. In drug treatment for disease, benefit typically outweighs risk. With healthy people, risks can loom larger, but that might not matter if the expected benefit is sweet enough, said Chatterjee. "If you have the worst disease, such as glioblastoma multiforme, you are more likely to risk taking all kinds of toxic things. For the healthy, I might say there's no risk worth it because I'm already healthy. But that flies in the face of empirical evidence for the way that professional athletes use steroids." Neural enhancement is likely to be enticing in any highly competitive, winner-take-all environment, he added, citing journalism and academia as examples. "You can construct all sorts of scenarios in which people convince themselves that an extra 5 IQ points would give them an edge." The evolution of antidepressants provides a case in point for the role of risk/benefit considerations in neural enhancement. The older tricyclic antidepressants tended to be prescribed for people with severe depression. Today, people with milder symptoms are offered the gentler selective serotonin reuptake inhibitors (SSRIs). The list of indications for these medications is growing, according to the President's Council on Bioethics. Nonclinically depressed people taking SSRIs report decreased brooding, oversensitivity, anxiety, and fear; increased confidence, self-esteem, and energy; and improved sleep and appetite, although underlying sadness may persist. The idea of neural enhancement is built on the premise that effects of cognitive- and mood-enhancing medications on the ill predict effects on the healthy. That might not always follow, said Farah. "Some people with high normal functioning actually show worse performance on some cognitive tests when they take stimulants compared with placebo. The assumption has been that stimulants lift all boats, that they can make people with an attention problem normal, and make the normal do super well. But it's not as simple as that." An added complication is the great range of normalcy. "Maybe an enhancer has different effects on people with differing personality characteristics. Do introverts and extroverts respond differently to stimulant medications, for example?" posed Chatterjee. Biomarkers may be helpful in identifying subsets of the healthy. For example, 2 variants of the enzyme catechol-O-methyltransferase have opposite effects on dopamine utilization, and therefore may affect how modafinil is metabolized. "This is the tip of an iceberg of situations where normal people with one kind of gene variant have a different response to the same medication as someone with a different gene variant," Chatterjee added. FIGHTING THE COGNITIVE CLOCK Neural enhancement has different meanings at different life stages. Might drugs in development for pathologic memory decline find a market among people experiencing the normal ebb in memory and cognition that accompanies advancing years? A session at the Society for Neuroscience annual meeting, "Healthy Brain Aging," briefly reviewed the basic research that is forming the foundation of this emerging field. Adam Brickman, PhD, a postdoctoral researcher at the Taub Institute for Research on Alzheimer Disease and Aging at Columbia University Medical Center, presented associations between age-related volumetric changes in white and gray matter, as shown on structural MRI, and cognitive tests of memory, attention, and language ability. The study tested 2 groups: one with a mean age of 24 years and one with a mean age of 73 years. All participants had similar IQ and educational levels, and all were free of brain disease. The study pinpointed loss of white matter in the thalamus, frontal cortex, temporal lobe, parietal lobe, anterior frontal cingulate, and corpus callosum. "Our results suggest that there are identifiable networks of gray and white matter regions that systematically decline with age. We also found that expression of both gray and white patterns is
associated with performance on cognitive tests, particularly tests that measure memory, attention, and executive function," Brickman reported. David Ziegler, a graduate student at the Massachusetts Institute of Technology, was part of a team that used diffusion tensor imaging (DTI) to track decline of white matter with aging. DTI measures how easily water moves through different types of tissues. The myelin of white matter blocks water flow. The researchers looked at people in their mid-20s and compared them with people aged 60 to 80 years to investigate the association between white matter integrity and cognitive performance. Tests measured episodic memory (events), semantic memory (fact recall), and frontal lobe cognitive control (planning and coordinating thoughts and actions). Older people with high white matter integrity in the frontal lobes had better cognitive control than age-mates with corresponding low white matter integrity. Greater white matter integrity in the temporal and parietal lobes was associated with better episodic memory. Concluded Ziegler, "White matter is a fresh target for developing therapies to slow the negative effects of aging." Shrinking brains need not alarm the over-50 set, said Paul Coleman, PhD, professor of neurobiology and anatomy at the University of Rochester Medical Center in New York, because changes are not global. "Not so long ago, it was thought that as we age, we lose neurons all over-10,000 per day. Prominent neuroscientists studied shrunken dendrites and likened them to a forest fire that had swept through. Aging brought an inevitable decline in cognition and memory. Now a different picture is emerging. Some specific changes do occur." While neuroscientists probe the basic biology of the aging brain and companies seek treatments for memory disorders (see sidebar), seniors need not await new drugs to maintain cognitive skills. "There are 3 ways to maintain cognition: mental activity, physical activity, and social engagement," said Coleman. The final 2 talks in the "healthy brain aging" session introduced 2 ways to do this: tango dancing and use of a computer program to improve listening skills. Patricia McKinley, PhD, associate professor of physical and occupational therapy at McGill University, loves to dance. So she randomly assigned seniors aged 62 to 90 years, who had a history of falling or a fear of it, either to group walking in a park or to tango dancing for 2 hours twice a week for 10 weeks. Before the end of 1 month, she assessed cognitive skills, strength, balance, risk of falling, social integration, spatial and numerical memory, walking tasks, and balance. Although participants were few and self-selected, and the study obviously was not controlled, "across the board, the tango group showed more improvement in all measures," McKinley said. The walkers, however, were able to chat instead of focusing on steps and reported better alleviation of loneliness. Why tango? "It is very complicated, like a game for 4 legs and 2 people. Tempo can vary. You have to learn a series of complex steps but improvise the order, going around the dance floor not knowing what the person in front of you is doing," McKinley said. It introduces all elements of neurologic rehabilitation: forward and backward movement, side-to-side weight shift, one-legged stance, walking in a straight line back and forth, increasing step length in all directions, and turning in a narrow space. "Tango dancing is an ideal leisure activity because it satisfies the basic requirements for exercise adherence: it's fun, it's a group activity, and it has a tangible goal that can be perceived not only by the dancer, but by family and friends," McKinley explained. Seniors stay alert in many ways, including reading and watching films, playing chess, and doing crossword puzzles. Posit Science of San Francisco offers a more formal type of mental exercise, billed as a "brain fitness program." The series of computer exercises isolates 1 cause of cognitive fuzziness: the increasing inability to distinguish speech sounds. Older people may experience difficulty in understanding the high voices of children, those who speak in low tones, or muffled speech. They may become increasingly unable to remember sound cues, follow fast speech, or isolate relevant sounds from a background cacophony. When incoming sound is garbled, memories do not form properly, according to Michael Merzenish, PhD, chief scientific officer at Posit Science and the Francis Sooy Professor at the Keck Center for Integrative Neurosciences at the University of California, San Francisco. The company recently studied 95 volunteers, aged 61 to 94 years, who were randomly assigned to 1 of 3 groups: one that completed an hour of auditory discrimination exercises 5 days a week for 8 weeks, a group that watched a lecture on a computer for the same amount of time, and a control group that did not use a computer. Standardized tests measured memory and cognition before and after training. "The majority of participants in the training program improved 10 or more years in neurocognitive status. Beyond the measurable results, participants in the study reported a range of benefits, from feeling more engaged in conversation to having more control over their lives," Merzenish said. Unlike puzzles or games, their exercises "create new pathways in the brain," which is inferred from the results of many animal studies, said Peggy Jara, director of communications. A residential community can purchase a license for the Brain Fitness Program. An individual purchase, which covers 2 people, is $495 without a pre- and post-test diagnostic, and $795 with them, Jara added. THE BIOETHICS OF NEURAL ENHANCEMENT if neural enhancement were
considered in a societal bubble where people didn't already depend on that morning cup of java or
spend thousands to boost SAT scores, ethical objections might emerge. Instead, cautious support
seems to be building. The President's Council on Bioethics endorses the approach. It concludes:
"Assuming that there were no physical or mental side effects . . . there is little obvious reason to be
concerned about the ethical or social implications." 7 Farah agrees. "If a medicine is safe, both
physically and psychologically, the person would be helped, and it is not asking to do something
illegal or unethical, a neurologist must ask, is that reasonable? Should physicians help patients to
lead better, more comfortable, more successful lives?" The Fort Rucker officers claim it would be
unethical not to enhance wakefulness in combat. But Farah also points out that neural enhancement,
should it become routine, poses concerns of necessity and access. Should a neurologist whose
schedule is typically booked with people suffering from neurodegenerative diseases or devastating
injuries make room for a college student who needs help in speaking up in class? If insurance does
not cover enhancement, will neural enhancement only be accessible to those who can afford it?
Murray takes a philosophical view, referring to his suggestion that neural enhancement can boost
billable hours in a law firm. "Is that the kind of society that we want to create?" We may already be
that sort of society, but embracing neural enhancement as a bona fide part of medical practice will
legitimize it. REFERENCES 1. Kadison R. Getting an edge-use of stimulants and antidepressants in
Caldwell JA Jr, Caldwell JL, Smythe NK 3rd, Hall KK. A double-blind, placebo-controlled investigation of the
efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter
Cosmetic neurology: the controversy over enhancing movement, mentation, and mood. Neurology.
neuropsychological functioning. Neurobiol Aging. In press. Ricki Lewis, PhD, a geneticist, textbook
author, and freelance writer in Scotia, NY, is a contributing editor for Applied Neurology. --- Should We Manipulate Memory? Will drugs to treat dementia-related memory loss or the flashbacks of
post-traumatic stress disorder find uses among the healthy? Because our memories so strongly
define us, this is a difficult question. The handful of companies working on drugs that alter memory
are targeting conditions such as Alzheimer disease and schizophrenia. They are also looking into
sleep disorders and sleep deprivation. For example, Helicon Therapeutics in Farmingdale, NY, is
developing drugs based on cAMP response element binding protein (CREB), a regulator of long-term
memory. Discovery of CREB in turn led to the discovery of functionally related genes. As stated on
Helicon's Web site, "All of these genes are targets for production of drugs that enhance and diminish
memory." But enhancing or diminishing memories among the healthy might not be as enticing as it
seems. Consider the case of Solomon Shereshevskii, a Russian newspaper reporter born in 1905 with
the mixed blessing of a photographic memory. He was a synesthete, his mind assigning colors and
smells to everything he saw. Shereshevskii could instantly memorize a string of 50 alphabet letters,
for example, because each had a distinctive hue and odor. People, however, looked different to him
each time because his brain focused on the minutiae of appearance. As the years went by, his mind
became so crammed with useless information that he could not establish or maintain relationships,
and as social inhibition overwhelmed him, he actually seemed stupid. He was famously miserable
with his "gift." In the film Eternal Sunshine of the Spotless Mind, a couple's memories of each other are
erased when their relationship falters, and then in true Hollywood fashion, they find their way
back to each other. In real life, dampening painful memories may aid healing for some individuals
but not others. "It is very much a matter of personal context," said Thomas Murray, president of the
Hastings Institute in Garrison, NY, at the 2005 Society for Neuroscience annual meeting. To a riveted
crowd, Murray quietly related his thoughts on erasing the memories of a brutal murder that had
occurred 5 years earlier. "If a drug to decrease the impact of traumatic memories was given to a
rape victim and it helped her recover, I'd be all in favor. But if it was offered to me to erase the
memories of the aftermath of learning of my daughter's death, I would have refused it. To have
dampened those memories would have deprived me of the intensity of the ties that bind a parent to
a child. It is a horrible thing one simply has to work through. The same drug with the same impact is
in one case a good idea, in another, not. Blurring the memory of my daughter's entire life would

have been a mistake." -Ricki Lewis, PhD

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