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Juicing the Brain: Research to limit mental fatigue among soldiers may foster controversial ways to enhance any person's brain

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NOTE: At the time of publication, the author Jonathan D. Moreno was affiliated with the University of Virginia. Currently January 2008, he is a faculty member at the Center for Cognitive Neuroscience at the University of Pennsylvania.

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Abstract
The article discusses the drugs being used to enhance performance and to limit mental fatigue among soldiers and its repercussions. It is a known fact that amphetamines such as Dexedrine are commonly prescribed to keep pilots alert even though questions have been raised about safety. The air force is considering alternatives to amphetamines, in particular a medication that has also gained the attention of long-distance business travelers, modafinil and the ampakines.

Comments
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Juicing the Brain

Research to limit mental fatigue among soldiers may foster controversial ways to enhance any person's brain

By Jonathan D. Moreno

Physicians have long tinkered with ways to "improve" the human brain, but as our understanding of that organ's inner workings quickly grows, artificial enhancement is becoming more feasible. Military research is at the forefront of this work, much of it focused on drugs. The goal is to produce a better soldier, but the emerging techniques could just as easily be applied to any individual.

The military wants to juice up personnel's brains because the human being is the weakest instrument of warfare. Although for centuries astonishing and terrifying advances have been made in the technology of conflict, soldiers are basically the same. They must eat, sleep, discern friend from foe, heal when wounded, and so forth. The first state (or nonstate) actor to build superior fighters will make an enormous leap in the arms race. In the short run, researchers are trying to devise aids that would overcome a person's inherent limitations, such as mental fatigue. Long-term results could lead to individuals everywhere who are tireless, less fearful or even better speakers.

Sleepless in Battle

Reducing human error caused by mental fatigue is crucial because death by "friendly fire" is a shockingly frequent occurrence. These tragic mistakes can partly be attributed to the sleep deprivation that accompanies lengthy deployments. An investigation into a 2002 incident in which two American pilots accidentally killed four Canadian soldiers and injured eight others in Afghanistan provided an unexpected glimpse into the U.S. Air Force's interest in sleep. Unnoticed by many, the pilots' attorneys in the resulting court-martial cases pointed out that their clients had been taking Dexedrine, sometimes called the go pill, otherwise known as speed. It was alleged that amphetamines such as Dexedrine are commonly prescribed to keep pilots alert for 30-hour missions, even though questions have been raised about safety. Use of such drugs can also lead to dependency.

The air force is considering alternatives to amphetamines, in particular a medication that has also gained the attention of long-distance business travelers: modafinil. Marketed as Provigil, it was approved by the Food and Drug Administration in 1998 to treat narcolepsy and to help control sleep disorders associated with diseases such as Parkinson's, Alzheimer's and multiple sclerosis. Modafinil is not a traditional stimulant; rather than bombarding various parts of the brain with arousal signals, it apparently nudges the brain toward wakefulness through specific pathways, perhaps by increasing serotonin levels in the brain stem. The precise mechanism is still not well understood.

The temptation for healthy people to use such a drug is tremendous; some individuals report that a dose leaves them as refreshed as a short nap. Frequent fliers already get prescriptions for the stuff, and it is sure to be the next craze on college campuses among students who want to pull all-nighters or just be able to party hearty for days. Long-distance truck drivers are also obvious candidates for use and, perhaps, abuse.

Neurostimulation might improve cognition during confusing battles or offset sleep deprivation.

Workers who shift from day to night schedules and back again are also interested. They often complain of drowsiness during the work¿period and insomnia when they want to sleep. The Air Force Office of Scientific Research and Cephalon, Inc., in Frazer, Pa., sponsored a study by Harvard University and the University of Pennsylvania in which 16 healthy subjects were treated like shift workers: they were deprived of sleep for 28 hours, then obliged to sleep from 11 A.M. to 7 P.M. for four days and to stay awake those nights. The subjects on modafinil did far better on cognitive tests than those on a sugar pill. Double-blinded, placebo-controlled studies have shown that some subjects can stay awake for more than 90 hours.

A few news outlets have made unconfirmed claims that American soldiers were using modafinil on the way to Baghdad in 2003. That would not be surprising. Minimizing the need for sleep has been a holy grail for war planners since time immemorial. Guards at China's Great Wall chewed an herb containing ephedrine; Incan fighters munched on coca

leaves; 19th-century Bavarian officers gave their men cocaine; soldiers from several countries used amphetamines during World War II; and, of course, armies consume countless tons of caffeine and nicotine. French soldiers took modafinil in the first Gulf War, and the *Guardian*
newspaper reported in 2004 that the U.K.'s Ministry of Defense had purchased 24,000 tablets of the drug.

Preventing Mistakes
Despite the interest in modafinil, questions persist. Does it mask natural sleep needs but fall short in keeping people as functional as they think they are? This could be critical for pilots and soldiers, who should not overestimate their readiness. After prolonged use, the endocrine and immune systems may be compromised by lack of sleep, too.

Military scientists are examining the safety issues. One researcher at the air force's Brooks City-Base in San Antonio told *Pentagram*, an online newsletter, that "all indications say modafinil is a safer drug, but we don't know that for sure." But even if the compound proves safe in terms of sound judgment in combat, what about the effects down the road for people who have been on and off the drug for years? The long-term risks associated with sleep deprivation are not well understood either. Evidence indicates that during sleep, memory and learning are consolidated and that the brain refreshes its store of energy.

Studies have shown that people who sleep only four hours a day for an extended period have an increase in insulin resistance, a prediabetic symptom. But without a proven explanation for the purpose of sleep, it is hard to assess the downside of doing without, other than the obvious discomfort that nonsleepers experience--the attendant loss of concentration and the increased accident risks.

An intervention that minimizes the need for sleep yet maintains cognitive capacity would be a significant advantage for a military force. Infantrymen commonly subsist on three or four hours of sleep nightly for weeks. Special Forces personnel may be awake for several days during search and rescue operations. The Defense Advanced Projects Research Agency (DARPA) is spending $100 million in grants on "prevention of degradation of cognitive performance due to sleep deprivation." DARPA's Defense Sciences Office has stated that "if you can prevent bad decisions from being made during sleep deprivation, you can dominate the battlefield." It is also interested in how to reverse losses that might occur during sleep deprivation and whether researchers can "expand the available memory space, so that people can retain cognitive function under tremendous stress and sleep deprivation."

The military effort includes investigation of another class of drugs, the ampakines, which show some promise in treating dementia and symptoms of schizophrenia by improving cognition when used with antipsychotic medication. Clinical trials have not found therapeutic value, but results from a company-sponsored study at Wake Forest University using an ampakine drug in sleep-deprived rhesus monkeys were encouraging. The monkeys' performance was reduced 15 to 25 percent when sleep-deprived, and reaction times doubled. But a single dose of Ampakine CX717 eliminated their performance deficit and sleep deprivation changes. An unpublished human trial sponsored by the company that makes CX717 reported that 16 men deprived of a night's sleep did better on memory and attention tests after taking the drug. The scientist who conducted the study said, "We didn't see any adverse events."

How Far Can We Go?
Military work is only the beginning of intense efforts to control sleep-wake cycles. There is a multibillion-dollar demand from civilians who wish to sleep only when they want to sleep. The neuroscientific key lies in a part of the hypothalamus called the suprachiasmatic nucleus (SCN), the brain's biological clock. About the size of a pinhead and nestled deep within the brain, the SCN, composed of 20,000 neurons, acts as the pacemaker for circadian rhythms in mammals. If the SCN is cut or removed in animals, their sleep-wake cycle can be profoundly disturbed. And when people are deprived of light, the SCN runs on a 25-hour clock; for some reason that is our innate length of a single day, which helps to explain insomnia and other sleep disorders in those who are blind. Though subject to some variation, the clock can be reset by exposure to light signals transmitted from the retina, which is why we can function on a regular 24-hour cycle.

There are very few hard data showing that prolonged sleep deprivation has truly deleterious effects in humans, according to Harvard neurobiologist Jerome Groopman. Yet University of Pennsylvania researcher David Dinges has raised provocative questions about Boeing Company's plans for a jetliner that would fly around the earth and need to land only once in 20 hours: How should the crew sleep, if at all? What are the rules that apply to sustained work on flights like that? As Dinges says: "Now is the time to have an open and frank discussion on how far we will go as a culture. What are our priorities? How regularly do we want to manipulate our brain chemistry? What are the limits?"

Some insights may come from the animal world. Dolphins seem to keep parts of their brains awake to control their breathing and guide them to the surface for air while the rest of their brain is allowed to sleep. Otherwise they would drown. Positron-emission tomographic (PET) scans are beginning to reveal how their brain architecture accomplishes this feat. If the mechanism can somehow be simulated safely in human brains, it will be hard to keep the method out of the hands of civilians eager to get an edge in a competitive world.

Electricity and Magnetism

Another approach to enhancing cognitive abilities may be electrical stimulation of select brain centers. Physicians at the Rehabilitation Institute of Chicago found that when they implanted electrodes in the motor cortex of stroke victims, patients regained about 30 percent of lost function as compared with 10 percent for other patients. Although the approach is not perfect, the gains for those whose arms had for years hung limply at their sides were wonderful. Some stroke patients with speech difficulties experienced improvement, too. Unfortunately, the doctors do not know exactly why the added electricity works.

Eliminating fear genes could satisfy parents who don't want to give birth to a "sissy."

An intriguing question is whether electrical stimulation might help uninjured people exceed their normal intellectual capacities. One technique being explored is direct-current (DC) polarization. At a 2004 Society for Neuroscience meeting, researchers from the National Institutes of Health reported that a tiny amount of electricity delivered to the brain through an electrode on the scalp produced measurable improvement in verbal skills. They asked volunteers to name as many words as possible that began with a certain letter. The subjects showed about a 20 percent improvement when the current (two thousandths of an ampere, far less than that needed to run a digital watch) was on.

Because the current ran through the prefrontal cortex, the researchers speculated that the firing rate of neurons was increased, activating cells involved in word generation. The tiny charge seemed to have no deleterious effects, other than to leave certain individuals with an itchy scalp. Moreover, the fact that the technique does not involve surgery makes it more practical than implanted electrodes.

Another noninvasive technique is transcranial magnetic stimulation (TMS). A magnetic coil is placed above the head, and magnetic pulses pass through the cortex. Different kinds of pulses can alter the firing rate of different sets of neurons. Volunteers complain only about a sensation of tapping on the skull as scalp muscles contract and about a popping sound from the magnetic coil.

The therapeutic goal for DC polarization and TMS is to treat patients with stroke or dementia. TMS seems to target specific brain regions more effectively, but DC polarization appears to carry less risk of inducing seizures. Of course, the long-term effects of frequent exposure to electrical or magnetic stimulation are unknown. Nevertheless, DARPA has awarded research grants to explore whether neurostimulation can improve impaired cognitive performance in confusing battle circumstances or to offset sleep deprivation, perhaps through helmets that deliver the tiny impulses needed.

Like so many potentially brain-enhancing technologies, neurostimulation can easily be oversold. Given how much we value cognition, however, even a modest improvement would be considered important by many people. Long-term problems for military personnel might be hard to identify and could seem worth the risk for even a marginal gain in mental agility in life-or-death situations. As neuroscientist Mark E. Huang of the Rehabilitation Institute of Chicago told the press in 2004: "There are many possibilities that have to be answered ethically. If you want to learn a new language, potentially the stimulator might help. Would I recommend you do it for that purpose? No. But down the road, who knows? Obviously the sky's the limit, and we're still in the infancy stage."

No Fear

Possibilities for mind enhancement indeed abound. A distinguished team of U.S. researchers reported in 2005 that a gene called *stathmin*, which is expressed in the amygdala (the seat of emotion), is associated with both innate and learned fear. The researchers bred mice without the gene and put them in aversive situations, such as giving them a mild shock at a certain point in their cage. Normal mice exhibited traditional fear behavior by freezing in place, but the altered mice froze less often. And when both types of mice were put in an open field environment--an innately threatening situation--the mice without *stathmin*
spent more time in the center of the field and explored more than the control mice.

Do individuals who have lesser *stathmin*
expression exhibit less fear? It is unlikely that there is a one-to-one correspondence, because humans are far more psychologically complex than mice, capable of modifying their genetically programmed behavior. Yet it is not difficult to imagine that a military official who overestimates the significance of genetic information will someday propose screening Special Forces candidates, or even raw recruits, for the "fear gene." Indeed, a few years ago the Burlington Northern Santa Fe Railway Company had to pay $2.2 million to employees who had been secretly tested for a gene associated with carpal tunnel syndrome, even though the scientists who developed the testing technique said it could not work for that purpose. The company was trying to see if the workers' medical claims were attributable to their jobs or their genes.

If DNA testing for a fear gene is both scientifically and ethically dicey, what about setting out to create people who lack that characteristic? Would breeding humans without *stathmin* or other genes associated with fear reactions engender more courageous fighters? Would parents sign on for such meddling if they harbored ambitions for a child capable of a glorious military career or just didn't want to give birth to a "sissy"? One problem, however, is that fear or its functional equivalent is one of those ancient properties exhibited by just about every animal. It surely has tremendous survival value. Removing it would be deeply counterevolutionary and would almost certainly generate numerous unintended and undesirable consequences for the individual, let alone thrust humans headlong into a fierce debate about whether enhancing ourselves has gone too far.

Proponents of such artificial enhancements argue that the changes may not be artificial at all. Is there even a valid distinction, they ask, between artificial and "natural" enhancements such as exercise and discipline? Aren't we just trying to gain whatever advantages we can, as we have always tried to do, or are these techniques cheating nature? Can we manage the consequences, or are the risks for the individual and for humanity too great?

Is there even a distinction between artificial aids like drugs and "natural" ones like exercise?

These questions are part of an ongoing argument about whether we should use new discoveries in neuroscience and other fields such as genetics to improve ourselves, our descendants and perhaps even the species. If it becomes acceptable to enhance civilians, then it would be hard to explain why national security agencies should be barred from giving war fighters an edge. And if it is not acceptable to enhance civilians, a special case might still be made for tuning up military personnel.

National research on enhancement technologies will require the close involvement of advisory bodies with members both in government and outside it, with as much transparency as possible. Whereas some general principles should be articulated and become part of our regulatory framework, much of the hard work will have to be done on a case-by-case basis.

As Dinges notes, the debates are ones we haven't had. Libertarians would argue that government regulation would be overreaching, conservatives would worry about changing human nature, and liberals would worry about inequitable access to whatever advantages neuropharmacology might confer on those who are already relatively well off. All these views deserve to be aired, and the discussion needs to be moved onto our national policy agenda.

Further Reading

Left Brains vs. Right Brains
What "Psychopath" Means
Sex, Math and Scientific Achievement
Smoking Away Schizophrenia?

What causes hiccups?
Is Disease "Inheritance" More Random than Once Thought?
Homing in on the Silenced Gene Behind Mental Retardation
Newborns Can Bond to a "Mother" from a Different Species