Mental Performance

Neuronal circuits
- Memory
- Creativity

Molecular events
- Attention
- Intelligence

Neurotransmitters
Nootropic Drugs

Greek:
noos – mind
tropein - toward

Memory Enhancing Drugs

Smart Drugs
Enhancement time!

- Neurons and Glia
- Nexus, Novelty, and Nutrition
- Strong brain currency

Thomas S Otis & Michael V Sofroniew
SMARTENING UP
Brain Enhancement Is Wrong, Right?
By BENEDICT CAREY
Published: March 9, 2008

So far no one is demanding that asterisks be attached to Nobel, Pulitzer or Lasker awards. Government agencies have not hired anthropologist departments, ruffling bunch hogs, testing professors' urine. And if there are illiterate trainers on campuses, shady tutors with wrap-around sunglasses and dive to basement labs in Italy, no one has exposed them.

Yet an era of doping may be looming in academia, and it has ignited a debate about policy and ethic that in some ways rivals the national controversy over performance enhancement accusations against elite athletes like Barry Bonds and Roger Clemens.

In a recent commentary in the journal Nature, two Cornell University researchers reported that about a dozen of their colleagues had admitted to regular use of prescription drugs like Adderall, a stimulant, and Provigil which promotes wakefulness, to improve their academic performance. The former is approved to treat attention deficit disorder, the latter narcolepsy, and both are considered more effective, and more widely available, than the drugs circulating in college a generation ago.
The symbol H+ is the code sign used by some futurists to denote an enhanced version of humanity. The plus version of the human race would deploy a mix of advanced technologies, including stem cells, robotics, cognition-enhancing drugs, and the like, to overcome basic mental and physical limitations.

The notion of enhancing mental functions by gulping down a pill that improves attention, memory and planning—the very foundations of cognition—is no longer just a fantasy shared by futurists. The 1990s, proclaimed the decade of the brain by President George H. W. Bush, has been followed by what might be labeled “the decade of the better brain.”

Obsession with cognitive enhancers is evidenced in news articles hailing the arrival of what are variously called smart drugs, neuroenhancers, nootropics or even “Viagra for the brain.” From this perspective, an era of enhancement has already arrived. College students routinely borrow a few pills from a friend’s Ritalin prescription to pull an all-nighter. Software programmers on deadline or executives trying to
COMMENTARY

Towards responsible use of cognitive-enhancing drugs by the healthy

Society must respond to the growing demand for cognitive enhancement. That response must start by rejecting the idea that ‘enhancement’ is a dirty word, argue Henry Greely and colleagues.

Today, on university campuses around the world, students are striking deals to buy and sell prescription drugs such as Adderall and Ritalin — not to get high, but to get higher grades, to provide an edge over their fellow students or to increase in some measurable way their capacity for learning. These transactions are crimes in the United States, punishable by prison.

Many people see such penalties as appropriate, and consider the use of such drugs to be cheating, unnatural or dangerous. Yet one survey estimated that almost 7% of students in US universities have used prescription stimulants in this way, and that on some campuses, up to 25% of students had tried them in the past year. These students are early adopters of a trend that is likely to grow, and indications suggest that they’re not alone.

In this article, we propose actions that will help society accept the benefits of enhancement, given appropriate research and evolved regulation. Prescription drugs are regulated so that not for their enhancing properties but primarily for considerations of safety and potential abuse. Still, cognitive enhancement has many campus to divest in enhancement use.

A newer drug, modafinil (Provigil), has also shown enhancement potential. Modafinil is approved for the treatment of fatigue caused by narcolepsy, sleep apnea and shift-work sleep disorder. It is currently prescribed off-label for a wide range of neuropsychiatric and other medical conditions and is proven safe and effective, but if one is it will surely be sought by healthy middle-aged and elderly people contending with normal age-related memory decline. As well as by people of all ages preparing for academic or licenciate examinations.
<table>
<thead>
<tr>
<th>Memories</th>
<th>Type</th>
<th>Formation</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Explicit memory
Implicit memory
Stages of memory formation.
Association Cortex
Alzheimer's Disease

Cholinergic system. *Acetylcholine* is the neurotransmitter.
1. Introduction

The purpose of this review is to marshal the evidence supporting the hypothesis that cognition enhancers exert at least part of their effects on cognition through activation of the brain cholinergic system. This does not mean that the activation should result from direct action, but the possibility of an indirect effect through AMPA receptors [6,24] or even peripheral mechanisms [33] could be envisaged.

The cholinergic pathways projecting to the cerebral cortex and hippocampus play a key role in mechanisms of learning and memory. In the central nervous system of aged and demented subjects, amnesia, as well as a significant functional and morphological decline, of varying severity, of the forebrain cholinergic neurons have muscarinic receptor antagonists such as scopolamine [25]. On the other hand, lesions of the septohippocampal pathway [21] and of the nucleus basalis magnocellularis (nbM) reproduce, in laboratory animals, some of the impairments associated with brain aging [28], although the behavioral effects induced by septohippocampal or nbM lesions are not identical, supporting the idea that these two cholinergic pathways subserve different roles in memory processes [12].

Alzheimer's disease (AD) is a form of dementia characterized by the deposition of amyloid plaques and neurofibrillary tangles in the brain of subjects and by changes in many neurotransmitter systems [26], the most striking of which is the degeneration of forebrain cholinergic neurons, which is in direct correlation with the degree of dementia [5,26,45].
Voltage-gated Ca\(^{++}\) channel

Vesicles with neurotransmitter

Ca\(^{++}\) ions

postsynaptic spine

Na\(^{+}\) ions

presynaptic terminal

receptors
Acetylcholine
Acetylcholinesterase Inhibitor (AChEi)
Acetylcholinesterase Inhibitor (AChEI)
Acetylcholinesterase Inhibitor (AChEi)
Acetylcholinesterase Inhibitor (AChEI)
Better cognitive performance

AChEIs

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Nivalin, Razadyne, Reminyl)

Not too much data on healthy adults
Frontal Lobe

ADHD
Dopamine
Reuptake transporter
Methylphenidate (Ritalin and Concerta)
BRAIN GAIN

The underground world of “nootropics” has become the latest—and rediscovered—nerd chic.

Margaret Talbot

Every one has his defining drug. Neurostimulants are perfectly suited for our efficiency-obsessed, BlackBerry-driven office culture.

I won’t name names; I’ll call them Alex. Alex recently graduated from Harvard. As a chemistry major, Alex wrote a thesis on dopamine receptors and mice. He also wrote a paper on the neurochemical basis of musical ability. Alex has been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and is a regular user of Adderall, the drug that has been found to improve focus and concentration. While at Harvard, Alex was one of the top students in his class and was awarded the highest honors possible.

Adderall is a stimulant that is commonly prescribed for children and adults who have been diagnosed with ADHD. However, it has recently become a popular choice among college students who use it to improve their academic performance.

Adderall has been found to improve focus and concentration, and has been shown to increase alertness and reduce fatigue. It is often used by college students to help them stay on task and complete their assignments.

Adderall is a Schedule II controlled substance, which means it is highly addictive and can be dangerous if used improperly. Despite this, it is still widely used among college students, who often use it without a prescription.

The New Yorker

The Adderall Advantage

By Andrew Jacobs

It was finals week at Columbia University and Angela needed a miracle. Like many of her classmates, Angela, a biology-major, had already pulled a pair of all-nighters to get through a paper on “Finnegans Wake,” a French test and an exam for her music humanities class. All that remained was a Latin American literature final, but as midnight approached, her stamina was beginning to fade. “This week is killing me,” she said, taking a cigarette break in front of the school library. “At this point, I could use a little help.”

Don’t think I could keep a 3.9 average without this stuff,” she said afterward.

At many colleges across the country, the ingredients for academic success now include a steady flow of stimulants, the class of prescription amphetamines that is used to treat attention-deficit hyperactivity disorder.

Since Ritalin abuse first hit the radar screen several years ago, the reliance on prescription stimulants to enhance performance has grown, becoming almost as commonplace as Yerba Mate, Red Bull and maybe even caffeine. As many as 20 percent of college students have used Ritalin or Adderall to study, write papers and take exams, according to recent surveys focused on individual campuses. A study released this month by the National Center on Addiction and Substance Abuse at Columbia found that the number of teenagers who admit to abusing prescription medications tripled from 1992 to 2003, while in the general population such abuse had doubled.

Dr. Robert A. Weinberg, director of University Health Service at the University of Michigan, Ann Arbor, sees a growing number of students who falsely claim to be A.D.D. so they can get a prescription. At least once a week, a jittery, frightened, sleep-deprived student who has taken too many tablets for too many days shows up at his office. “Things have really gotten out of hand in the last four to five years,” he said. “Students have become convinced that this will help them achieve academic success.”

On campus, the drugs are either sold or given away by people with prescriptions, or they are procured by students who have learned to navigate the psychiatric exams offered by campus health centers, which usually provide the drugs at a discount. Unlike Ritalin, two newer members of the family of amphetamines—Adderall and Concerta—come in time-release forms and can keep a patient medicated an entire day.

The New York Times
Amphetamine (Adderall)
Amphetamines (Adderall)
Temporal Lobe
hippocampus
WATCH WHAT I CAN MAKE PAVLOV DO. AS SOON AS I DROOL, HE'LL SMILE AND WRITE IN HIS LITTLE BOOK.
Increased release of neurotransmitter

Presynaptic sprouting terminal button

Increased receptors

Changes in electrical resistance in the post-synaptic neuron
Molecules in Long Term Memory

Presynaptic neuron

Postsynaptic neuron

Neuron Nucleus
Synaptic vesicles

Presynaptic neuron

Glutamate neurotransmitter

Postsynaptic neuron
Presynaptic neuron

Postsynaptic neuron
Presynaptic neuron

Postsynaptic neuron

Influx of Na\(^+\) into the neuron
Presynaptic neuron

Postsynaptic neuron

Influx of Ca++ into the neuron
Presynaptic neuron

Signal cascade

Postsynaptic neuron

Cyclic AMP
Presynaptic neuron

Postsynaptic neuron

cAMP switches on CREB molecules

Activated CREB
**Presynaptic neuron**

**Postsynaptic neuron**

**CREB acts on DNA to trigger synapse protein synthesis**
AMP A receptor modulators as cognitive enhancers
Gary Lynch

AMP A (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptors mediate fast excitatory transmission throughout the central nervous system. Positive modulation of these receptors can potentially enhance cognition by, firstly, offsetting losses of glutamatergic synapses; secondly, promoting synaptic plasticity; and thirdly, increasing the production of trophic factors. The advent of small molecules that selectively enhance AMPA receptors in the brain made it possible to test these hypotheses. Preclinical experiments indicate that the compounds accelerate the encoding of memory and have positive effects on models of cognitive dysfunction. Initial results with human subjects are also positive. AMPA receptor modulators thus represent an entirely new approach to cognitive enhancement and the treatment of diverse brain disorders.

Addresses
University of California, Department of Psychiatry and Human Behavior, Irvine, CA 92616, USA
e-mail: glynch@ucl.edu

Categories of positive modulators
AMP A receptors are heteromeric complexes composed of four subunits, each of which has a binding pocket for the transmitter glutamate. Recent work with site-directed mutagenesis and x-ray crystallography has gone a long way towards explaining how the receptors gate synaptic current and desensitize in the continued presence of transmitter [3**]. Transmitter binding changes the linkage between the extracellular domains and the transmembrane pore of the receptor. This perturbation opens the channel and allows current to pass through the postsynaptic membrane. Termination of the current occurs when the transmitter is released from the binding
Memory Enhancers...

Presynaptic neuron

AMPA receptor

AMPAkines

Postsynaptic neuron

![Diagram of a synapse with AMPA receptors and memory enhancers.](image-url)
Ethical Issues

University campuses around the world, students are striking deals to buy and sell prescription drugs such as Adderall and Ritalin — not to get high, but to get higher grades, to *provide an edge* over their fellow students or to increase in some measurable way their capacity for learning.

Prescription drugs are *regulated* as such not for their enhancing properties but primarily for considerations of safety and potential abuse.
Many of the medications used to treat psychiatric and neurological conditions also improve the performance of the healthy.

It is too early to know whether any of these new drugs will be proven safe and effective, but if one is it will surely be sought by healthy middle aged and elderly people contending with normal and accelerated memory decline, as well as by people of all ages preparing for academic or licensure examinations.
A multitude of means of enhancing our brains through inventions such as written language, printing and the Internet.

We are all aware of the abilities to enhance our brains with adequate exercise, nutrition and sleep.

Should cognitive enhancers be viewed in the same general category as education, good health habits, and information technology?
The first **concern is safety**. Cognitive enhancements affect the most complex and important human organ, and the **risk of unintended side effects is therefore both high and consequential**.

The **second concern is freedom**, specifically freedom from coercion to **enhance**.

The **third concern is fairness**. Consider an examination that only a certain percentage can pass. It would seem **unfair** to allow some, but not all, students to **use cognitive enhancements**.