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***Untitled (Pharmacy),* by Joseph Cornell**

Seeking "Smart" Drugs

New treatments for Alzheimer's disease and other neural disorders are pointing to drugs that could boost memory in young, healthy individuals

by Marguerite Holloway, *staff writer*

The ancient bards didn't need them. Their well-toned memories bespoke tomes: the *Iliad* and the *Odyssey,* the *Ṛg Veda* and the Mahābhārata, among thousands of hours of other recited epics. But in our era, filled with more information in more forms than we could ever productively use, we seem to want them. Just as we want beauty sculpted not by our genetic heritage or by our exertion but rather by the scalpel or by silicone, we desire brains that are artificially boosted: we want drugs that make us think more quickly, that enable us to remember more readily, that give us a competitive edge.

The pursuit of these "smart" drugs has been celebrated since the early 1990s, when books and bars (many of them in California) offered recommendations for diets or formulas or herbs such as ginkgo biloba that could better one's brain. In the intervening years, a huge market for these items has sprung up, facilitated by the ease of sales over the Internet. In Japan alone, for instance, there are now 20 or so such compounds available and at least $2 billion in sales every year.

"Ninety-nine percent of that is hype," says James L. McGaugh, head of the Center for the Neurobiology of Learning and Memory at the University of California at Irvine. And, to him, worrisome hype. "We don't know how many of these drugs work and how they interact with other drugs, so there is the purely biological danger," McGaugh explains.

Nevertheless, the public obsession with smart drugs mirrors a scientific one. And what McGaugh and neuroscientists the world over are studying could one day lead to clinically tested drugs to enhance memory. The first wave of these are being designed to help older people who are losing their ability to remember or those suffering from dementia. The only two drugs approved by the U.S. Food and Drug Administration to boost memory, in fact, are Tacrine and Donepezil, both for Alzheimer's patients. Several new compounds for this disease are in the final stage of testing and may soon be on the market. Hundreds more are being investigated. And behind this first wave—but well off in the future—is the tsunami of promise that such compounds could work in anyone.

The cognitive enhancers under study work in many different ways because research on memory is as rich and varied as memories themselves. Scientists have looked at short-term (or "working") memory, long-term memory, emotional memory and olfactory memory; they have examined the molecular and genetic webs of memory, the role of hormones in memory, and the regions of the brain that light up in tomographic scans when a person remembers a sound as opposed to words. In each of these areas, neuroscientists garnered great insights over the past few decades, offering the possibility that some of the gears of memory could be oiled or recast.

In spite of the advances and the optimism engendered, though, many investigators note that memory is so complex and so intertwined with other mental activities that it is unlikely that one drug could be precise enough to just help you find your glasses or remember names at a cocktail party. "It really calls for a carefully balanced approach, recognizing that many of the mechanisms that may be critical for memory may also be critical for transmissions that are deleterious,"

observes Ira B. Black of Robert Wood Johnson Medical School.

Further, augmenting short-term memory, say, or increasing attention span does not necessarily translate into greater intelligence. "It doesn't make you smart," McGaugh cautions. "If you attend to the wrong things in life, that makes you dumb." Larry Cahill, a colleague of McGaugh's at Irvine, adds his own caveat, borrowed from philosopher and psychologist William James: "'Selection is the very keel on which our mental ship is built.' In other words, if we remembered everything we would 'be as ill off as if we remembered nothing.'"

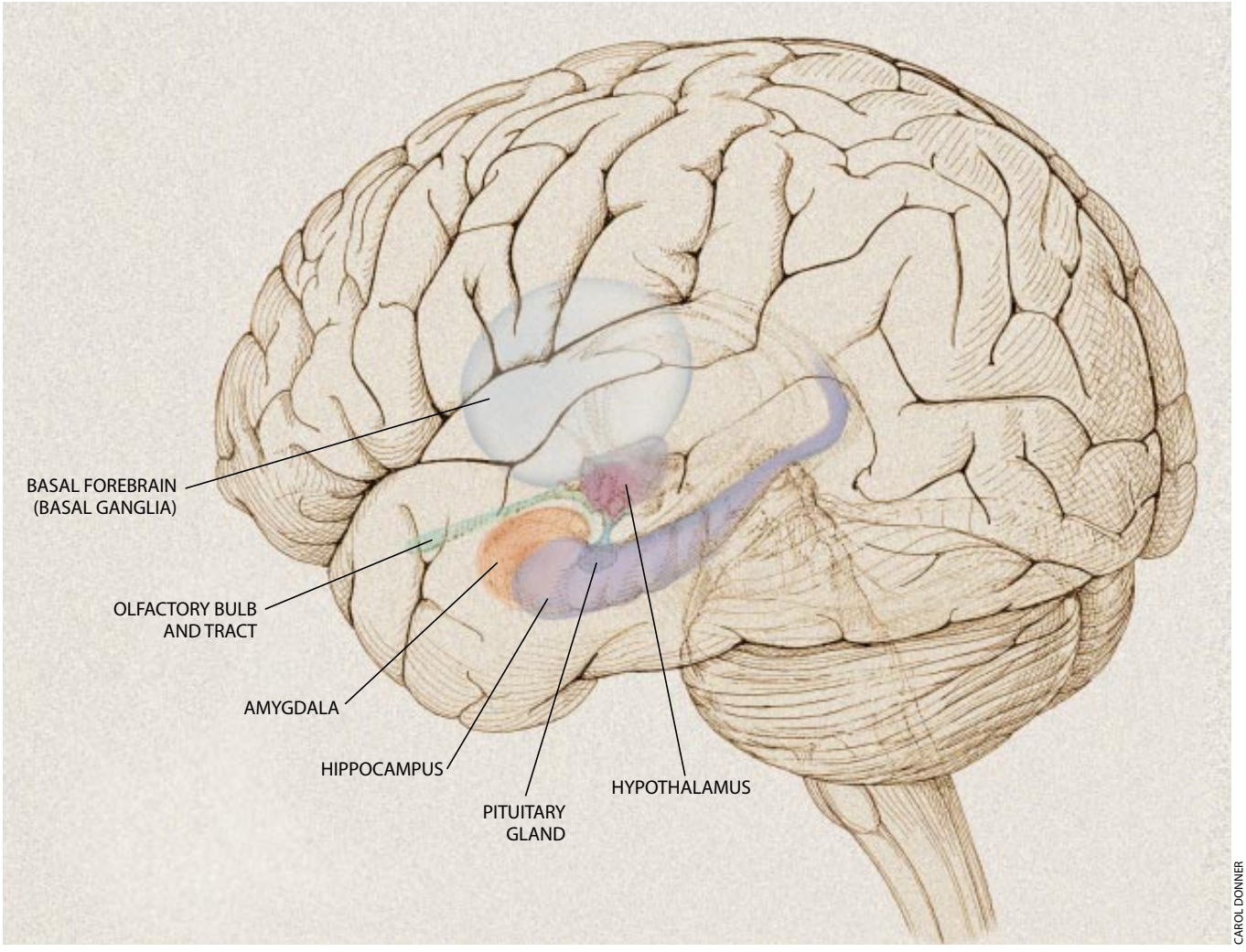
We could end up worshipping intelligence even more than we already do—but using it even less.

Transmitter Turn-ons

How we recall anything comes down to the basic currency of the nervous system: the giving and taking of neurotransmitters. These chemical messengers are released from a nerve cell into a tiny space called the synapse. On the far side of this gap sit other nerve cells studded with receptors shaped to receive specific neurotransmitters. Once these receptors have caught the molecules wafting across the synapse, they trigger chemical changes that allow information—in electrical form—to travel down the receiving neuron to its end, where, in turn, more neurotransmitters set sail across a synapse. Understanding which transactions control memory is a matter of figuring out which of the brain's 100 billion neurons—each making an average of 10,000 connections to other neurons—and which of the 50 or so neurotransmitters are involved.

Researchers have known since the 1950s that the hippocampus—part of the limbic system, which controls emotion and sits under the cerebral cortex on top of the brain stem—is crucial for memory. And since the 1980s they have known that the neurotransmitter glutamate, which binds to so-called NMDA receptors, underlies a form of learning in the hippocampus. Called long-term potentiation, it is thought to bring about memory by strengthening the path of communication

MEMORY FORMATION includes many areas of the brain, but central to this activity is the hippocampus. Nestled in the innermost part of the brain, the hippocampus, along with the amygdala and other structures, makes up the limbic system—the center of emotional response. The amygdala and hippocampus also sit next to the olfactory nerve, which explains why smells can conjure up strong emotions and memories. Stress hormones released by the hypothalamus, the pituitary gland and the adrenal glands, which sit atop the kidneys, orchestrate some forms of memory as well.



CAROL DONNER

between neurons—just as walking the same route through a forest again and again etches a permanent trail.

Several efforts to develop cognitive enhancers center on NMDA receptors—in particular, making them more active and, hence, more likely to establish long-term potentiation. Gary S. Lynch of U.C. Irvine, for instance, is investigating drugs—named ampakines—that interact with a particular kind of NMDA receptor called AMPA.

NMDA receptors may also respond to neurotropins, compounds crucial for the survival and differentiation of neurons. In a surprising finding a few years ago, Black and his co-workers discovered that brain-derived neurotrophic factor—the king of the nerve growth factors—increases synaptic strength between neurons in the hippocampus. "We sort of wandered into the area [of cognitive enhancers] through the back door," Black explains. It now appears the hippocampus is lousy with neurotropins and that—at least in petri dishes and in rats—brain-derived neurotrophic factor may act on NMDA receptors.

Jump-Starting Genes

For the moment, Black is just figuring out the fundamentals. Getting large compounds across the blood-brain barrier and into the brain is very hard. So Black and others are studying how to coax genes to turn on and produce growth factor in the right place. For example, James W. Simpkins, Edwin M. Meyer and their colleagues at the University of Florida at Gainesville are using a viral infection as the shuttle to carry a nerve growth factor gene into the brains of laboratory animals. They watch to see which neurons take up the gene and generate nerve growth factor, which ones take it up but do not do anything with it and which ones ignore it altogether. "We're asking fundamental questions," Simpkins says. "How can we get the gene to the central nervous system? How can we enhance the hit?"

Genes, of course, orchestrate every mnemonic—and every other—physiological activity, whether it is the creation of nerve growth factor or of more NMDA receptors. By documenting the molecular and genetic machinations of memory, researchers at several institutions are hoping to find other forms of memory boosters. Work on marine snails done by Eric R. Kandel's team at Columbia University and on fruit flies by Timothy Tully's group at Cold Spring Harbor Laboratory in New York State has pinpointed a gene, known as *CREB,* that appears to be central to some kinds of memory formation. With it, total recall. Without it, none. The hope is that years from now, cognitive enhancers could perhaps tickle silent *CREB*s into life and, consequently, improve memory.

CREB may prove to be just one way of manipulating the same process. Researchers at the University of Toronto reported recently in *Science* that long-term potentiation in the hippocampus can be forestalled by blocking the action of a particular enzyme dubbed Src. Src belongs to a class of enzymes

PHOTOGRAPHS BY C. DOMINIQUE TORAN-ALLERAND

RECEPTORS FOR ESTROGEN and nerve growth factor (dark spots in top image) *have been found in mice on the same neurons in the basal forebrain, a region damaged in Alzheimer's disease. This discovery suggests that estrogen may keep this—and perhaps other—parts of the brain healthy. Indeed, in the presence of small amounts of estrogen, nerve cells flourish* (middle); *higher amounts yield even healthier and more robust cells* (bottom). *Studies are now being conducted to see whether estrogen can prevent Alzheimer's disease or can improve memory function in women with the disease.*

The Proustian Connection: Popping a Madeleine

It is no surprise that smell triggers what are sometimes described as the most powerful memories: the olfactory nerve is just two synapses away from the amygdala, the center of human emotions, and just three from the hippocampus, headquarters of at least some forms of memory. Many researchers have been intrigued by this proximity, among them Rachel S. Herz of the Monell Chemical Senses Center in Philadelphia.

Herz recently examined whether smell could serve as a form of cognitive enhancer in emotional situations. She tested students who were about to take an exam and who were, as a consequence, exceedingly anxious. One set of nervous students was given a list of words to remember at the same time that they were exposed to a smell; the other group saw the same words, but their room remained odorless. A week later Herz found that those reexposed to the smell had 50 percent better recall than the control subjects did.

In another experiment, Herz tried to determine whether memory evoked by smell was more accurate than memory evoked by other cues, such as images. She found that odor did not increase accuracy but rather the emotional intensity of the recollection. So if your cognitive enhancer of choice proves to be perfume or whatever spice you have on the shelf, beware: your emotions may get the better of you. *—M.H.*

Those reexposed to the smell had 50 percent better recall.

PATTI MURRAY *Earth Scenes*

PEPPERMINT is among the scents used in experiments to evoke emotional memory.

that had been shown by Kandel and others to be important to long-term potentiation. Now it appears that Src regulates—no surprise—NMDA receptors.

Hormonal Clout

Still, not all roads lead to NMDA. Estrogen, one of the strongest and most promising cognitive enhancers currently being studied, seems to work in a different way. In the early 1990s C. Dominique Toran-Allerand of Columbia University noticed that many neurons in the basal forebrain—an area not far from the limbic system and one that is devastated by Alzheimer's disease—had receptors for both estrogen and nerve growth factor. She hypothesized that these acetylcholine-producing (or cholinergic, as they are called) neurons needed estrogen and nerve growth factor to stay healthy. Her next thought was to consider what a sudden shortage of estrogen would do to these neurons. (Previous work had shown that the neurotransmitter acetylcholine is pivotal to memory, although how it works remains mysterious. Research had also established that people with Alzheimer's have damaged cholinergic neurons and low levels of acetylcholine. The two drugs mentioned earlier—Tacrine and Donepezil—work by attacking the enzymes that break down acetylcholine.)

Toran-Allerand's findings fit nicely with those of a few other researchers as well as with anecdotal reports that more women than men develop Alzheimer's. The large clinical trials needed to examine rigorously the protective effects of estrogen have just begun: the Women's Health Initiative-Memory Study enrolled 6,000 women and will have data in 2005, and a study of 900 women whose relatives have Alzheimer's is under way at Johns Hopkins University, in conjunction with Columbia University and the Mayo Clinic. But in the past few years, several small studies have found that estrogen replacement therapy not only reduces the risk of developing Alzheimer's but also improves short-term memory in women with the disorder and in normally functioning postmenopausal women.

Men have a source of estrogen as well: testosterone is converted to its female counterpart in the brain. Unlike women, however, men do not experience a precipitous hormonal decline in their later years. Nevertheless, work by Simpkins and his colleagues shows that estrogen enhances short- and long-term memory in animals of both sexes and that it protects the brain from damage such as that caused by the loss of oxygen during stroke. So Simpkins and his team are developing nonfeminizing estrogens that could be used in men and that could reduce the estrogen-associated risk of cancer in women. "Our approach has been to discover estrogenlike compounds that are cognitive enhancers but, and we believe more important, are neuroprotective compounds," Simpkins explains.

A host of other hormones play a critical role in memory as well. Researchers studying stress responses, including McGaugh and Benno Roozendaal of U.C. Irvine, know that stress hormones such as corticosteroids can lead to powerful memory formation. Cahill is among the many neuroscientists looking at how such arousal lays down memory, which hormones do what and how to exploit this system. He is currently setting up clinical trials to test a beta blocker, Inderal, that could dull unpleasant memories in people who suffer post-traumatic stress disorder. (Cahill is quick to point out that Inderal was listed as a cognitive enhancer in *Smart Drugs and Nutrients,* the book that started the U.S. craze. "We have shown in humans that it is quite bad for memory," he laughs.)

STORYTELLING is an ancient tradition. The poets who recited the great Indian and Greek epics needed no "smart" drugs to keep their memories powerful. James L. McGaugh of the University of California at Irvine passes on this thought from a friend: "All one needs to strengthen memory is application—application of the seat of the pants to the seat of the chair."

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As cognitive enhancers, stress hormones pose a bit of a paradox. They can be good for memory, but they take their toll on the body. The same holds true of a few of the other legal and widespread smart drugs, such as caffeine, which enhances mental alertness but can cause gastrointestinal problems. It seems that caffeine works as a stimulant because it blocks one of the receptors for adenosine—a neurotransmitter that seems, among other actions, to dull concentration.

Taking Taboos

A cup of coffee with sugar in it would work even better. "Perhaps the smartest smart drug out there is glucose," Cahill comments—although excess can be unhealthy. The first clue that sugar is a smart drug came from stress studies. Among the hormones released during stress is epinephrine, which causes blood levels of glucose to shoot up. Paul E. Gold and others at the University of Virginia at Charlottesville found that rodents and people of all ages show memory improvement when given sugar. Gold also reports that glucose enhances some forms of cognition in people with Alzheimer's disease or Down syndrome. Again, all the studies so far have been small and are not yet conclusive.

According to Gold, it appears that glucose directly triggers the production of acetylcholine. Several other researchers have fingered the hormone insulin, rather than sugar, as the crucial memory enhancer. Regardless, it would appear that a hit of jelly beans could be salubrious.

And while you are at it, a nicotine patch could help. Various studies have found that nicotine improves people's short-term memory. Nicotine, like other pleasure-inducing drugs, is an analogue of a naturally occurring neurotransmitter: it resembles acetylcholine and binds to the acetylcholine nicotinic receptor. Because of the importance of cholinergic neurons in Alzheimer's disease, some researchers have focused on understanding the nicotinic receptors. Meyer is one of these scientists, and after eight years of study, he has synthesized a drug that—to his surprise—proved to be a potent cognitive enhancer in a small group of young, healthy men. "We didn't expect the drug to work in normal people, because you don't see Alzheimer's agents working in non-Alzheimer folks," Meyer says. More evidence, he adds, that "no one really knows how memory works."

Which is why the wait for the right brain boosters may be a long one. But they are on their way, and given society's desire for elixirs and quick fixes, it is worth thinking about what it would mean to rely even more on drugs, who would be able to afford them and what memory—and perhaps intelligence—would mean to us if we had dominion over it.

The idea of helping people who have impairments get some relief is exciting. The idea of raising a normal, healthy person's IQ a few points for certain tasks seems fair enough. But farther down this slippery slope lies the possibility of dramatically augmenting someone's intelligence—or, at least, that of someone who can afford it. That possibility seems less fair and much more likely to institutionalize fully the social and economic stratification that already exists.

Paradoxically, such smart drugs could even inculcate intellectual lassitude, much as the good feeling from a mood enhancer or antidepressant allows some people to avoid grappling with emotional problems. We could end up worshipping intelligence even more than we already do—but using it even less. "We should take care not to make the intellect our god," Albert Einstein wrote in *Out of My Later Life*. "It has, of course, powerful muscles, but no personality." SA