

## Shaping the Smart Brain with Drugs

*Man is not going to wait passively for millions of years before evolution offers him a better brain.*

—Corneliu E. Giurgea, 1970

Training is one aspect of brain enhancement, and it seems intrinsically acceptable—work hard and your efforts will be rewarded. With enhancers that can facilitate sensory-motor efficiency or speed, the ethical issues are of a different kind from those involving change in a mental state, such as intelligence and memory. Dealing with the idea of enhancing actual intelligence and memory is trickier because it takes training out of the equation. It’s one thing to suggest that studying hard is a way to increase intelligence. But can we get away with improving by simply taking a pill? This is not science fiction. Many “smart drugs” are in clinical trials and could be on the market in less than five years. Some drugs currently available to patients with memory disorders may increase intelligence in the healthy population.

Few would lament the use of such aids to ameliorate the normal aging process. As we age, word-finding problems are commonplace and inevitable, and forgetfulness worsens. Drugs that counter these deficits will be widely adopted and used gratefully by millions of people.

Just as Ritalin can improve the academic performance of hyperactive children, it can do the same for normal children. It is commonly thought to boost SAT scores by more than a hundred points, for both the hyperactive and the normal user. Many healthy young people now use it that way, and quite frankly, there is no stopping it. Drugs designed for therapy can also be used to enhance some other, normal mental function. In a way, we are living through various versions of the story of illegal drugs. Morphine is a terrific drug to help with pain produced by burns and other somatic ills; it is also a mind-altering drug that in some areas of society causes tremendous social and psychological problems. Does one stop researching the development of such pain-relieving drugs, just because they might be misused? Should we outlaw the evening martini or glass of wine, just because some will choose to abuse these mood enhancers?

No medical drug on the market is without side effects—which is to say costs—despite the good medicines do. Biology isn't advanced enough to allow replacement chemicals to treat only the problem under consideration. Each substance always has a downside. Everyone knows this; yet somehow when the drug in question manipulates a mental state, we see great moral concern and posturing about what it may mean for the human condition. Even when the issue is simply memory enhancement, we hear of great social concern, and the outcry is worse over the possible manipulation of intelligence. Why do we resist changes in our cognitive skills through drugs?

It seems to me that it is because we think cognitive enhance-

ment is cheating. If, somehow, someone gets better though hard work, that's okay. It's okay to review vocabulary cards, rehearse lines in a play, or repeat lists of facts for a history class. But popping a pill and mastering the information after having read it only once seems like cheating. When you think about it, this makes no sense.

Among the normal population are people with incredible memories, fast learners of language and music, and those with enhanced capabilities of all kinds. Something in their brains allows them to encode new information at lightning speed. We all know people like that, and none of us are offended by their ability. We accept the fact that they must have some chemical system that is superior to ours, or some neural circuitry that is more efficient. So why should we be upset if the same thing can be achieved by a pill? In some way we were cheated by Mother Nature if we didn't get the superior memory system, so for us to cheat her back through our own inventiveness seems like a smart thing to do. In my opinion, it is exactly what we *should* do.

Memory may be viewed as less threatening to our sense of self than our intelligence. But what is intelligence? Can it be changed with a pill? Any child or teacher can tell you that some people are smarter than others, but what is the difference between the brain of a Caltech student and the brain of your average Joe? If we can figure that out, is it ethical to turn average Joes into geniuses? One could argue that evolutionary theory suggests that if we are smart enough to invent the technology to increase our brain capacity, we should be able to use it. It is the next step in the survival of the fittest. We all attempt to find a mate who is the smartest, richest, most attractive, and most engaging we can find—this is sexual selection at work. Yet no matter whom we end up with, we turn in the millions to products and services provided by the culture to enhance ourselves and

our children. While some people's avidness or narcissism in pursuing these activities can be annoying and offensive, the freedom to engage in them should ultimately be in the hands of the individual, not society.

That said, gnawing concerns persist when it comes to artificially enhancing intelligence. And as with most neuromedical and biomedical issues, the sci-fi fears are greater than the achievable realities. Geneticists and neuroscientists have made great strides in recent years in understanding the brain differences that underlie individual variance in intelligence. With our increased understanding of what constitutes a "smart brain," we also gain knowledge of which genes, brain structures, and neurochemicals might be altered so as to artificially increase intelligence. The fear this brings to mind is that a nation of achievers will discard methods of perseverance and turn to prescriptions to get ahead.

But think about it: in many ways this experiment has been done. Take your average smart person, the person who excels, say, at Glendale High School (full disclosure: my alma mater). He enjoys the presence of other smart pals, but they are all in a setting that is also full of average and below-average minds. Our Joe finds himself accepted to an elite school like Dartmouth (also my alma mater). Suddenly, he is surrounded by smart students. It is as if all of Joe's peers at Glendale High had swallowed a "smart pill" and are now ready for quantum mechanics. Does the world become bizarre for our once-rare smart guy? Does he fret and feel inadequate in the face of all the competition? No. The answer, again, is rooted in how easily we adapt to our ever-changing contexts. It is also rooted in the fact that sped-up problem-solving skill does not an end-all person make. Speedy thought does not necessarily mean wise thought.

### Memory Enhancers

Already available, or making their way through the FDA approval process, are several cognitive enhancers, or “smart drugs” (also called nootropes,<sup>1</sup> from the Greek *noos*, for “mind,” and *tropain*, for “toward”), that reportedly improve memory. Whenever a study shows that a certain chemical produces even a moderate increase in memory in an animal population (whether fruit flies, mice, or humans), one of two things happens. If the drug or chemical is not on the market, a drug company quickly pops up to create a new nootrope to exploit the finding. If the drug is already on the market but is used to treat a known disease—for instance, Alzheimer’s or attention deficit hyperactivity disorder—a huge surge takes place in “off label” use (that is, for a purpose other than its intended use).

Dr. Eric Kandel at Columbia University won a Nobel Prize for his research on learning and memory in the sea slug *Aplysia*. He found that learning occurs at the synapse (the junction between two neurons) by several means—when the synapse is made more efficient, the number of neurotransmitter receptors is increased, the synapse surface area is increased, or more synapses are created. He found that these changes occur when a protein called CREB is activated. Later, CREB was shown to play a role in memory formation in *Drosophila* (fruit flies) and in mice. With these discoveries came the birth, in 1998, of Kandel’s New Jersey-based company, Memory Pharmaceuticals, which hopes to create a drug (one of the most promising of which is MEM 1414) that will increase the amount of CREB in the human neuron and thus facilitate the formation of long-term memories.<sup>2</sup> At least one other company (Helicon Therapeutics) hopes that CREB will also be found to increase memory formation in humans.<sup>3</sup> If clinical trials go well, MEM 1414 could be on the market sometime after 2008.<sup>4</sup>

Other drugs are also in the works, based on other brain mechanisms. Before a neuron naturally increases CREB, certain channels on the membrane of the neuron must open to allow positive ions to flow into the cell (which then activates a cascade of events, leading eventually to the activation of CREB). One of the channels present in synapses is known as the NMDA channel. In 1999, Dr. Yu Ping Tang and her colleagues at Princeton University discovered that increasing the number of NMDA receptors in the mouse hippocampus led to better performance on a spatial-memory task.<sup>5</sup> Now researchers and drug companies are pursuing NMDA receptor agonists (they combine with the receptors) as nootropes. A gene on chromosome 6 that has been implicated in increasing intelligence codes for a growth factor. So research into growth factors as nootropes has begun. At least a dozen more new drugs of this kind are making their way toward clinical trials.

Scientists have known for many years that more commonplace drugs like adrenaline, glucose, and caffeine increase memory and performance, and we all know it too: procrastinators find clarity of mind in the adrenaline rush to meet a deadline; we know not to try to work “on an empty stomach;” and we’re willing to pay a premium for a venti latte—all testimony to our appreciation of these “legal drugs.”

Self-medicating with Starbucks is one thing. But consider the following. In July 2002, Jerome Yesavage and his colleagues at Stanford University discovered that administering donepezil, a drug approved by the FDA to slow the memory loss of Alzheimer’s patients, improves the memory of the normal population.<sup>6</sup> Researchers trained pilots in a flight simulator to perform specific maneuvers and to respond to specific emergencies that developed during their mock flight. They gave half the pilots donepezil and half a placebo. One month later they retest-

ed the pilots and found that those who had taken the donepezil remembered their training better, as evidenced by their improved performance on the maneuvers they had learned—specifically their approach for landing—and on their response to stressful emergency situations. The possibility exists that donepezil could become a Ritalin for college students. I believe nothing can stop this.

Off-label use of Ritalin reminds us that the unintended use and misuse of drugs is a constant. Trying to manage it, control it, and legislate it will bring nothing but failure and duplicity—a fact of life that needs to be aired and that our culture should develop an attitude about. Aricept (the commercial name for donepezil) works, caffeine works, Ritalin works. Individuals will use such drugs or not use them, depending on their personal philosophy about enhancement. Some people like to alter their mental states; others do not. Some people are reluctant to “cheat” with plastic surgery or balding remedies, and some are reluctant to cheat using steroids.

My guess is that normal-functioning adults will choose not to use memory enhancers or the theoretically more obscure IQ or cognitive enhancers. Why? Because when memory is in the normal range, we adapt to our level of memory and set our personal psychological life in that context. To increase our memory capacity might well send a ripple effect across the landscape of our daily lives. After all, we spend a good part of each evening trying to forget many of the day’s memories. Over a lifetime we have built up our personal narrative based on the efficiency of our memory and our capacity to forget. Any significant or even slight change in these capacities will have to be integrated into the backbone of that narrative, producing a subtle change in the mental life of a person.

For a society that spends more time and money trying to be

liberated from past experiences and memories, the arrival of new memory enhancers has a certain irony. Why do people drink, smoke pot, and engage in other activities that cause them to leave their senses? Why are psychiatry offices full of people with unhappy memories they would like to be rid of? Why do victims of horrendous emotional events such as accidental trauma, abuse, and stressful relationships suffer from their vivid memories? All of these are actual facts of life.

Having a pill that enhances memory may lead to a whole new set of disorders. Maybe the haunting memories of a bad experience will be joined by the haunting derivations of Kepler's laws—the difficult material learned that becomes ever present in consciousness after taking an enhancing pill. Maybe we will discover that what is haunting in a memory is not the content, but the desire for other thoughts. These and dozens of other problems may well be the outcome of having revved up normal memories.

It is therefore unlikely that many people will seek memory-enhancing drugs that do anything more than help us remember names and dates—meaning drugs that slow normal memory loss. The real concern is drug development. Currently available memory drugs are mild and marginal in their effects. Future drugs are expected to be much more powerful; not only will they better fight the disease they are meant to address, but their off-label use will be more dramatic.

Of course, many steps precede success in drug development, and some doubt we will see these newer memory enhancers in our lifetime. While studies on animal models find that certain drugs improve memory or performance on specific tasks, it is not entirely clear that they would improve memory in humans. Many nootropes that were promising in animal models have failed miserably when brought to clinical trial.<sup>7</sup> Is this because

millions of years of evolution have led to a current human brain whose neurochemical concentrations are at optimal levels? Another hurdle for these drugs is that while they may aid in memory enhancement, they could cause deleterious effects. Some accounts of mice with altered, “smart” brains, for instance, show that the mice are not only more receptive to learning but also more sensitive to pain.

### Pursuing Intelligence

Putting aside for the moment that memory skills go hand in hand with measures of intelligence, making people smarter—able to resolve complex issues and ideas with greater ease and facility—somehow seems more problematic. Can we really populate the world with only doctors, lawyers, CEOs, and philosophers? Do we want or need a nation full of Harvard undergraduates? On the surface it seems like a horrible thought and utterly insane. But the basic science suggests that this is not far-fetched.

Defining what it means to be *smart* is a task that has frustrated psychologists for years. Our current measures of intelligence are only as good as the tests we create. IQ and SAT tests, while good indicators of academic success, are far from perfect indicators of success in the “real world.” Generally these tests of intelligence (especially the IQ test) measure people’s analytical skills, verbal comprehension, perceptual organization, working memory, and processing speed. This type of intelligence is called psychometric intelligence, and while it is not the only type of intelligence (some people believe in “multiple intelligences,” which even include athletic ability),<sup>8</sup> it is *testable* and so remains one of the primary ways we gauge intelligence.

In 1904, Dr. Charles Spearman, an English psychologist, reviewed the literature of the nineteenth century on intelligence

and found that people who performed well on one test of intelligence seemed to perform well on all tests of intelligence. They consistently received high scores on tests that evaluated any of a multitude of intelligences, including verbal comprehension, perceptual organization, working memory, and processing speed. Spearman theorized the existence of a “general intelligence,” which he termed *g*, that is used to process intelligence in many domains (verbal, perceptual, memory-based, and so forth) and thus makes some people good at nearly all tests of intelligence.<sup>9</sup> Many tests since 1904 have confirmed and supported Spearman’s idea of a general intelligence, and the current consensus among scientists and psychologists is that a *g* factor accounts for a very large amount—about 50 percent, though some reports have said as much as 70 percent—of the variance in scores on intelligence tests.<sup>10</sup>

Recently geneticists have discovered that even such abstract qualities as personality and intelligence are coded for in our genetic blueprint. Studies of the genetic basis of *g* are just beginning, and because *g* is most likely built from the influences of many genes, the hunt for those genes will be a long one. However, a recent study has already found that a gene on chromosome 6 is linked to intelligence.<sup>11</sup>

“Genetic brain mapping” has been developed to search for genes involved in intelligence. This type of study looks at the structural features (size, volume, and so on) of the brains of many individuals, including twins, familial relations, and non-related individuals. By scanning all these brains in an MRI machine and then looking at the differences between them, researchers have been able to determine which areas of the brain are most under the control of genes (for example, which are most similar between a pair of twins or between a mother and daughter). These studies have emerged only in the last three to

four years. Geneticists hope that once they know which brain areas are most heritable, they will be able to figure out which genes are responsible for those brain areas. With this sort of reverse mapping, geneticists should be able to learn more about the genetics of intelligence.

These recent brain-mapping studies reveal that 94 percent of the volume of the brain is heritable.<sup>12</sup> Certain areas in the brain—including the frontal, sensorimotor, and anterior temporal regions—are under genetic control, with the middle frontal region showing a highly determined genetic structure heritability of 90 to 95 percent. Studies also show that the patterns of the raised convolutions called gyri that give the brain a sort of “fingerprint” are not much influenced by genes. Similarly, the hippocampus (the brain structure that is involved in converting short-term memories into long-term ones) is more affected by environment than by genes.<sup>15</sup>

It seems geneticists and neuroscientists are in agreement: the areas of the brain that are apparently most under the influence of genes are the same regions neuroscientists are finding to be involved in intelligence and cognitive ability. Indeed, the genes that affect intelligence may be coding for the structure and functions of specific brain areas that underlie Spearman’s *g*. When researchers combine genetic brain-mapping studies with IQ tests, they can begin to tease out the correlations between the size, structure, and volume of brains, and intelligence. Neuroscientists have determined that overall brain size has a statistically significant correlation with IQ. More detailed investigations show that the amount of gray matter (consisting mainly of the cell bodies of neurons) in the frontal lobes varies significantly with differences in intelligence scores.<sup>14</sup> That suggests the frontal lobe may be the location of Spearman’s *g*.

When John Duncan and his colleagues at Cambridge Univer-

sity searched for one area of the brain that is activated when smart people perform a multitude of tasks that put demands on their intelligence and would thus be responsible for *g*, they found that the lateral part of the frontal lobe (on both the left and right sides) may be the resting place of general intelligence.<sup>15</sup> While undergoing positron-emission tomography (PET) scans, Duncan's subjects selectively activated the lateral frontal cortex during several intelligence tests. Some researchers are skeptical of the importance of Duncan's study, saying it is "suggestive" at best, because we do not yet fully understand what the frontal lobes do.<sup>16</sup> But his findings undoubtedly solidify the fact that we have entered a new era in scientific history—an era that allows neuroscientists to investigate individual differences in intelligence, an investigation previously left to the field of psychology.

Accordingly, a robust literature has recently arisen, reporting neural investigations into individual differences in intelligence—among these, studies of Albert Einstein's brain. One study of the cerebrum of this great scientist, generally considered to be one of the smartest men of all time, showed that an area of the frontal region of his brain<sup>17</sup> (on the left side only) had more neurons than glial cells (which provide structural support, among other functions) than was true in a control population.<sup>18</sup> Could it have been these extra neurons that helped him come up with the theory of relativity?

Further support for the role of the frontal lobe in intelligence comes from the observation that people with frontal lobe damage usually score twenty to sixty fewer points on IQ tests than the normal population; these people also have deficits in what is called fluid intelligence. *Fluid intelligence* refers to the type of intelligence that decreases with age and includes abstract reasoning, accurate responses during time constraint, use of novel materials, and processing speed. Similarly, people

with Down's syndrome who have severely decreased IQs are known to have less gray matter in the frontal lobe.<sup>19</sup>

### Perspectives

The future is here. We have isolated one gene involved in intelligence, and others will follow. We know which parts of the brain are influenced by particular genes and which parts correlate with high IQ. We also know some of the neurochemicals involved in learning and memory. With such knowledge, we will gain the understanding of what needs to be manipulated to increase intelligence in people who were not blessed with perfect genomes (or further increase the intelligence of those who already have "smart brains"). Gene therapy could insert, delete, turn on, or turn off genes that we find to be associated with intelligence. Neurochemicals could be increased or decreased pharmacologically—indeed, some already are. Smart drugs are currently on the market, including herbal medicines not regulated by the FDA as well as some regulated medicines. Entire stores (called smart bars) have popped up along the West Coast to sell these items.<sup>20</sup>

My own belief is that none of this is threatening to our sense of self. The opportunities to enhance one's mental state abound. Backstopping many of the ethical concerns about unleashing millions of really smart people on the world is the fact that millions of really smart people are already here. As the old statistician's joke goes, "Half of the people of the world are above average in intelligence." Increasing the pool size of smart people won't change or challenge our values.

While there is little question that being smart correlates with better living, it is also the case that being smart is only part of the story. *Smart* describes how well one processes information and figures out tasks. Once something has been figured

out, much work must then be applied to the solution, and the smartest people in the world rarely say that the work applied to solutions is easy. They worked hard to achieve insight *and* solutions. So we may all get faster at figuring out new problems, but it is not clear what it would mean to get smarter. *Smarter* is frequently just another word for *faster*.

Whatever develops, we can count on one universal: cognitive enhancement drugs will be developed, and they will be used and misused. But just as people don't drink all the liquor in their liquor cabinet, just as most people don't alter their mood with Prozac, and just as we all reorient our lives in the face of unending opportunities to change our sense of normal, our society will absorb new memory drugs according to each individual's underlying philosophy and sense of self. Self-regulation of substances will occur; those few who desire altered states will find the drug, and those who don't want to alter their sense of who they are will ignore the availability of the drug. The government should stay out of it, letting our own ethical and moral sense guide us through the new enhancement landscape.