

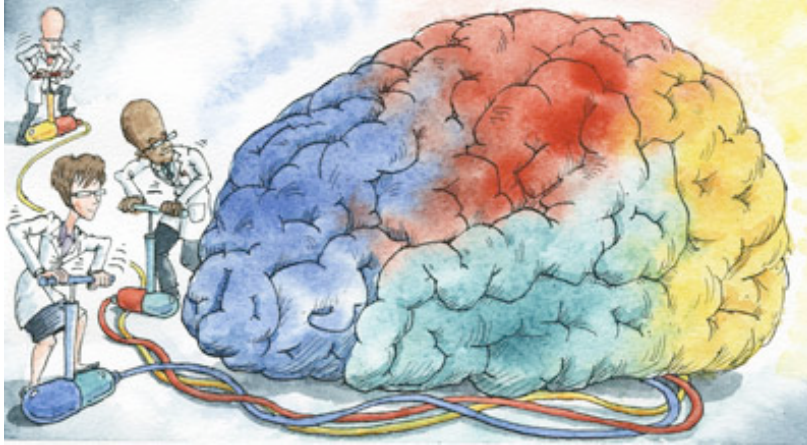
Cognitive enhancement

All on the mind

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Illustration by David Simonds

**Prepare for drugs that will improve memory, concentration and learning**

FOR thousands of years, people have sought substances that they hoped would boost their mental powers and their stamina. Leaves, roots and fruit have been chewed, brewed and smoked in a quest to expand the mind. That search continues today, with the difference only that the shamans work in pharmaceutical laboratories rather than forests. If asked why, the shamans reply that they are looking for drugs to treat the effects of Alzheimer's disease, attention-deficit disorder, strokes, and the dementias associated with Parkinson's disease and schizophrenia—and that is the truth. But by creating compounds that benefit the sick, they are offering a mental boost to the healthy, too.

Such drugs are known as cognition enhancers. They work on the neural processes that underlie such mental activities as attention, perception, learning, memory, language, planning and decision-making, usually by altering the balance of the chemical neurotransmitters involved in these processes. This week a report* from the Academy of Medical Sciences, a British learned society, says that a large number of such brain-affecting drugs are likely to emerge over the next few decades. Sir Gabriel Horn, a researcher at Cambridge University who chaired the group that produced the report, reckons that scientists are working on more than 600 drugs for neurological disorders.

History suggests that most of these will fall by the regulatory wayside, but given their numbers, a fair few are likely to be approved. And although none of the companies working on cognition-enhancing drugs designed to treat illness intends to license them for wider use, that is what is likely to happen—at least going by the growing “off-label” use of existing drugs such as Ritalin (methylphenidate) and Provigil (modafinil) by people who want to pep themselves up.

Provigil and Ritalin really do enhance cognition in healthy people. Provigil, for example, adds the ability to remember an extra digit or so to an individual's working memory (most people can hold seven random digits in their memory, but have difficulty with eight). It also improves people's performance in tests of their ability to plan. Because of such positive effects on normal people, says the report, there is growing use of these drugs to stave off fatigue, help shift-workers, boost exam performance and aid recovery from the effects of long-distance flights.

Earlier this year, *Nature*, one of the world's leading scientific journals, carried out an informal survey of its (mostly scientific) readers. One in five of the 1,400 people who responded said they had taken Ritalin, Provigil or beta blockers (drugs that can have an anti-anxiety effect) for non-medical reasons. They used them to stimulate focus, concentration or memory. Of that one in five, 62% had taken Ritalin and 44% Provigil. Most users had somehow obtained their drugs on prescription or else bought them over the internet.

Given results like this, and the number of drugs of this kind that look likely to emerge, many people, including the authors of the report, believe that the use of cognition-enhancing drugs is going to grow a lot.

There are a number of approaches to cognition enhancement. One of them, according to Trevor Robbins, a colleague of Sir Gabriel's at Cambridge and another member of the working group, is to activate the brain's "off" and "on" switches. Crudely put, the brain's neural networks can be thought of as electrical circuits. Neurotransmitters throw the switches.

Thanks for the memory

One such neurotransmitter is glutamate. This throws switches to the "on" position in memory-forming circuits. Members of a newly discovered class of compounds, ampakines, boost the activity of glutamate and thus make it easier to form memories.

Cortex Pharmaceuticals, based in Irvine, California, is one firm that is developing ampakine drugs. One of its compounds, code-named CX717 to disguise its exact identity, is undergoing testing for Alzheimer's disease in elderly patients. Early trials have already shown that the drug can make people more alert. Unlike caffeine, amphetamines and other stimulants, CX717 causes no increase in blood pressure or heart rate. Nor does it offer any "high", so is unlikely to be addictive.

Paradoxically, another glutamate-booster, D-cycloserine, is being tested not to enhance memory, but to abolish it. The paradox is resolved because unlearning (or "extinction", in neurological parlance) is a process similar in its details to learning.

By binding to certain glutamate receptors, D-cycloserine selectively enhances extinction, suppressing the effects of conditioned associations such as anxiety, addiction and phobias. According to Dr Robbins, experiments have shown that if a rat is given a cue that it previously associated with fear at the same time as it receives D-cycloserine, the bad memory can be eliminated. Not only may this help remove unpleasant memories, such as those involved in post-traumatic stress disorder, but it may also help to return the brains of addicts to their pre-addicted states. It may, for example, be able to remove the triggers that cause smoking.

Another approach to cognitive enhancement, says Dr Robbins, is through a neurotransmitter called acetylcholine. Cholinergic neurons—the name for those that respond to this molecule—are involved in concentration, focus and high-order thought processes, as well as memory. It is the cholinergic system that degenerates in Alzheimer's disease.

Interest has thus focused on drugs that inhibit the breakdown of acetylcholine, and also on nicotine, which works by mimicking its effect. Dr Robbins says that cholinergic drugs may offer minor cognitive benefits for things like alertness, and similar drugs could be "potentially useful in normal humans".

Mind-expansion may soon, therefore, become big business. Even though the drugs have been developed to treat disease, it will be hard to prevent their use by the healthy. Nor, if they are without bad side-effects, is there much reason to. And if that is so, there may be a very positive side-effect on the profits of their makers.

* "Brain science, addiction and drugs". The Academy of Medical Sciences, 10 Carlton House Terrace, London SW1Y 5AH

