Scientists on Drugs

Photo: Fotolia/ Robert Kneschke

Can drugs make us better researchers? Debates about improving human performance have moved from the physical boosts of sports, bodybuilding and Viagra to questions of cognition. Can we really think better if we take the right pill? In 2008, the question took an unexpected turn when *Nature* asked scientists directly about their drug-taking habits. "One in five scientists takes drugs" was the subsequent headline. Jeremy Garwood looks at who has been enhancing what.

The story starts in 2007 with the publication of a study document by the British Medical Association (BMA), "Boosting your brainpower: ethical aspects of cognitive enhancements." Prior to this, the issue of deliberately taking drugs to enhance performance had been dominated by the highly publicised cat-and-mouse efforts of sports authorities to catch competitive athletes seeking a pharmacologically-inspired edge. The idea that healthy individuals might also be taking drugs to improve their conscious mental faculties had belonged to the murky realm of military research, particularly in the US.

In the pursuit of happiness

Meanwhile, it seems the medical profession itself has benefited from its privileged access to pharmaceutical drugs to do a bit of self-administration. Drugs marketed for treatment of mental diseases, psychological 'problems', insomnia and depression can also affect the mental outlook and behaviour of 'healthy' individuals, especially overworked medical students and junior doctors.

In November 2007, Philip Campbell, *Nature*'s Editor-in-Chief wrote an editorial, 'Enhancing, not cheating', in which he compared the positive stance of the BMA's study to the US bioethics' report, 'Beyond Therapy'. Despite the subtitle, 'Biotechnology and the Pursuit of Happiness', this 2003 US report considered drug-based enhancement as "cheating against oneself", since personal achievements "impersonally achieved are not truly the achievements of persons". But, Campbell wondered, what "if a researcher could improve his or her ability to memorize the postulated connections in a complex signalling pathway central to tumour development?" Surely then, "far from cheating on themselves or others, they would be delivering a higher return on their investment of effort, and indeed on society's investment in them. We all benefit!" (Although Campbell, a physicist, might possibly be more bewildered by intracellular signalling than your average biologist).

A month later, *Nature* published "Professor's little helper", an article by Barbara Sahakian, Professor of Clinical Neuropsychology at Cambridge University, who had contributed to the BMA report. She posed a series of ethical questions about cognitive enhancement, beginning with clinically ill patients: Should adults with severe memory and concentration problems from neuropsychiatric disorders be given cognitive-enhancing drugs? "We believe the answer is a resounding 'yes'."

The questions then passed through grey areas: Are mild side effects acceptable? Is it okay to treat children with neuropsychiatric disorders? Before arriving at the key question:"Would you boost your own brain power?" the idea was drawn out through sub-questions like "If offered by a friend or colleague, would you, the reader, take a pill that would help you to better focus, plan or remember?" or "Under what conditions would you feel comfortable taking a pill, and under what conditions would you decline?" And even if you weren't initially tempted to try them: "How would you react if you knew your colleagues, or your students, were taking cognitive enhancers?"

The *Nature* 'Brain Doping' survey

The article ended with positive calls for the development of more effective cognitive-enhancing drugs, "so desperately needed" by the sick. Only in the subsequent small print, under 'competing financial interest statement', did we learn that Sahakian actively consults pharmaceutical companies, including Cambridge Cognition (whose speciality is, you guessed it, cognitive enhancement) and that she holds

shares in CeNeS Pharmaceuticals, a company specialising in the research, development and sale of drugs for the treatment of CNS disorders, which also happens to own Cambridge Cognition.

Nature received so much correspondence about this article that they decided to launch an online survey of drug use by scientists. Responses came from 1,400 people in 60 countries and the data was analysed in "Poll results: look who's doping" (2008, vol 452:674-5).

The questions were directed to three of the most commonly used drugs: methylphenidate (Ritalin), a stimulant normally used to treat ADHD (attention-deficit hyperactivity disorder) but well-known on college campuses as a 'study aid'; modafinil (Provigil), prescribed to treat sleep disorders but also used off-label to combat general fatigue or overcome jet lag; and beta blockers, drugs prescribed for cardiac arrhythmia that also have an anti-anxiety effect.

One in five respondents said they had taken these drugs, or others, for non-medical, cognition-enhancing purposes. The most popular drug was Ritalin, taken by 62% of users, while 44% admitted to taking modafinil, and 15% said they had taken beta-blockers, such as propanolol. Obviously, some respondents were in the habit of mixing-and-matching their drugs.

Other drugs being taken included Adderall (a mixture of several amphetamine salts similar to Ritalin), but also Centrophenoxine (also called meclofenoxate, used to treat senile dementia), Piracetam (useful for treating cognitive impairment in alcoholics), dexedrine (Dextroamphetamine – another drug for ADHD) and various alternative medicines such as extracts from the Ginkgo plant, and omega-3 fatty acids (prepared from sardines).

Improving focus and partying

The main reasons given for taking these drugs were to improve concentration and the capacity to focus on a specific task. Counteracting jet lag was also popular, although some people also claimed to have used them for partying and "house cleaning".

Around the same proportion of respondents said they took drugs daily, as those who admitted to monthly or less frequent use. Roughly half of those taking drugs for non-medicinal reasons reported unpleasant side effects, including headaches, jitteriness, anxiety and sleeplessness. Although some said they had discontinued drug use because of this, it did not appear to deter almost half of the daily users.

Around one-third of the drugs being used for non-medical purposes were purchased over the Internet, the rest being obtained from pharmacies, or on prescription. However, it wasn't clear whether the drugs came from other people's prescriptions, or if they'd been prescribed for different purposes or at different doses for the user.

When asked about their attitudes to drug-taking in children, one-third of the respondents admitted they would "feel pressure to give cognition-enhancing drugs to their own children if other children at school were taking them".

So, what are these drugs that "one in five scientists" have admitted to taking?

Ritalin: Methylphenidate was identified as a psychostimulant drug in 1954. It increases the levels of dopamine and norepinephrine in the brain through reuptake inhibition of the monoamine transporters. It possesses structural similarities to amphetamine and has pharmacological effects similar to cocaine, that are less potent but longer in duration. Its main effects are to maintain or increase alertness, improve attention and to combat fatigue.

Since the 1960s, medical use of Ritalin has been intimately linked to the treatment of children with minimal brain dysfunction (MBD), now more commonly known as ADHD. In itself, ADHD is an extremely controversial condition, characterised by the co-existence of attentional problems and hyperactivity in young children. There are still disputes as to whether it is really a disorder at all, regarding the extent of genetic predispositions in certain families, and its accurate diagnosis, especially by school psychologists confronted with children displaying disruptive classroom behaviour.

Criminal researchers

Unfortunately, a boost for Ritalin use was associated with fraudulent, but influential, research by Stephen Breuning, a psychologist at the Universities of Illinois and Pittsburg. In 1988, he became the first researcher to be criminally convicted of scientific fraud (*Science* 1987, vol 235:1566-7). As an expert in drug treatment of hyperactive mentally retarded children, Breuning had published a series of completely invented papers between the mid-1970s and 1984 showing the superiority of Ritalin to anti-psychotics, the standard treatment. US health authorities modified their medication based on these fake results, and Breuning's papers are still mistakenly cited in the literature.

Diagnosed cases of ADHD have skyrocketed in the US. It now affects an estimated 8% of children aged 4–17 and 3-4% of adults. Between 1991 and 1999, Ritalin sales in the US increased 500%, reaching 19 million prescriptions by 1999. Ritalin is now taken daily by > 2 million US children and a million adults. Similar increases have been seen in other countries, e.g. in the UK, ADHD was <0.1% before 1990 but is now claimed to affect up to 5% of children.

With such an abundance of Ritalin available, non-medicinal abuse has become routine, especially in the US. Surveys estimate that 7% of students in US universities have used prescription stimulants to try to improve their academic performance, particularly Ritalin and Adderall.

Ritalin affects arousal, i.e. the level of wakefulness, but does this really translate into improvements in complex cognitive processing? In 'The likelihood of cognitive enhancement' (*Pharmacology, Biochemistry and Behavior* 2011, 99:116), Gary Lynch from the University of California, Irvine, questions whether Ritalin does, in fact, produce such effects in the absence of disturbances to other aspects of cognition. "This reflects the fact that the great majority of animal and human studies on Ritalin are concerned with its effects on ADHD and other psychiatric problems; a much smaller number of experiments deal with control animals or healthy humans. It seems likely that Ritalin's positive effects on attention are most apparent in relatively simple tasks requiring sustained engagement and less evident for more difficult problems requiring selective attention."

Something to keep you awake

Perhaps, in the lab environment, Ritalin might have a use in helping researchers to stay awake during their more repetitive and mind-numbing experiments. Or couldn't they have regular coffee breaks instead?

Modafinil: sold under names like Provigil and Modalert, it derives from benzhydryl sulfinyl compounds developed in France during the 1970s, and has since been prescribed for the treatment of narcolepsy, shift work sleeping disorders and excessive daytime sleepiness. Despite extensive research into the interaction of modafinil with a large number of neurotransmitter systems, its precise mechanism of action is still not clear. Modafinil increases the release of monoamines from the synaptic terminals, notably the catecholamines, norepinedrine and dopamine. However, it also elevates hypothalamic histamine levels. Hence, it shares some of the actions of amphetamine-class stimulants, like Ritalin, but seems to be more of a "wakefulness promoting agent".

Modafinil is widely used non-medicinally to suppress the need for sleep. Cephalon, the company that makes modafinil, was fined $425 million in 2008 for misleading marketing that promoted its off-label use as a remedy for tiredness. It is mainly used by academics to combat the disorientating effects of jet-lag but has also gained a reputation as a cognitive enhancer, an effect that is disputed by research on healthy non-sleep-deprived people. However, modafinil does seem to improve some aspects of working memory, such as digit manipulation and pattern recognition memory.

Modafinil has replaced amphetamines as the favoured drug for keeping operation-

When coffee no longer does the trick...

Photo: Fotolia/Eric Simard

al soldiers and military pilots alert. There have also been suggestions that it could be used to 'enhance' the working performance of air-traffic controllers, airport-security screeners, as well as hospital doctors and surgeons. There are concerns that the adoption of such a practice could lead to coercion, e.g. obliging people to take drugs to keep their jobs or deciding that overworked junior hospital doctors could work an extra few hours each week.

Precision pipetting made easy

Beta blockers: beta-adrenergic antagonists block the action of endogenous catecholamines, notably epinephrine (adrenaline) and norepinephrine (noradrenaline), on β-adrenergic receptors, part of the sympathetic nervous system that mediates the 'fight or flight' response. In 1962, propanolol was first used for treating heart disease, going on to become the world's best selling drug.

However, beta blockers have found widespread non-medicinal use as a means of combatting performance anxiety and panic. There is a significant reduction in the physiological symptoms (pounding heart, cold hands, increased respiration and sweating) enabling anxious individuals to better concentrate. A 1987 survey of the 51 largest US orchestras found that 27% of its musicians had used beta blockers. Professional dancers, actors and public speakers have all been known to use them to avoid 'stage fright' and tremors during public performance. Researchers faced with large or potentially hostile audiences have also been known to succumb to the temptation. Perhaps it could also be used for tremor-free 'precision pipetting'?

In 2004, Anjan Chatterjee, a neurologist at the University of Pennsylvania's Center for Cognitive Neuroscience, chose the term 'Cosmetic Neurology' to describe the increasing demands on medical doctors to prescribe medicine to healthy people, who believe that it might make their bodies and brains "function better" by modulating their motor, cognitive and affective systems (*Neurology* 63:968-74).

Cosmetic neurology

In a world of private medicine, where people can pay to have what they want, Chatterjee says that the very purpose of medicine is being challenged. There is a distinction between treating disease in sick patients and improving quality of life. 'Therapy' is treating disease, whereas 'enhancement' is improving normal abilities. "Most people would probably agree that therapy is desirable. By contrast, enhancing normal abilities gives pause to many."

There are three general categories: improvement of motor abilities, cognition and affective systems. "With the current and future impact of aging in our society, these prospects are particularly germane."

Targets for enhancement of motor abilities encompass cardiovascular, peripheral motor and central nervous systems. For example, human erythropoietin is used to increase the oxygen-carrying capacities of the cardiovascular system to improve endurance. Athletes commonly use anabolic steroids to enhance motor systems and insulin-like growth factor may also increase muscle mass and prevent muscular decline. Targetting the CNS with dopamine agonists may improve the acquisition of motor skills.

Other drugs used to treat cognitive disorders, such as Alzheimer's disease, are likely to modulate attention, memory and learning in healthy individuals, e.g. cholinesterase inhibitors and atomoxetine. However, the effects of these medications may be influenced by genetic factors, such as which catechol O-methyltransferase alleles are inherited. This observation raises the possibility that enhancement cocktails might eventually be tailored to individual genetic profiles.

Chatterjee notes that it is "desirable" to modify affective systems since there are so many depressed people around. Up to one in five Americans are depressed, and half of adult Americans suffer from affective and substance abuse illnesses! Selective serotonin reuptake inhibitors (SSRIs) like Prozac are widely used and seem to promote 'affiliative behaviour' in healthy states. New ways to control affective states might be based on the modulation of neuropeptides, such as substance P, vasopressin, galanin and neuropeptide Y. Corticotropin release factor (CRF) seems to mediate the long term effects of stress and blocking CRF may blunt these effects. However, past experience with anti-depressants like Valium suggest that it may be hard to modulate affective states with "subtlety".

New drugs for memory

Have we reached a point where new classes of drugs are being developed primarily for enhancement of the healthy rather than for curing medical disease? New classes of drugs are being developed that promote the intracellular cascade of events leading up to the structural neural changes associated with the acquisition of long term memories. For example, ampakines are positive modulators of AMPA-type glutamate receptors. They work by exaggerating the effect of the fast-signalling neurotransmitter, glutamate, in key cognitive structures of the brain like the cerebral cortex and hippocampus, and may facilitate learning and memory as well as general alertness. US military research (DARPA) has been actively studying their use for improving 'military effectiveness'.

To enhance creativity instead of productivity, some natural products could be helpful. But caution is advised.

'Neuroethics' is a new research area, defining the moral and legal issues arising from the use of enhancement drugs. It is seen as a precursor to future government regulation and control of neuro-enhancement. There are a number of common themes.

The first is obviously safety: most medications have unpleasant side effects. What level of risk justifies the hoped-for benefits of taking drugs for enhancement?

Secondly, there is the question of character and individuality. Chemically changing the brain could threaten our notion of "personhood", affecting the essential characteristics of what it means to be human. If a personality is considered to be the sum of our experiences, then would selectively eliminating the impact of painful memories change who we are? This is a difficult issue to deal with. In the US, Chatterjee notes that sudden transformational changes in the form of 'religious epiphanies' are often welcomed. "Americans often take pride in 'reinventing' themselves. Is medically doing so any different?"

At the same time, major concerns about "coercion" emerge because what starts out as a matter of choice could end up as a coercive force, whether explicit or implicit.

Ethical implications

Explicit coercion might apply to classes of individuals who are expected to take certain medications for the greater good. Such precedents exist in the military and may seep into other specialised professions. One study found that commercial airline pilots taking a cholinesterase inhibitor performed better in emergency situations on flight simulators. If these results were robust and reliable, implying that pilots fly better on drugs, then could we imagine a situation where pilots are 'encouraged', or even required, to take such medication?

Implicit coercive pressures are even more complicated. In competitive, 'winner takes all' environments, slight incremental advantages have disproportionate consequences.

"It is not unusual for professionals to work 80 or 90 hours a week, while their children enrol in several sports programmes and after school music programmes to ensure they can make competitive applications to colleges. The pressures for such children to take stimulant drugs to help with academic performance are already evident." In his clinical practice, Chatterjee says parents regularly ask him to help 'improve' their children. Academics are by no means immune from such pressures. In the 'Disposable academic' (*LT* 05/2011), I de-

Jonathan Eisen and the April Fool's joke

On 1st April, 2008, a group of science bloggers began simultaneously discussing the significance of the latest 'official' announcement:

"The National Institutes of Health today announced three new initiatives to fight the use of brain enhancing drugs by scientists. The new initiatives are (1) the creation of the NIH Anti-Brain Doping Advisory Group (NABDAG), a new trans-NIH committee, (2) a collaboration with the World Anti-Doping Authority (WADA) and the European Commission to create the World Anti-Brain Doping Authority (WABDA) and (3) the adoption by the NIH of the World Anti-Brain Doping Code – a set of regulations on the use of brain-enhancing drugs among scientists.

"These new initiatives are designed to level the playing field among scientists in terms of intellectual activities," said then NIH Director Elias A. Zerhouni, MD. "These three activities are designed to get NIH ahead of the curve in terms of performance enhancing drug use among scientists."

While "doping" is now accepted as a problem among athletes, it is less widely known that so-called "brain doping" has been affecting the competitive balance in scientific research as well. Together with WABDA, NABDAG will work to develop the international rules for the use of performance-enhancing drugs among scientists as well as testing and punishment procedures. Most importantly they will administer the World Anti Brain-Doping Code, a set of uniform anti-brain doping rules.

The NIH and European Commission have formally adopted this Code for the conduct of all scientists who receive funding in any form (intramural or extramural) from these agencies. The Code includes regulations on which drugs are prohibited, what the recommended testing procedures should be and what the punishments should be for positive tests. We note that the implementation will include testing of all NIH-funded scientists, both at the time they receive funding as well as at random times during the course of working on an NIH-funded project. Testing will also be implemented at all NIH-funded or NIH-hosted events such as conferences and workshops and at grant review panels."

Written by Jonathan Eisen, an evolutionary biologist at the University of California, Davis, the fake announcement was posted and discussed on his own site ('The Tree of life', *http://phylogenomics.blogspot.com/*). Other blogsites also spread rumours about receiving anti-doping affidavits from the NIH with their first research grants.

Two weeks later, the anti-'brain doping' joke got into print. *Nature* reported its survey results about scientists taking drugs and discussed Eisen's 'insight' that 'brain doping' was affecting competition among US scientists for research funding. Eisen said he had been aiming for a joke "so ridiculous" that it would make scientists "chuckle" but their responses made him realise, he'd actually hit on a point of genuine concern to many researchers: "I think it did make it less funny because it is actually too real."

A year later, Eisen told the *New Yorker* ('Brain Gain' 27/04/09) he was actually sceptical about scientists taking neuro-enhancers to 'grind out' grant proposals, "It's weird to me that people are taking these drugs to write grants. I mean, if you came up with some really interesting paper that was spurred by taking some really interesting drug – magic mushrooms or something – that would make more sense to me. In the end you're only as good as the ideas you've come up with."

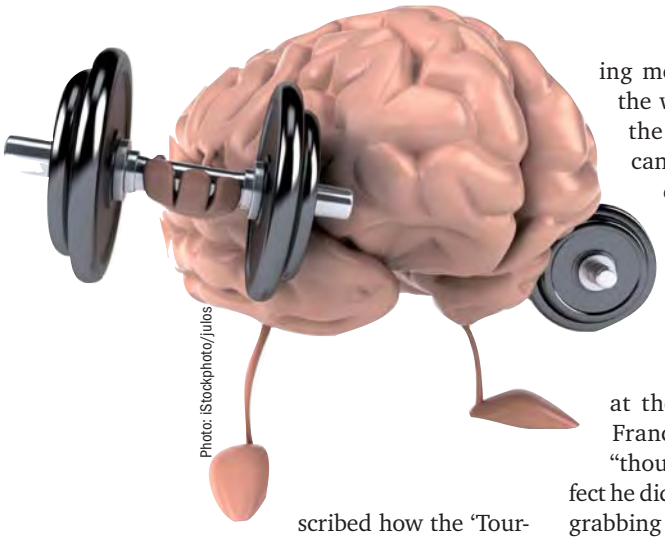
Photo: iStockphoto/julos

scribed how the 'Tournament Model' applies to bioscience research. In such a situation, how would you react to the competition?

Look at the case of John Reed, age 49, MD PhD at the Burnham Institute for Medical Research in California. In 2008, he was featured in *Nature* (vol 452:259) as one of the most successful NIH grant winners, receiving eleven NIH grants worth almost $11 million in 2007. Between 1995 and 2005, he was the most highly cited author in all of cell biology, with 23,729 citations (he specialises in cell death). Imagine competing with him!

"He wakes up at 3 a.m. to write grants and papers. At 6 or 6:30, he goes for a long run, swim or bicycle ride. By 7:30, Reed is at work juggling roles as president of the institute and director of a 35-person lab. If his researchers need him urgently, they e-mail a secret address that goes directly to him. They each have weekly goals that must be met and progress is measured with project-management software." Reed describes his lab as a no-nonsense, get-the-job-done, focused environment. Concerning all his grants, he says, "The evidence is that some labs and some people can handle a larger portfolio. I don't think we should apply a one-size-fits-all mentality."

Sleep ins and washboard abs

One of Reed's postdocs spoke of his muscular physique, "I don't know many principal investigators at that level who have washboard abs. He does everything 100%, which is 200% for the rest of us." But don't worry, Reed does have a life outside the lab: "Every other evening, he goes home to spend time with his family. At weekends, he even sleeps in – until 4:30 a.m."!

And *Nature* has recently published an article on "The 24/7 Lab: Working weekends, leaving at midnight, Friday evening meetings. Does science come out the winner?" (1/09/11). It describes the punishing work routine in the cancer lab of neurosurgeon, Alfredo Quiñones-Hinojosa, at Johns Hopkins University. "The people in my lab, they work 24 hours a day. They're here over Christmas and New Year writing grants."

When he was a medical resident at the University of California, San Francisco, his three young children "thought he lived in the hospital. In effect he did, putting in 140 hours a week and grabbing 10-minute naps when he could." Quiñones-Hinojosa credits his professional rise to his resilience and a seemingly limitless capacity for hard work. "When you go that extra step, you are training your brain like an athlete," he says. And the fact that his group has published 113 articles in the past six years and holds 13 funding grants is not, he says, because he is brighter or better connected than colleagues. "It's just a matter of volume."

Enhanced creativity

One of the qualities that does not seem to be associated with stimulants like Ritalin, Adderall, or modafinil is creativity. For more 'inspirational aid', original thinkers have favoured hallucinogens.

For example, Kary Mullis who won the 1993 Nobel Prize in chemistry for developing the polymerase chain reaction (PCR). In his autobiography, 'Dancing Naked in the Mind Field', he spoke about the benefits of using mind-expanding drugs, like marijuana and LSD. Mullis said he "might have been stupid in some respects, if it weren't for my psychedelic experiences." After his first LSD trip in 1966, he was inspired to understand more about neurology and biochemistry.

And the astronomer, Carl Sagan, was a regular user of marijuana from the early 1960s until his death in 1996. He publicly disputed the "myth" that the insights achieved while stoned on marijuana are illusory: "I am convinced that this is an error and that the devastating insights achieved when high are real insights; the main problem is putting these insights in a form acceptable to the quite different self that we are when we're down the next day."

Meanwhile, it seems unlikely that drugs like Ritalin or Adderall help people think more creatively. Martha Farah at Pennsylvania University has studied how healthy people use these neuropsychiatric medications for brain enhancement. She says that individuals who are better able to focus on one thing and filter out distractions tend to be less creative. "More and more of our young people are using these drugs to help them work. They've got their laptop, their iPhone, and their Adderall. This rising generation of workers and leaders may have a subtly different style of thinking and working, because they're using these drugs or because they learned to work using these drugs, so that even if you take the drugs away they'll still have a certain approach. I'm a little concerned that we could be raising a generation of very focused accountants."

That might explain a lot!

Jeremy Garwood

ONE FINE DAY IN THE LAB...

BY LEONID SCHNEIDER