

# Fuel for tho

**M**OST of us accept that the capacity for exercise can be enhanced by increasing the delivery of glucose or oxygen to muscles. Could the same principles be applied to brain function? At the Human Cognitive Neuroscience Unit (HCNU) we have been investigating the possibility that cognitive performance can be improved by increasing the availability and delivery of the brain's basic fuels.

The human brain is excessively greedy. Contributing only 2 per cent to the average person's weight, it is constantly burning away some 20 per cent of the body's calories, making it easily the most energetic organ. The energy supply of the body originates from oxygen (breathed in from the air) and glucose (from food). These circulate in the blood until they are delivered, sushi-like,

to active tissue for immediate use or storage.

Unfortunately the brain has a fairly serious design fault. Despite requiring more than its fair share of energy, it cannot store glucose. This means that it relies on a constant supply of glucose through its rich blood supply.

### **Fast and slow burn**

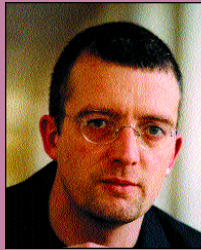
Many biological textbooks will tell you that if the brain's supply of oxygen is cut off for a matter of minutes then its cells – neurons – start to die. It turns out that even second-by-second fluctuations in the levels of glucose and oxygen can impact on brain function. Two common brain imaging techniques, positron emission tomography and functional magnetic resonance imaging exploit the fact that more active brain regions 'burn' more glucose and oxygen

respectively depending on the mental task being performed.

So as with other organs, the brain's 'performance' can be measured directly. This usually involves expensive and partially invasive measures of neuronal activity. But of course we also gauge the level and integrity of brain function via its capacity to make decisions, to concentrate, and to generate memories, thoughts, perceptions and emotions.

So what happens to cognitive performance if the availability of glucose and oxygen is restricted? Individuals with diabetes (an inability to utilise glucose) report difficulties with concentration and memory when they are 'hypo' (i.e. hypoglycaemic or in a state of low blood glucose). Likewise, cognitive deficits are evident at altitude where, owing to decreased atmospheric pressure, less oxygen is carried in the blood.

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**ANDREW SCHOLEY** on research of the Human Cognitive Neuroscience Unit, University of Northumbria, using supply and demand in the brain to improve cognitive performance.

consequences. The cognition-enhancing effects of glucose are well documented. Generally speaking, individuals given a drink containing 25 or 50 grams of glucose perform better on tasks of cognitive function than those given a placebo. The effect seems most pronounced where there is 'room for improvement' – for example in the elderly. But similar, less dramatic, results have been demonstrated in so-called 'healthy young adults' (usually psychology undergraduates).

Under normal conditions the breakdown of glucose relies on a constant supply of oxygen. The two are used together to provide the energy for every cell in the body. The cellular uptake of oxygen and the breakdown of glucose to provide energy are intrinsically linked. The two processes are like interlocking cogs in a machine turning together to provide energy. The rate at which the machinery of energy production works is dictated by the amount of energy required at any given moment.

It seems plausible then that, as with glucose, the provision of oxygen should enhance cognitive function. Despite reports of reversal of altitude- and age-related memory impairments by oxygen breathing, until recently no one had looked at the possibility that increasing the body's levels of the gas could improve cognitive function in otherwise healthy individuals in normal situations.

A few years ago Mark Moss, a bright undergraduate on the psychology degree at the University of Northumbria, had seen American footballers breathing oxygen to help their game. He came to me with the idea that oxygen might have a similar effect on psychological performance. Aerosols of compressed oxygen with a facemask attached are available from some chemists. Mark's convictions were given further impetus when he bought one of these canisters and found that a good blast of oxygen helped to clear a hangover.

We designed a simple experiment to test the possibility that oxygen might improve cognitive function. There were three experimental groups. All of them heard

a list of words, performed a distractor task for 10 minutes, and then had a recall test. Participants inhaled oxygen from the aerosol for a minute either immediately prior to hearing the words, immediately prior to recall, or not at all. Oxygen did improve memory – but only for the group who inhaled the gas immediately prior to learning.

We went on to increase the learning-delay interval to 24 hours and found the same effect. At this point expectancy effects couldn't be ruled out, so we attempted to set up a placebo condition. In these early experiments this involved feeding air from an aquarium aerator along a tube and into the facemask for our volunteers to inhale. It worked – oxygen, but not air, administered immediately prior to learning significantly enhanced memory performance (Moss & Scholey, 1996).

Later experiments used more rigorous double-blind, placebo-controlled methods often with concurrent measurement of blood oxygen levels. These included assessment of oxygen's impact on a range of tasks using the Cognitive Drug Research (CDR) computerised test battery developed by our close collaborator Keith Wesnes. The battery allows exquisitely sensitive measurement of fundamental aspects of cognitive performance.

The general finding was that oxygen inhalation improved cognitive performance on most measures of memory and attention in a 'dose-dependent' manner ('dose' here refers to the length of time oxygen is inhaled). Like many pharmacological agents the dose-response curve followed an inverted-U shape where the optimum dose was typically 30 seconds or a minute (Moss *et al.*, 1998). We also confirmed the results of the original study. Consolidation (or 'laying down') of memory could be improved by oxygen inspiration, but it did not affect retrieval (i.e. access to material already stored) (Scholey *et al.*, 1998).

### Having a gas?

Around the same time as the HCNU were examining the effects of oxygen on

Such effects are not due to the pathology of diabetes, nor to being at the top of a mountain. Laboratory studies have shown that inducing low blood glucose levels produces similar psychological effects to diabetes. Similarly the cognitive deficits seen at altitude can be mimicked by reducing the amount of oxygen in the air from its usual 20 per cent.

The day-to-day lapses in concentration and memory that occur with ageing have also been attributed by some researchers to problems with the delivery of these energy sources to the brain. Such processes may even contribute to the neuropathology of Alzheimer's disease.

### Adding fuel to the fire

This begs the question of whether increasing the levels of these essential neural fuels could have beneficial cognitive

memory, 'oxygen bars' started springing up in North America and in the UK. Perhaps there was something in the air that made oxygen interesting! People who use these bars report that inhaling pure oxygen improves their mood and energy levels.

We have examined the effects of oxygen on mood and found no difference between oxygen-breathing and air-breathing groups. Indeed following double-blind experiments we routinely ask participants to indicate whether they think they received oxygen or air. People's responses indicate that they really can't tell (Scholey *et al.*, 1999). It seems that the individuals who frequent oxygen bars are experiencing a placebo effect, as was Mark himself during the original hangover that helped to start the research.

### **Why you can't think straight**

The notion that oxygen (and glucose) can improve cognitive performance raises an intriguing possibility. It seems that under certain conditions, brain function is 'fuel-limited'. There appears to be a 'ceiling' on cognitive performance which can be raised by simply adding more fuel.

This notion flies in the face of the given wisdom that the brain has evolved to function optimally. Perhaps this is not surprising – it does seem ridiculous and arrogant to assume that, in the human brain, evolution has somehow 'arrived'.

As the early oxygen results started to be released into the public domain, I was approached by a Californian games company. They were interested in developing an arcade game where five or six players played against each other, possibly in some sort of 'shoot-em-up' scenario. Such games often include aspects of attention and memory. After accruing a certain number of points, instead of getting a bigger and better gun, players would be given the opportunity of a 'time-out' while oxygen-enriched air was pumped into their face mask before they went into the next battle.

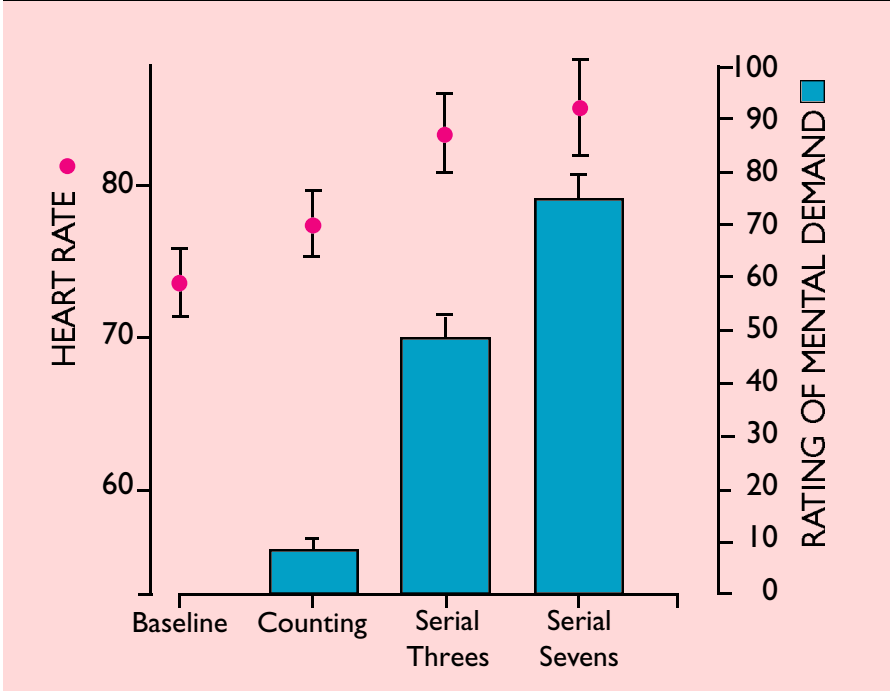
The idea sounded like fun, not to mention potentially lucrative. The company, however, went bust. Luckily not before they had sponsored some research into the effects of oxygen on game play. We used the computer game Tetris, which was popular in the Division at the time.

Tetris involves the manipulation of falling geometric shapes – simple blocks, Ts and Ls – which the player attempts to fit together snugly as they pile up at the bottom of the screen. As the game progresses this becomes more difficult as the blocks start to fall faster. Tetris involves aspects of reaction time, planning, mental rotation and motor programme execution – at least some of these should be affected by oxygen.

The effects of oxygen on Tetris were crystal clear – it improved performance at the highest game levels only (Scholey *et al.*, 1999). A similar picture has since emerged from a number of experiments using various measures.

As a general rule (though not an immutable one) it appears to be those tasks involving the greatest amount of 'mental effort' that are most affected by oxygen and glucose. Mental effort, or 'cognitive demand', involves aspects of memory load, intensity of processing and other features that make a task more difficult to perform. Definitions aside, it is possible to compare tasks and say that one is more or less cognitively demanding than the other.

**FIGURE 1** Ratings of mental effort and changes in heart rate during tasks with differing cognitive loads (means and standard errors are shown)



In the HCNU we moved from computer games to tasks such as ‘serial subtraction’ to investigate the relationship between cognitive demand and task performance. Serial subtraction involves a participant being presented with a random number between 800 and 1000. They are then asked to repeatedly subtract a fixed sum (usually three or seven). Given a starting number of 923 the correct responses during serial sevens would be ‘916, 909, 902, 895, ...’. For serial threes they would be ‘920, 917, 914, 911, ...’. The task can be scored both for errors and for the number of responses made.

Serial subtraction tests aspects of concentration and working memory. For our purposes however, it is enough that fewer responses and more errors are made during serial sevens than during serial threes – suggesting that the former is more cognitively demanding.

More intense cognitive processing is associated with a number of physiological responses, particularly with an increase in a person’s arousal levels. Physiological arousal includes most of the bodily changes associated with the ‘fight-or-flight’ response. This makes perfect sense in terms of the excessive energy demands of the brain. The changes include the liberation of glucose, faster breathing, increasing heart rate and widening of blood vessels. Many of them would increase the

availability and delivery of glucose and oxygen to the brain.

These examples provide a neat illustration of nature’s parsimony. On the one hand, the processes occur during intense cognitive processing to mobilise energy reserves and feed the brain as it cries out for more glucose and oxygen. On the other hand, when they occur *during* stress, as well as toning up the body for fight-or-flight, they may help ‘thinking on your feet’ and facilitate laying down the memory of a stressful stimulus.

But only up to a point. If these effects occur to extremes then effective cognitive processing may be drowned out by the resulting neural noise. This may contribute to the phenomenon of ‘not being able to think straight’ associated with higher amounts of stress, as well as the inverted U of oxygen’s dose-response curve.

Performing a task like serial sevens for a couple of minutes results in heart rate acceleration – typically resulting in a rise from about 70 beats per minute to about 80. This response may be involved in increasing the blood-borne transport of glucose and oxygen, which are then sucked out of the blood by the brain, fuelling the neural mechanisms involved in intense cognitive processing.

It turns out that people whose heart rate reacts more during cognitive processing actually perform better on the task. Similar

physiological individual differences identified in people’s ability to use glucose have been extensively investigated by David Benton’s group in Swansea (e.g. Donohoe & Benton, 1999).

Another way of gauging mental effort is to ask people. In a recent glucose experiment, as well as measuring heart rates during tasks, we asked our participants to place a mark on a 10 centimetre line indicating how mentally demanding they had found each task (Kennedy & Scholey, 2000).

Serial sevens was the only task whose performance was significantly enhanced by a glucose drink. It was also rated as the most mentally demanding, followed by Serial Threes, then counting upwards in ones in time to a metronome, which in turn was rated as more demanding than sitting around relaxing. Heart rate changes during the tasks followed a strikingly similar pattern to these subjective ratings (see Figure 1).

Figure 1 illustrates that there is a pretty good correspondence between people’s ratings of the mental effort associated with a task and their physiological response to it. Such results suggest that there may be tantalising similarities between such physiological processes and mental states.

### When the going gets tough

Because of the fundamental nature of oxygen and glucose in medicine, techniques to measure them are readily available. Blood glucose levels can be determined by taking tiny fingerprick blood samples. The concentration of blood oxygen can be measured, online, using a non-invasive finger cuff.

This has allowed the usual question of human psychopharmacology to be turned on its head. As well as asking ‘what is the effect of glucose or oxygen on this task?’; we can now ask ‘what is the effect of this task on to the levels of glucose and oxygen?’.

To investigate this we need to know what happens without any cognitive testing. Give someone a glucose drink and their blood glucose levels will rise, peak between 30 minutes and an hour later, then fall back to baseline.

A similar response occurs with oxygen, albeit with a much shorter timescale of a few minutes. When the gas is inhaled for 30 seconds or a minute, blood oxygen levels rise from 97–98 per cent saturation to 100 per cent (actually, far more oxygen than this extra 2 or 3 per cent becomes available to tissue such as the brain – but

that's a separate story). Like glucose, the rise in blood oxygen concentrations is followed by an inevitable decline back to baseline levels.

We can time the performance of cognitive tasks in relation to different parts of the absorption curves that follow a glucose drink or a blast of oxygen. When a task such as serial sevens occurs after the peak of the curve, incredibly, there is an increase in the rate of decay. The downward slope in Figure 2 is steeper during intense cognitive processing (as illustrated by the broken line and shaded panel) than when performing a non-demanding control task such as counting upwards in ones. Obviously something is using up glucose and oxygen more quickly during a period of cognitive demand.

Could it really be that by measuring the levels of glucose and oxygen in the finger, we can detect increases in their uptake by the brain? Unfortunately the picture is not as clear as we would like. As mentioned earlier those tasks requiring higher amounts of mental effort also cause an increase in heart rate. The increase in cardiac activity will inevitably use up some of the glucose and oxygen circulating in the blood.

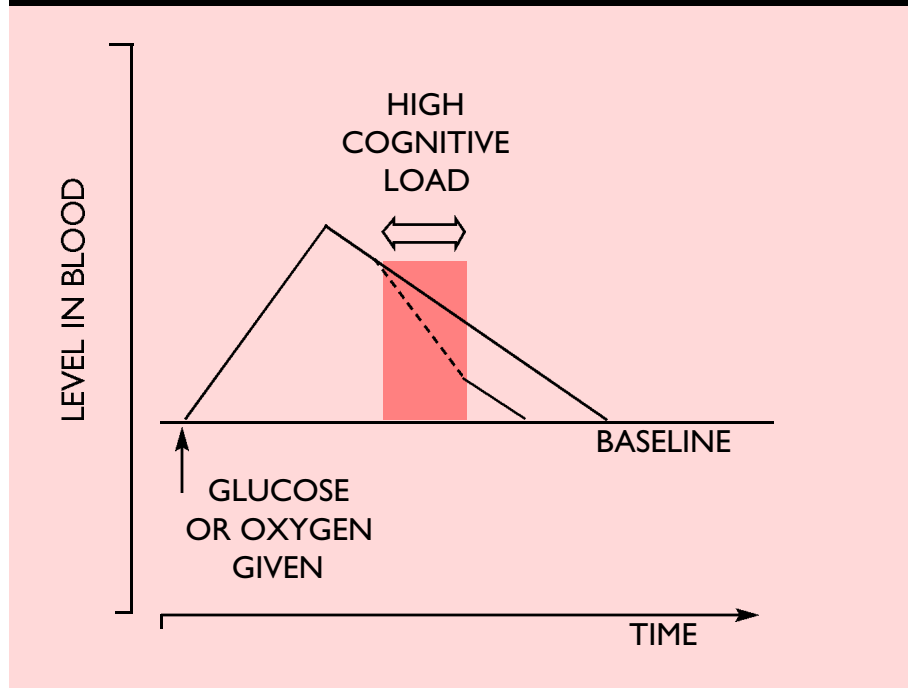
We are currently conducting experiments using glucose, oxygen, exercise bikes, mentally demanding tasks and tasks that actually decrease heart rate. With these we hope to tease apart the relative contributions of cardiac and brain activity to the accelerated fall in blood glucose and oxygen during intense cognitive processing.

### Inside the engine

The underlying mechanisms of the effects described above are not known. One possibility is that the provision of oxygen and glucose targets one or more of the 50 or so chemical transmitters in the brain. A likely candidate is the neurotransmitter acetylcholine, formed as a by-product of the cellular production line involving the use of oxygen and glucose to produce energy.

Acetylcholine is known to be crucially involved in the neural machinery of attention and memory. It is plausible that oxygen and glucose are having their effects by increasing acetylcholine levels. One way of stimulating the cholinergic system is to get smokers to have a cigarette (nicotine mimics the effects of acetylcholine). Early results suggest that the effects of consuming oxygen or glucose are not like those observed following nicotine.

**FIGURE 2** The impact of a cognitive load on the level of glucose and oxygen in the blood



There is another possibility. Within cells, including neurons, glucose and oxygen are broken down into a usable form for energetic processes. This universal energy 'currency' (called adenosine triphosphate or ATP) acts like the travellers' cheques of nature and is 'cashed in' wherever and whenever there is a need for energy. This tiny molecule is continually being made and broken down. In fact an average adult makes between 50 and 100 kilograms of ATP every day!

It seems possible that availability of oxygen and glucose may increase the availability of this energy currency. This may 'turn up the volume' of the synaptic Chinese whispers which underlie communication between brain cells. The consequence would be that neural processing and cognitive performance would improve. But only up to a point: presumably, when there is too much fuel around, the signal of efficient processing gets lost in the background chatter of neuronal signalling. Another contribution to the inverted-U dose-response curve.

### Putting the machine to work

One obvious question is whether these findings have any practical applications. The answer is 'yes and no'. Work carried out elsewhere has found that measures of everyday cognitive functioning such as putting names to faces or remembering

a shopping list, can be improved by brief inhalation of oxygen (Winder & Borrill, 1998).

In the HCNU we have evidence that a dose of oxygen can temporarily reverse some of the deficits associated with ageing. Other work (carried out at the HCNU by Pat McCue and others) suggests that brief doses of oxygen appear to provide temporary relief from the profound cognitive deficits associated with chronic fatigue syndrome.

Unfortunately the emphasis must fall on the 'temporary'. Clearly it is neither practical nor desirable to carry oxygen cylinders and to attempt to coincide inhalation of the gas with cognitive requirements! Is it possible that this effect could be achieved through other means? In the 1970s the popular children's cartoon character Marine Boy could breathe underwater by chewing 'Oxygum'. Presumably Oxygum increased the amount of available oxygen in the blood – could a similar product help cognitive functioning on dry land?

One answer to this may come from recent studies by David Kennedy (HCNU) into the cognitive effects of herbal extracts. There is fairly good evidence that some of these improve cognitive function following long-term treatment. Some of the known mechanisms of the extracts have parallels with the physiological effects of oxygen

and glucose. This raises the possibility of acute cognitive effects – measurable differences in the immediate aftermath of a single dose.

The first set of experiments tested the effects of extracts from the leaves of the ginkgo tree (*Ginkgo biloba*). If you ever have to name a fascinating tree, ginkgo would be a good bet: it is the only living member of a group of trees that flourished over 300 million years ago; and the ‘Hiroshima tree’ is a ginkgo still growing less than a kilometre from the epicentre of the wartime atom bomb blast (which it survived).

In our tests into cognitive changes following ginkgo extracts, we exploited the parallel forms of the CDR test battery, since the participants (20 University of Northumbria psychology undergraduates) were tested 25 times in all.

Each visit consisted of the student coming to the lab and having baseline measures of cognitive performance taken. They then swallowed a handful of pills containing all placebo, all ginkgo, or a dose in between.

Participants underwent the same set of cognitive tests (using different stimuli) one hour, two-and-a-half hours, four hours and six hours after their pills. Following a wash-out period of a week, they underwent the same procedure with a different amount of ginkgo. This was repeated a week later, and so on until all doses had been completed (the order in which each dose was taken varied across participants).

The results were unequivocal. Single doses of ginkgo improved ability to sustain attention over the day (Kennedy *et al.*, 2000). Participants who took a single dose of ginkgo at 9am had significantly faster responses on attentional measures by 11.30; this effect was still there at 3pm, though we had originally chosen the six-hour testing point believing that any effect would have worn off by then!

We have used similar designs to test the effects of root extracts from ginseng plants (*Panax spp.*). This time the effect was specific to memory rather than attention. Again we found a dose-specific enhancement of cognitive performance. In fact a different dose of ginseng actually decreased the speed of attention and self-rated alertness (Kennedy *et al.*, in press). This is bad news for people who take ginseng for its purported stimulant properties.

So by what mechanism might these plants affect cognitive function? Intriguingly, as well as affecting

neurotransmitter systems, ginkgo and, to a lesser extent, ginseng improve aspects of blood flow, oxygenation and glucose metabolism. Work by our collaborator in Newcastle, Elaine Perry, has shown that biochemically isolated fractions from whole medicinal plant extracts have puny neurochemical activity individually – the effect of the whole is greater than the sum of its parts. One possibility is that these extracts are so effective because they synergistically target specific neurotransmitter systems fuelling these effects further by increasing the delivery of oxygen and glucose.

The effects of ginkgo and ginseng have also been tested on tasks of low and high cognitive load (serial threes and serial sevens). The findings on these simple arithmetic tasks were pretty much what you would expect from the more comprehensive CDR data. Ginkgo speeded responses and ginseng improved accuracy (though the cost of this was that responses slowed slightly).

It was when we tested a combination of ginkgo and ginseng that we found the most dramatic results. On the serial sevens task the ginkgo/ginseng combination resulted in participants making more responses and fewer errors. In fact, at one dose participants were generating 10 to 15 per cent more responses during subtractions of sevens compared with the placebo group. It was if the treatment was making the arithmetic easier!

While such startling performance enhancement is of interest in itself, in the longer term such effects may have important applications. We are currently investigating the possibility that these and

other herbal extracts may have beneficial effects both acutely and following longer-term regimes. In fact *Ginkgo biloba* is already the treatment of choice for Alzheimer’s disease in some European countries.

## Conclusions

The results of these studies carried out at the HCNU suggest a beautiful symmetry in the reciprocal relationship between cognitive processing and the use of physiological resources. On the one hand, the body appears to mobilise such resources as and when necessary. On the other hand, directly or indirectly increasing the availability of oxygen or glucose can improve cognitive performance – particularly under conditions of cognitive ‘strain’. Moreover it appears that the physiological responses to a cognitive load and a person’s experience of mental effort are closely integrated.

As well as using these principles to fuel the fires of neural function in the short term, in certain circumstances it may be possible to turn up the temperature of the smouldering ‘slow burn’ of neural and cognitive activity. It remains to be seen whether this phenomenon can be used where it is really needed.

■ *Dr Andrew Scholey is a Reader at the Division of Psychology and Director of their Human Cognitive Neuroscience Unit, University of Northumbria, Newcastle upon Tyne NE1 8ST. Tel: 0191 227 3471; fax: 0191 227 3190; e-mail: a.scholey@unn.ac.uk.*

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