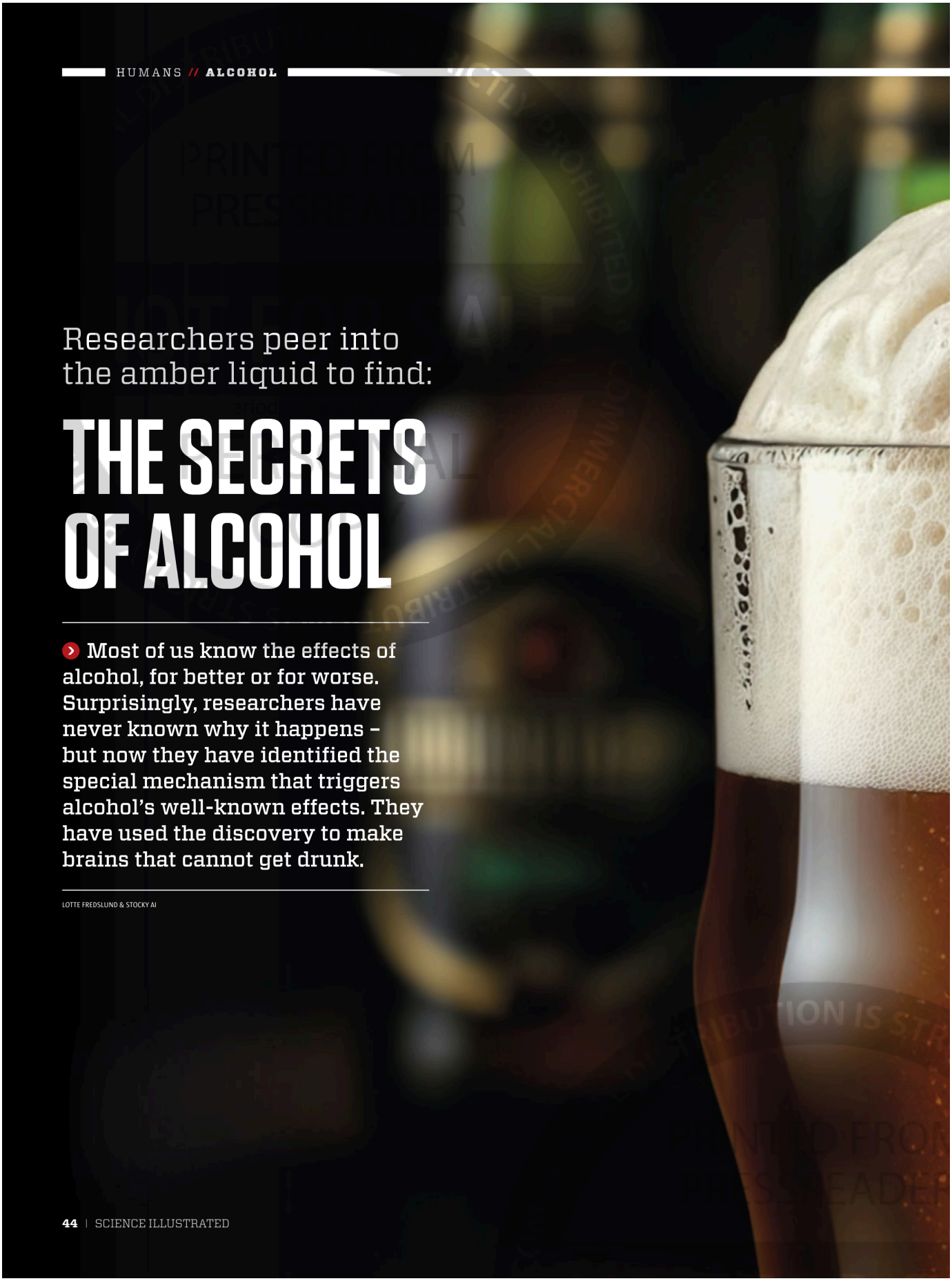
- Drinking of alcoholic beverages



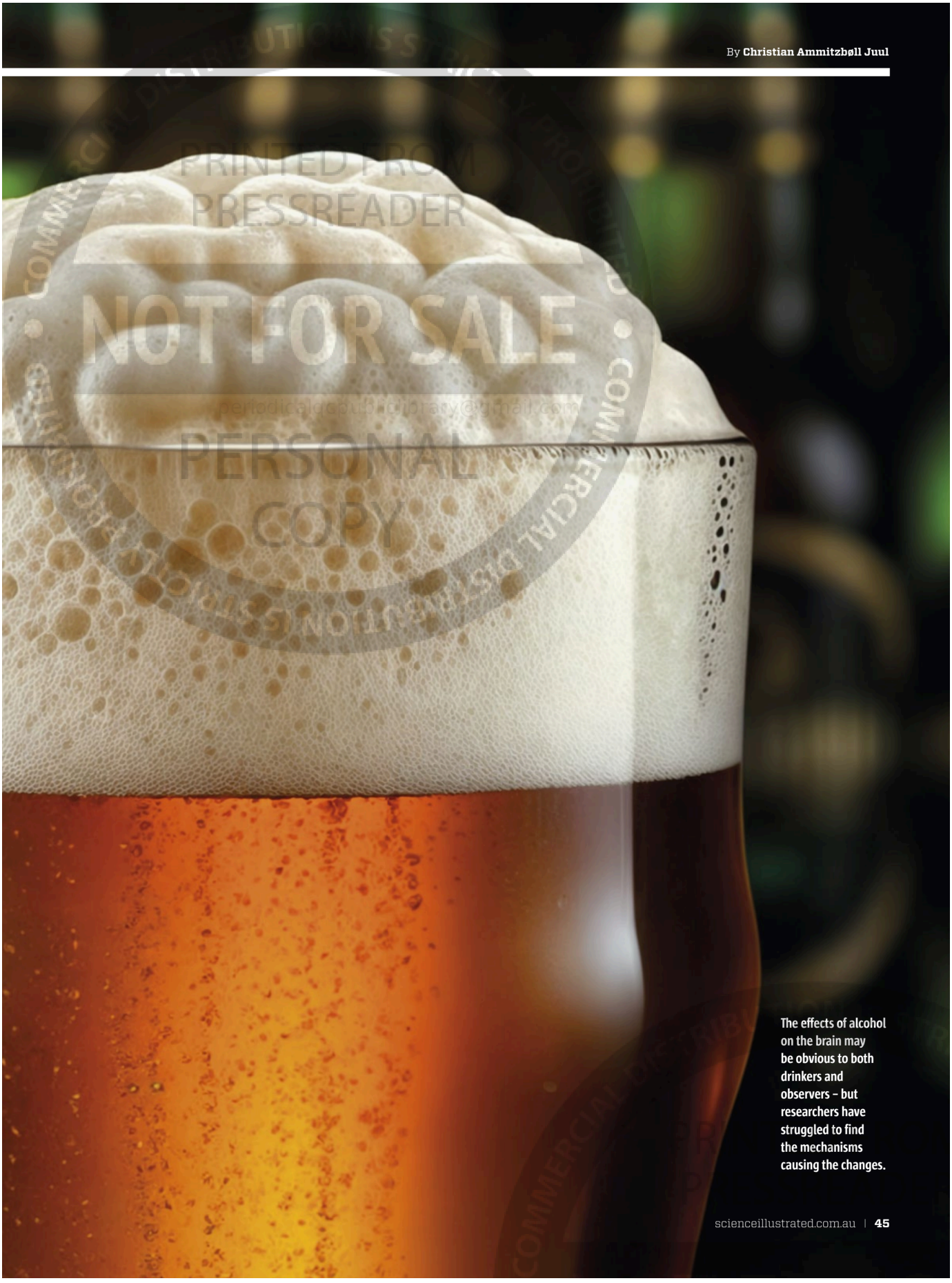
Researchers peer into the amber liquid to find:

THE SECRETS OF ALCOHOL

Most of us know the effects of alcohol, for better or for worse. Surprisingly, researchers have never known why it happens – but now they have identified the special mechanism that triggers alcohol's well-known effects. They have used the discovery to make brains that cannot get drunk.

LOTTE FREDSLUND & STOCKY AI

By **Christian Ammitzbøll Juul**



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The effects of alcohol on the brain may be obvious to both drinkers and observers – but researchers have struggled to find the mechanisms causing the changes.

You would think that the idea of researching alcohol and its effect might be popular with many a young science researcher. And you'd be right. Intoxicating drinks have been an important part of our culture for thousands of years, and countless scientific studies have delved into the secrets of alcohol.

But the precise ways in which alcohol affects the brain have remained something of a mystery – until recently.

A US research team has finally found at least part of the answer, thanks to an innovative approach to the problem. They discovered a key mechanism by which alcohol manipulates our bodies and minds.

Their discovery enabled them to create something remarkable: a brain that is unable to get drunk.

Disadvantages and advantages

Ethanol is the type of alcohol used in drinks (being the only type safe for human consumption). It is produced by single-celled yeast fungi when they break down sugar in plants. It's a process that has been known to humans for thousands of years, and we have probably been studying the effects of alcohol on the body for almost as long.

Scientific studies confirm that, at least in the short term, alcohol improves our mood and reduces stress and anxiety. This stress-relieving effect may explain why people who regularly drink small quantities of alcohol have a lower risk of developing severe cardiovascular problems such as heart attacks and strokes than people who do not drink at all.

However, positive effects of alcohol can be outweighed by a wide range of harmful consequences. In the short term, alcohol can make us dizzy, slowing our reactions, and impairing our memory. Long-term effects can be much worse. Heavy alcohol consumption can damage the liver especially, which may lead to severe and even life-threatening diseases.

26.8%

of adult Australians exceeded the Australian Adult Alcohol Guideline in 2022 (35.8% of males, 18.1% of females) according to the ABS.

In addition, even small quantities of alcohol increase the risk of cancer. And despite the immediate stress-relieving effects, long-term alcohol consumption can lead to mental disorders such as anxiety and depression. As a result, alcohol kills around 2.6 million people annually, which is why most doctors recommend we reduce consumption. But the advice is difficult to follow – our brains resist it.

Alcohol changes the brain

Alcohol is addictive. Some people develop an almost unstoppable urge to drink, and may then experience extreme discomfort if they abstain from alcohol.

According to the WHO (World Health Organisation), roughly 209 million people worldwide were addicted to alcohol as of 2019. Around twice as many are thought to struggle with alcohol-use disorders.

Addiction initially develops because alcohol increases the activity in the brain's reward system, so we get a feeling of happiness while at the same time activity in the amygdala, the brain's centre of fear, is suppressed, reducing anxiety.

However, the brain's response changes with frequent consumption. The uplifting effects wear off, and the brain begins to need alcohol just to maintain a certain level of happiness and peace of mind. Ultimately, even alcohol may not prevent depressive thoughts and anxiety.

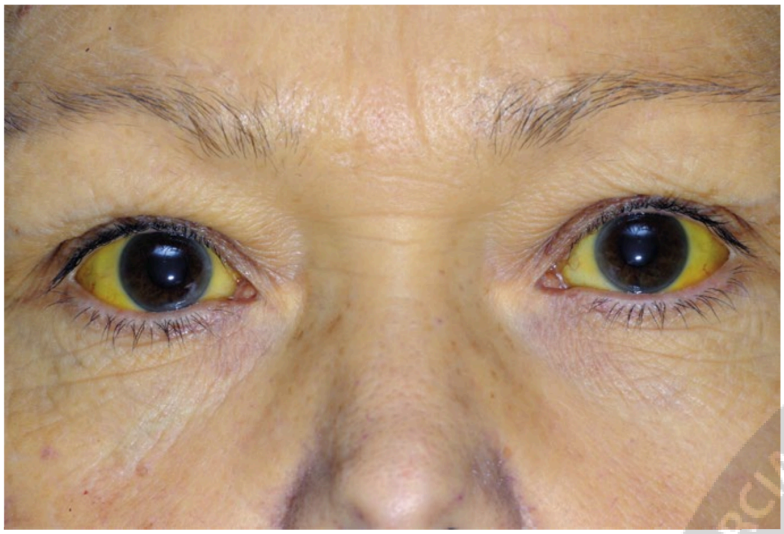
Why does alcohol have this effect on the brain? And why does the brain react differently when alcohol consumption has been going on for a period of time?

These are questions that need answering to help the many people that struggle with alcohol abuse. Brain researchers have been getting closer to the answers for decades, but without finding the precise mechanism by which alcohol works.

The brain becomes restrained

Thousands of scientific studies have helped us understand how alcohol affects us. One important discovery back in 1990 was that the brain's consumption of glucose drops by 10-30% when we get drunk. Later studies showed that even low doses of alcohol (below 0.05%) can cause substantial reductions in glucose utilisation. And that is important: glucose is the brain's primary fuel, and drives all brain activity.

The drop in glucose consumption seems to have two factors. First of all the brain starts to use the acetate produced when the liver breaks down alcohol as an alternative fuel. Secondly, the brain ▶



SPL

Alcohol abuse affects physical and mental health: this woman's liver has become so damaged by alcohol that yellowish waste products have accumulated in her skin and eyes.

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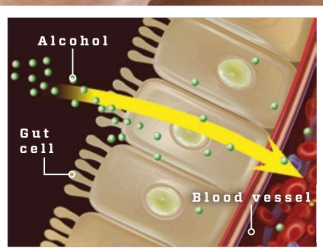
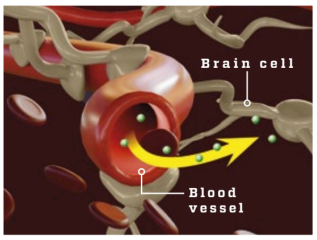
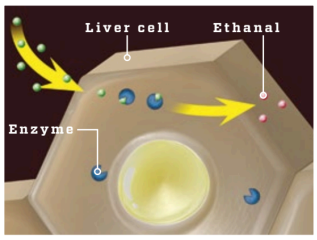
How alcohol takes over your body

It takes only 10 minutes from the first sip until you start to feel the effects. Alcohol has taken over your body – and it is painful to get it out again.

JAN MIKA/SHUTTERSTOCK







SHUTTERSTOCK & LOTTE FREDSLUND

The small intestine absorbs the most

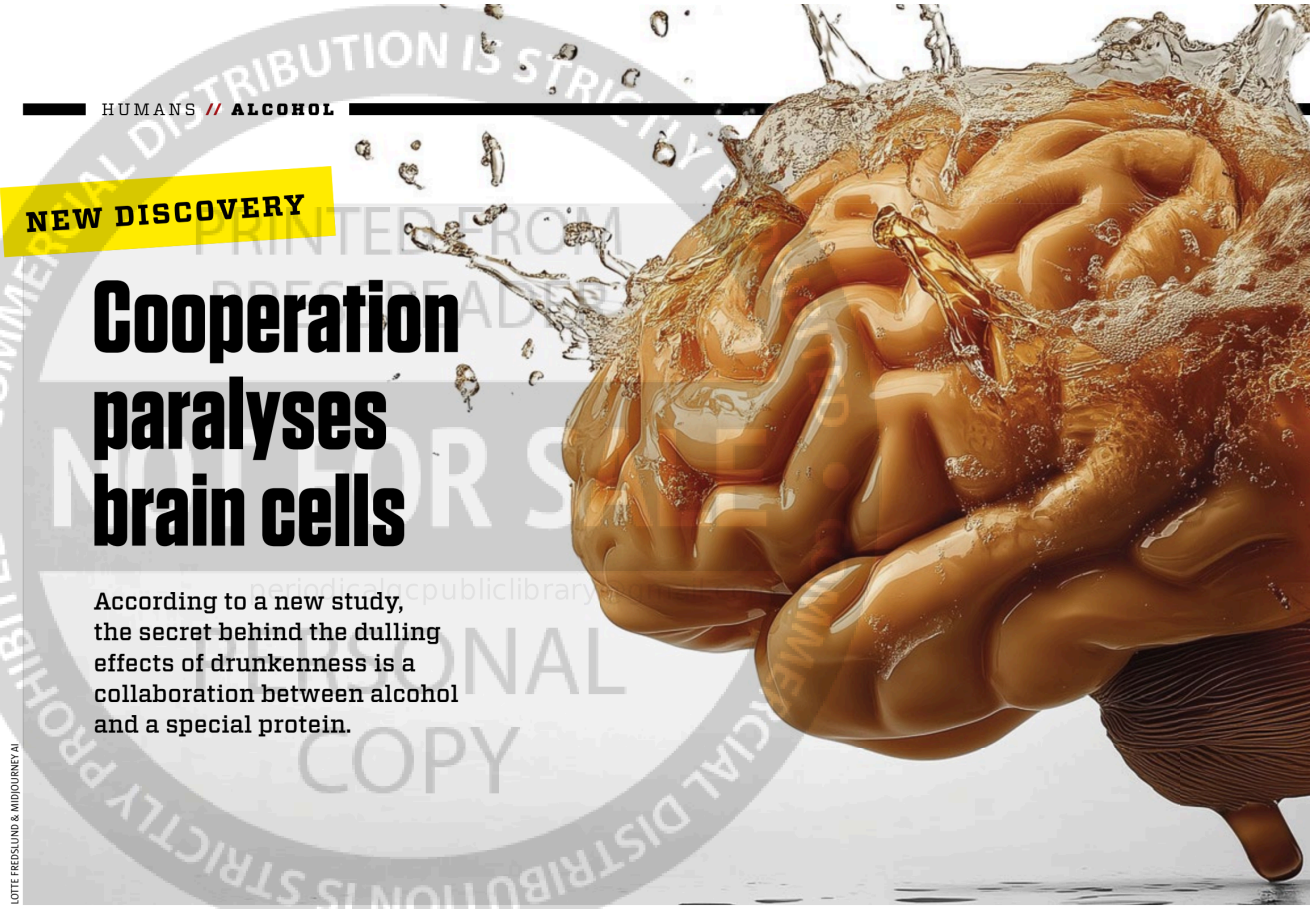
1 Alcohol (green) can be absorbed in several places of the alimentary tract, but most is absorbed through cells in the small intestine (brown). If you have just eaten, the alcohol takes longer to reach the small intestine so is absorbed more slowly.

The brain's defences fail

2 Alcohol reaches the brain via the bloodstream. Normally, alien substances cannot pass from blood vessels into brain cells (brown), but the chemical properties of alcohol allow it to pass freely, reaching the brain cells to influence them.

Liver enzymes clean up the mess

3 Enzymes in the liver (blue) continuously break down the alcohol passing through. One breakdown product, ethanal (red), contributes to nausea and other hangover symptoms, but it is later broken down into water and carbon dioxide.



LOTTE FREDSLUND & MIDJOURNEY AI

NEW DISCOVERY

Cooperation paralyses brain cells

According to a new study, the secret behind the dulling effects of drunkenness is a collaboration between alcohol and a special protein.

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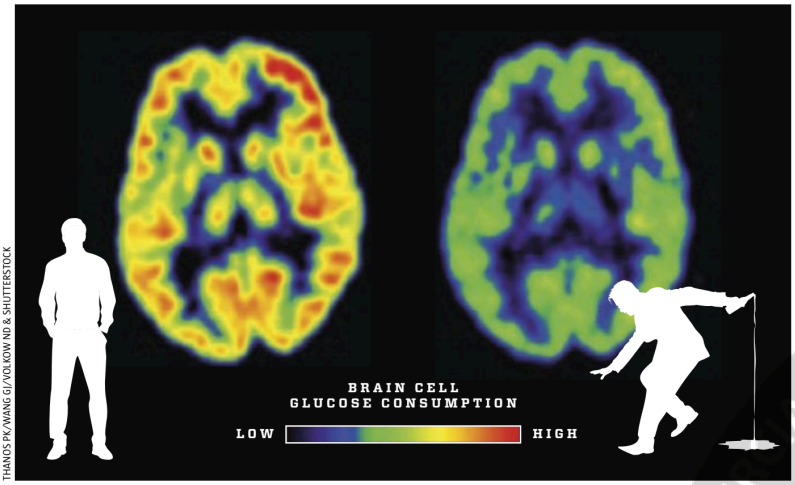
▶ cells actually consume less energy. The switch to acetate is not really a problem for the brain, but the decrease in energy consumption is key to understanding many of the different effects of alcohol.

Energy consumption decreases because alcohol inhibits nerve signals in certain parts of the brain, resulting in impaired thinking, coordination, and memory loss – just the phenomena that many people are probably familiar with. Studies have suggested that this reduction in brain activity is primarily due to alcohol somehow activating $GABA_A$ receptors located on the surface of many nerve cells throughout the brain; these can switch off nerve signals. But exactly how it happens has remained a mystery.



THANOS PK/WANG GJ/VOLKOW ND & SHUTTERSTOCK

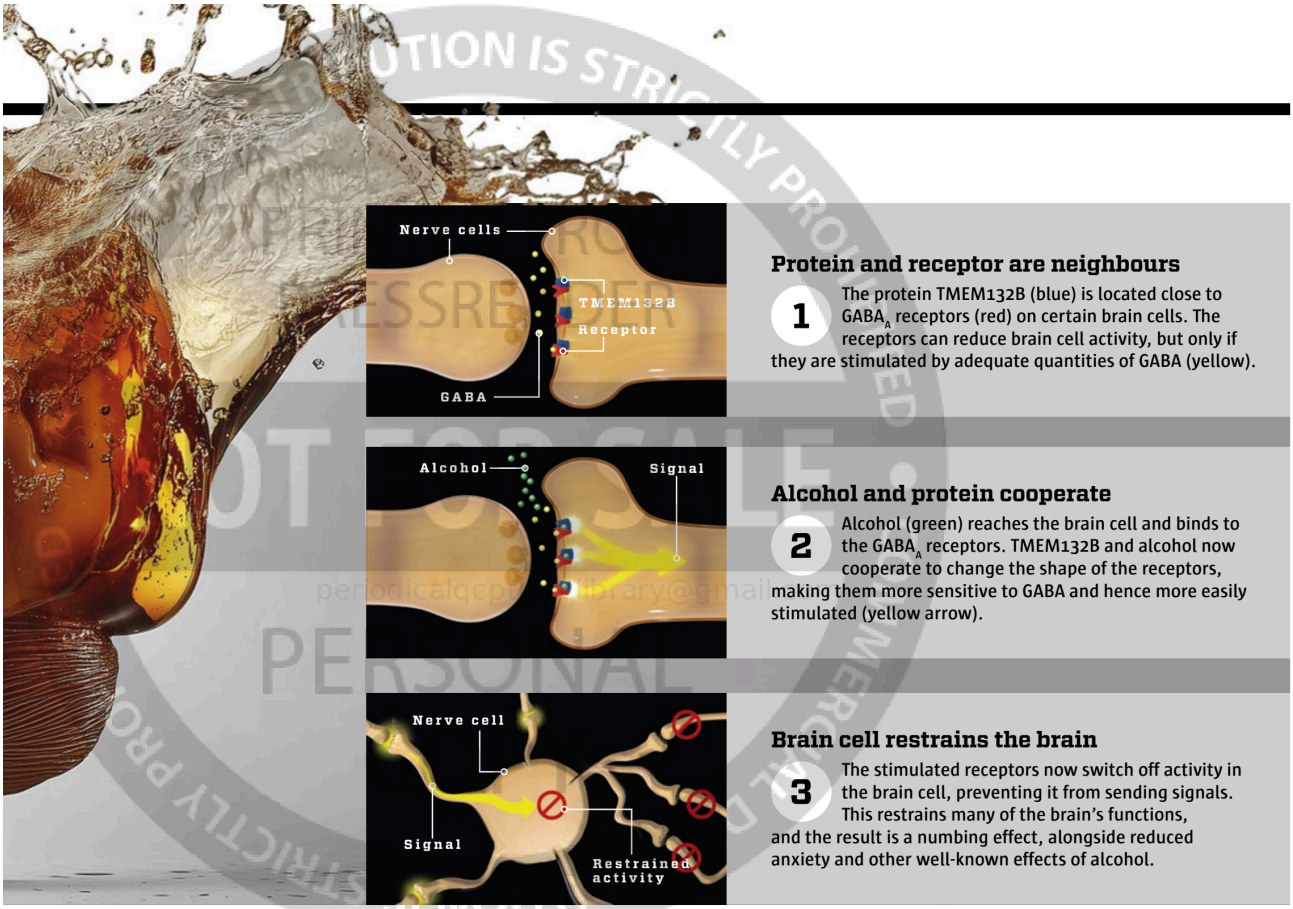
A sober brain (left) shows a high consumption (red and yellow) of glucose. But once we get intoxicated (right), the brain's consumption drops to a significantly lower level (blue and green).

Protein the key to being drunk

A group of brain researchers led by Wei Lu from the National Institute of Neurological Disorders and Stroke in Maryland, USA, approached the problem from an innovative angle. Dr Lu's research at NINDS centres on synaptic plasticity and GABA-based signalling, which turn out to be highly relevant to how alcohol affects the brain. To discover exactly how, they looked for differences between brains of alcoholic and non-alcoholic people.

They used brains from people who had died, both alcoholics and non-alcoholics, and looked for differences in the proteins on the surface of the brain cells. And they found them.

The researchers became particularly interested in a protein called TMEM132B, the function of which had never been studied before. They found that levels of this protein were much lower in alcoholics. When the researchers examined the protein more closely, they discovered that



SHUTTERSTOCK & LOTTE FREDSLUND

it attached to the GABA$_A$ receptors which restrain the brain's nerve cells. Further analysis showed that TMEM132B actually helps alcohol activate the receptors.

To be absolutely certain that their conclusion was correct, the researchers took an additional step, creating modified mice that completely lacked the protein TMEM132B. The mice, together with a control group, were given alcohol and then subjected to tests designed to create anxiety-like behaviour or sedative effects. The results showed that, like humans, the normal mice became significantly less anxious under the influence of alcohol. But the genetically-modified mice behaved as if they had been drinking water.

2.6

million deaths are caused annually by alcohol, according to the World Health Organisation.

With the sedative tests, again alcohol also had a consistent anaesthetic effect on normal mive, but again not with the genetically-modified mice. Some of them did experience slight sedation, but others remained unaffected.

In other words, the researchers had created mice that could not get drunk, confirming that TMEM132B plays a key role in the common effects of alcohol.

New possibilities

The new insight does not mean that we now know everything about alcohol and the brain. Nor are we likely to learn how to remove TMEM132B from our systems and so enjoy a drinking session with no ill effects: there would be little point, as you would lose the beneficial effects also.

Besides, ethanol affects many other mechanisms in brain cells, and it remains unclear what significance each of these might have. But the breakthrough does help us better understand the effects of alcohol on our minds.

When we consume alcohol, ethanol enters the brain and reduces brain cell activity, together with TMEM132B. Signalling is dampened in areas such as the cerebral cortex, the fear centre (amygdala), and memory centre (hippocampus), slowing thoughts and coordination, reducing anxiety, and shutting down memory.

At the same time, alcohol appears to dampen signals that would otherwise keep the brain's reward system in check. In this way, alcohol boosts mood.

But in people with alcohol abuse, the brain reacts in a completely different way, and the new study indicates that this can largely be explained by the fact that frequent alcohol consumption reduces the brain's production of TMEM132B.

These new insights into how alcohol changes our brains over time could pave the way for new treatments to help people with alcohol abuse. And with more than 5.2 million Australian adults — over 25% of all people aged 18 and over — estimated to exceed alcohol guidelines, it's something to think about next time you are offered a glass of ethanol. SI

Overleaf: 6 MYTHS ABOUT ALCOHOL ▶

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