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Feature

What coffee does to body and mind

The coffee plant evolved the use of caffeine as a chemical defence against herbivores, with the added benefit of manipulating the memory of pollinating bees. The collateral effect was that much of the human population ended up using its seeds to make a complex concoction that may have up to 1,000 molecular ingredients, affecting us in many ways yet to be fully explored. **Michael Gross** reports.

Johann Sebastian Bach never wrote an opera, simply because his employers had no use for one and kept him busy with other things. An intriguing glimpse at what the world missed is afforded by the secular cantata *Schweigt stille, plaudert nicht* (BWV 211), a half-hour mini-opera about a young woman addicted to coffee and her father trying to persuade her to quit. Bach is thought to have composed the work known as the 'coffee cantata' on the words of Picander in the 1730s, when he was the St Thomas Cantor at Leipzig and conducted an orchestra at the Café Zimmermann as a sideline.

It dates from a time when coffee was a new-fangled fashion craze gradually spreading across Europe. From myth-shrouded origins in the kingdom of Sheba, today's Yemen or Ethiopia, the culture of making and drinking coffee expanded across the Arabian Peninsula and into the Ottoman Empire, reaching its capital, Istanbul, in 1554. After the Ottoman advance into Europe was stopped just outside Vienna in 1683, the victorious Austrians confiscated the coffee supplies of the fleeing Turks and used them to launch their legendary coffee-house culture, which spread across Europe. An independent early entry route was provided by Venetian traders.

From the beginnings of this spread there had been attempts by religious leaders, in both Islamic and Christian societies, to ban coffee, as they found its powerful stimulating effect suspicious. Thus, the lively conflict in Bach's coffee cantata reflected a very real debate that must have taken place many times between lovers of the dark brew and authorities suspicious of its effects.

Back in Bach's time, science didn't have much to say about the issue, but by now we are beginning to get a clearer picture of what coffee does to us and why.

How *Coffea* got its caffeine

Various myths surrounding the origins of coffee involve animals such as goats snacking on the berries of the coffee plant (*Coffea canephora*) and then getting conspicuously animated. As human observers found the berries bitter and unpalatable, they tried roasting and boiling them, and accidentally developed the first protocol for brewing coffee. Even if this is not how it happened, the stories suggest that we are not the only animals responding to caffeine. The fact that the ability to produce this powerful psychoactive compound evolved independently in several separate plant lineages, including the plants we use for making tea (*Camellia sinensis*) and chocolate (*Theobroma cacao*), and even in *Citrus* trees, suggests an important ecological role, which could be connected to herbivore defence in cases like tea leaves and coffee beans or in attracting pollinators when it occurs in flowers, as it does in *Coffea* and *Citrus* plants.

The group of Geraldine Wright, then at the University of Newcastle, UK, showed that the small concentrations of caffeine present in *Citrus* flowers, while too low to be detected by bees' taste receptors, affected their memory and made it more likely that they remembered the caffeine-laced flowers (Science (2013) *339*, 1202–1204). If caffeine is present in doses above the taste threshold, however, the bees are repelled by the bitter taste. Wright, who has since moved to the University of Oxford, UK, is continuing to investigate the neuroanatomical and molecular details of the effect in bees. At the molecular level, the effects of caffeine are known to be due to blockage of the adenosine receptor — as it is also a purine, caffeine is structurally similar to adenine.

The presence of caffeine in the fruits is only observed in a minority of *Coffea* species, most prominently in *C. canephora*, the beans of which are traded as Robusta coffee. The Arabica variety (*Coffea arabica*) is a hybrid of *C. canephora* and *Coffea eugenioides*,

Bee memories: *Coffea* and *Citrus* flowers contain low doses of caffeine, imperceptible to bees but proven to manipulate their memory. (Photo: Forest and Kim Starr/Flickr (CC BY 2.0).)

Best beans: Roasting beans is a crucial step in producing the complex mixture of flavours found in coffee. (Photo: Alexas_Fotos/Pixabay.)

which has a lower caffeine content and a less bitter taste.

Tongue to stomach

Our encounter with coffee's complexities starts with the rich smell, followed by the taste on the tongue. Both will depend on the conditions of preparation, but a crucial parameter is the bitter taste note. Although caffeine itself is bitter, a recent systematic investigation of taste receptors and coffee compounds has revealed a much more complex picture.

The group of Maik Behrens at the Leibniz Institute for Food Systems Biology at Freising, Germany, has systematically tested the response of 25 human receptors for bitter taste (TAS2R) in response to five bitter-tasting substances found in coffee (J. Agric. Food Chem. (2020) *68*, 6692–6700). Like other taste and smell receptors, the ones in the TAS2R family are also G-protein-coupled receptors embedded in the membrane, which essentially respond to the docking of a suitable molecule on their binding site on the outside of the membrane by causing the release of a calcium signal on the inside.

The Freising research group had developed an 'artificial tongue' with each of these receptors expressed by a cell line derived from human embryonic kidney cells. Using standard fluorescence imaging methods, they measured the calcium response to the arrival of coffee substances at the receptor-carrying cells. They identified two main receptors responsible for the bitter taste reception of coffee, namely TAS2R46 and TAS2R43.

These receptors duly responded to the bitter taste of caffeine, as well as to that of the diterpenoid compounds kahweol and cafestol. Two other compounds caused much stronger responses, however. Mozambioside, a furokauran glycoside found in the fresh seeds of Arabica coffee and partially lost in roasting, triggered the response 30 times more efficiently than caffeine. And bengalensol, a compound produced from mozambioside during roasting, was even 300 times more efficient.

The authors also found that kahweol, although its taste response is weak, has a strong affinity for the bitter receptor TAS2R43. They therefore suspect that, in a real-world situation with all these compounds mingling on the tongue of a coffee consumer, the kahweol may be reducing bitterness by blocking access to the receptor for competing molecules that would be much more effective agonists.

Such interactions aren't limited to the tongue, as these receptors are also found in other organs, including the stomach. TAS2R43 is known to be involved in gastric acid control in the stomach, but whether or not coffee consumption interferes with this role remains to be established.

A matter of the heart

Coffee once had a reputation of inducing low-key damage to the drinker's health. Based on the stimulating effect on heart rate and blood pressure, the basic assumption was that it must be bad for the heart. In 1991, the World Health Organisation even included it in the list of food items suspected of causing cancer.

This suspected association turned out to be a textbook case of not controlling for confounding factors. As Amanda Vest from Tufts Medical Center in Boston, USA, recalls in a recent perspective piece (on the paper discussed below), the effect arose because coffee drinkers were more likely to smoke than people who didn't drink any coffee (Circ. Heart Fail. (2021) *14*, e008297). Once researchers controlled for smoking status, the cancer risk disappeared.

Whether a coffee habit is good or bad for heart health remains to be decided, but recent studies have tended to swing towards a beneficial effect of two or three cups of coffee a day, typically delivering on the order of 300 mg of caffeine. The group of David Kao at the University of Colorado at Aurora, USA, has contributed to the good news for coffee drinkers with a major analysis applying machine learning to discover correlations in three long-term health datasets covering more than 20,000 individuals (Circ. Heart Fail. (2021) *14*, e006799).

Using a hypothesis-free approach, the researchers discovered that the consumption of two or three cups of regular coffee (at 8 oz or 240 ml each) was associated with a reduced risk of heart failure. Intriguingly, this correlation did not occur in those who consumed decaffeinated coffee.

While the study has the bulk to establish statistically significant correlations, these aren't proof of causation, as Vest warns in her perspective piece. Specifically, selection bias can be a problem in such observational studies, she warns, as "it is entirely plausible that a healthy-user bias exists, whereby individuals without baseline cardiovascular concerns consume more coffee than those already experiencing precursors of heart disease". Even the fundamental information of how much coffee a person consumes can become skewed

by misperceptions or different habits in different groups of people. With a drink so deeply ingrained in many people's lives, it would be very difficult to conduct meaningful clinical trials on timescales relevant to heart health, and given the known effects of caffeine it may be impossible to run blind studies.

Thus, observational studies and correlations are likely to remain the main source of information on heart health, and most of these are now fairly reassuring reading for coffee aficionados. Beneficial correlations also chime with the known effects of antioxidants, as coffee is known to contain phenolic and polyphenolic compounds that fall into this group.

Heart warming: Moderate consumption of coffee has a multitude of effects on the heart and circulation, and these are difficult to establish but no longer considered detrimental to health. (Photo: StockSnap/Pixabay.)

Brain and mind

While any long-term effects of coffee on our physiology are difficult to prove or discount, the short-term stimulating effect on the brain and mind is easy to study. There is an abundance of studies demonstrating the influence of caffeine on attention, memory and every other brain function.

A surprising effect came to light, however, when researchers wanted to establish if caffeine harms the brain by impeding sleep. Carolin Reichert and Christian Cajochen from the University of Basel, Switzerland, conducted a small placebo-controlled clinical study of the effect of caffeine on sleep and brain structures (Cereb. Cortex (2021) bhab005). Participants were habitual coffee drinkers who had their daily brew replaced by either caffeine tablets or a placebo.

While the researchers could find no significant difference in sleep, the placebo group displayed an increase in the volume of grey matter in specific areas of the brain, including the medial temporal lobe and the hippocampus, which is associated with memory functions. From their observations, the researchers conclude that daily exposure to caffeine may cause the grey matter to shrink but that this change is reversible when the caffeine is withdrawn.

Whether or not this apparent shrinkage is causing any harm remains to be established. As with the questions surrounding long-term health effects on the heart and circulation, it is a challenge to establish any causal relations. It is conceivable that the short-term effects we know and appreciate are linked to longer term changes, but this is difficult to prove.

The short-term stimulating effect, on the other hand, is now so deeply ingrained into the psyche of the billions of users that it can be triggered by the mere thought of coffee. The psychologists Eugene Chan and Sam Maglio at Monash University, Australia, and the University of Toronto, Canada, respectively, showed that evoking thoughts associated with coffee led to a stimulation effect, which they measured quantitatively based on parameters such as participants estimating time intervals to be shorter and using more concrete and precise concepts (Conscious. Cogn. (2019) *70*, 57–69). By contrast, the thought of tea did not trigger this effect.

When we do actually consume our coffee instead of just thinking of it, we enjoy a multimodal experience influenced by many more factors than just the flavours and the stimulating effect of the caffeine. Charles Spence from the University of Oxford, UK, has reviewed the accumulating evidence showing how the sensory experience of coffee can be influenced by the surroundings (Front. Comp. Sci. (2021) doi: 10.3389/fcomp.2021.644054). Experimental paradigms for such assessments include the ranking on a bitter–sweet scale as well as psychological quantifiers, such as the willingness to pay for a drink. These measurable responses are influenced by visual impressions, including the looks of the cups and machinery used in preparation and the sounds of coffee preparation and consumption.

Even ambient music has been shown to affect the perception of coffee taste, with low-pitch notes being more likely to reinforce or highlight bitter tastes, while high-pitch notes reinforce sweetness. Conceivably, this crossmodal interference may be a question of directing our attention one way or another — faced with a complex concoction of bitter and sweet impressions, we may be paying more attention to the sweet ones when we hear sweet music.

Johann Sebastian Bach likely conducted performances of his coffee cantata at the Café Zimmermann, although, sadly, no report or review of such an event has survived. The audience will have enjoyed their coffee while listening to the cantata, and they may just have found it sweeter when the soprano enthused about its sweet taste and more bitter when the bass grumbled about his daughter's disobedience. Intuitively, Bach may already have grasped the multimodal complexities of drinking coffee.

Michael Gross is a science writer based at Oxford. He can be contacted via his web page at www.michaelgross.co.uk