A penny for your partner's thoughts

What does it take to know that we think?

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The methods of Artificial Intelligence have created a mechanised view of the process of thought, but there are features that mark AI as clearly "artificial". One of the questions raised is, even if we consider that a computer is thinking, can we say the computer knows it is thinking? And extending the question, are animals aware of thought, like humans are?

Katherine McAuliffe, Lindsey A Drayton, Amanda Royka, Mélisande Aellen, Laurie R Santos and Redouan Bshary, at Boston College, Massachusetts, Yale University and the University of Neuchâtel, Switzerland, describe in the journal, *Nature Communications Biology*, a study of a species of fish that fashions its actions based on what her partner may be thinking. Such ability has been considered restricted to humans and some human-like primates. "Much of human experience is informed by our ability to attribute mental states to others," says the paper. The capacity has been seen in primates, mainly, but could there be situations where something akin appears in other kinds of animals?

The paper says most studies in non-human primates are with the help of competitive, food seeking situations. The paper cites a previous study where rhesus monkeys consider whether a competitor can or cannot see them when trying to steal food — they reach for the food more readily if the face of the competitor is covered, compared to when the competitor's body alone is hidden.

Similarly, with chimpanzees in a dominant-subordinate relationship, the subordinate animal prefers to take food that is hidden behind a barrier, over food that is in front of the barrier. "Non-human primates can also track what a competitor has seen in the recent past and can strategically conceal visual and auditory information in an attempt to deceive their rivals," says the paper. And, that while the mechanisms are not understood, it looks like the animals share with humans the ability to form an image of what others see and know.

The evidence collected so far is of primates, and some animals with comparable brain-size-to-body ratio, like corvids. But, is it the large brain that helps this behaviour arise? Could there be circumstances which enable the capacity to evolve in other species? The authors find that the answer is in the affirmative — they describe the behaviour of a small fish, the blue streak cleaner wrasse, just 10-14 centimetres long, found in many coral reefs, which appears to take into account what her male partner could be thinking, while planning her own strategy in a highly characteristic form of behaviour.

The cleaner wrasse is so called because the fish feed on parasites and dead tissue on the bodies and in the mouth and gills of larger fish, in a kind of symbiotic relationship. The larger fish get the service of being cleaned, while the smaller ones find food, and protection. While finding food in this way, however, wrasse, which often work in pairs, also take a nibble at the living tissue of the client fish, or a bit of mucus. When this happens, the client fish considers the bargain violated and swims away.

Over a decade ago, co-author Bshary and others at Neuchâtel had studied the co-operative behaviour of pairs of wrasses, in their foraging. In the further study, now published, the authors discover features that show that wrasses must think, and be aware of what their partners know, while they regulate the way they feed.

As we have said, the wrasse, sooner or later, takes a bite of living tissue, and this is the end of the feeding session. But, how long do the fish restrain themselves? It had been noted that this was like picking apples in an orchard. One way is to take a few apples from each tree and move on to the next. This has the advantage of getting the lowest hanging fruit but has the cost of having to move frequently to the next tree. On the other hand, if we picked more fruit from the same tree, we would save the need to move, but we would need to reach higher after the first few fruits. The best way would be somewhere in between. Wrasse, too, find it progressively more difficult to find flakes as they start feeding. And at some stage, taking a bite of living tissue is worth the loss of the feeding station.

Things become a little different when a pair of wrasses are cleaning a client fish. The moment one of the pair takes a bite of living tissue, the feeding stops for both. There is hence an incentive for each of the wrasse to be the first to take that bite. Except that, if one fish kept being the first one, the partner would feel deprived of feeding, with no pleasure of living tissue, and may decide to terminate the union. This, it was found, led to pairs of wrasses staying on for longer than when there was only a single wrasse, and it was found that the female was more often the one that showed greater patience.

The current study has gone one further. It finds that when the female of the pair goes first for the forbidden nip, the male does not just feel resentful and think of breaking the partnership. Being the larger built of the couple, the male pursues the female and gives her a bite, as punishment. This behaviour may be what drives the female to forebear, and the reason that the female is less frequently the partner who causes the client to depart.

But what does this have to do with knowing what one's partner is thinking? Well, the female knows that she is in for it if she is caught taking an early bite of living tissue. The authors of the paper arranged for screens to be placed so that the female got an opportunity for a go at a model of the client either in view of her partner or when she was concealed. And the result of the trials was that when the male saw the female biting the client he went after her to chastise her. But if the client left and the male cleaner had seen nothing, well, he was not likely to think the female needed instruction.

The trials also revealed that the female was more inclined to nick the client when she was hidden, than when in sight. And further, that the behaviour was more pronounced when the male was the one who believed in more severe punishment. Arrangements were also made to keep the male in sight of the female or concealed. And it was seen that she displayed more vigorous cleaning of dead tissue when the male was watching! And even that she sought to be visible when she was cleaning dead tissue, to show that her behaviour was co-operative, as opposed to competitive.

The study hence shows that the blue streak cleaner wrasse is sensitive to what her partner may be thinking, and then acts deceptively, to condition his thinking. And more significantly, that a species like fish, which is genetically far removed from humans, as opposed to primates who are closely related to us, can display this ability!

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PLUS POINTS

Marked by coherence

The brain's "storytelling station" has been identified by scientists in a discovery that could lead to earlier treatment of dementia. It lies in the hippocampus — an area that controls memory where neurons link separate distant events into a single narrative.

First author Brendan Cohn-Sheehy, a PhD student at California University in Davis, United States said, "Things that happen in real life don't always connect directly. But we can remember the details of each event better if they form a coherent narrative."

Volunteers underwent magnetic resonance imaging, or MRI, as they learned and recalled a series of short stories. They featured main and side characters and an event — and were created specifically for the study. The stories were constructed in a way that some formed connected, two-parters and others did not.

Participants were in the scanner as recordings were played to them — and next day as they were asked to remember them. And the patterns of activity in the hippocampus were similar for learning pieces of a coherent story than for those that did not connect.

The results published in the journal *Current Biology* showed the coherent memories being woven together. Cohn-Sheehy said, "When you get to the second event, you're reaching back to the first event and embedding part of it in the new memory."

When recalling stories that formed a coherent narrative, the hippocampus triggered more information about the second event than when remembering non-connected stories.

Further tests found the ability to bring back hippocampal activity of the second event was linked to the amount of detail the volunteers could recall. Other parts of the brain are also involved in the process of memory. But the hippocampus appears to bring pieces together across time and form them into connected narrative memories.

Cohn-Sheehy said that it could lead to better clinical tests for early stages of memory decline in ageing or Alzheimer's. Potential dementia drugs have a high failure rate because they are prescribed to trial participants once the disease has taken hold.

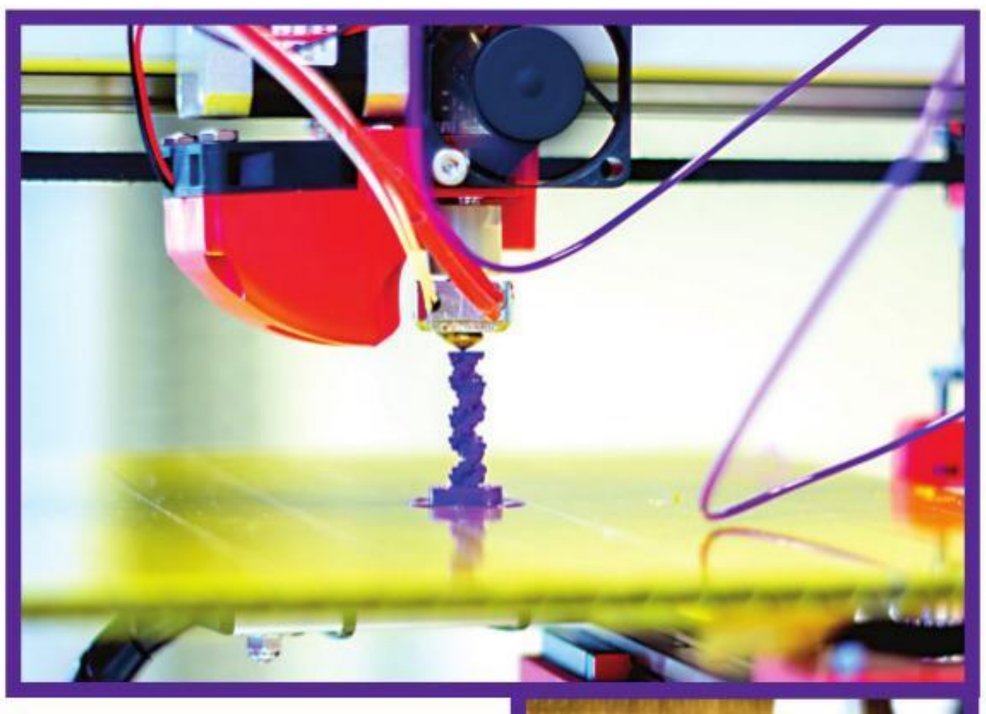
The findings also open the door to more efficient assessments of damage to memory from brain injuries.

— The independent

THE FUTURE IS BESPOKE

Three-dimensional printing is a game-changing technology for drug manufacture

JIN DING



Early this year, a drug manufactured through three-dimensional printing, or 3DP, was approved for its "investigational new drug" application by the United States Food and Drug Administration. The drug is named T19, which is indicated for the treatment of rheumatoid arthritis. T19 has been developed by Triastek, a Chinese pharmaceutical company specialising in 3DP technology.

The "melt extrusion deposition" technique, which deposits molten powder layer by layer, is used to fabricate drugs with special shapes and complex internal geometric structures. This technique enables the drug delivery system to precisely control the release of the drug according to the circadian cycle. Via the chronotherapeutic drug delivery system, "melt extrusion deposition" can maximise a drug's therapeutic effects and minimise side effects. T19 is expected to become the second USFDA approved 3D-printed drug in 2023.

The first 3D-printed drug, Spritam, developed to treat seizures in people with epilepsy, was approved by the USFDA in 2015. Manufactured by Aprecia, a U S pharmaceutical company, Spritam is fabricated with a proprietary 3D manufacturing process called "zipdose". It is a binder-jetting technology, by which the printer repeatedly deposits tiny droplets on the powder bed to bind powders together at a microscopic level. The unique process allows the delivery of high drug strengths and the porous structure enables the drug to dissolve instantly in the mouth. The tablets made by "zipdose" fulfil the unmet medical needs of people with high pill burdens and swallowing difficulties.

Recent regulatory successes in 3D-printed drugs have ushered in a new era for pharmaceutical manufacturing.

Breakthrough technique

Currently, most drugs are made by batch processing, in which the ultimate finished product is made through a stepwise process in a large batch. Tablets are formed by compressing the granules of active ingredients and excipients. This process hasn't changed much for a hundred years, and conventional facilities have many limitations, such as manufacturing drugs in small quantities.

3DP is a novel technique for rapid prototyping, which fabricates objects by depositing materials layer by layer. It is cost-efficient, providing a big advantage for small-scale production of highly complex drugs.

The advantages of 3DP in pharmaceutical manufacturing can be structured into five categories,

- **Customised:** emphasises on the customers' perceived value with the ability to produce customised objects
- **Complex:** realises complex geometries and release profiles
- **Low-cost:** refers to the lower production process costs in producing objects with low throughput and high complexity compared with conventional manufacturing techniques
- **Flexible:** allows for manufacturing on-demand precision tailored tablets including different shape, dosage, release form and combination of active pharmaceutical ingredients
- **Eco-sustainable:** refers to the reduction in waste and energy consumption

There are a variety of 3DP technologies but binder-jetting, fused filament fabrication, stereolithography, selective laser sintering, and material jetting are mainly used for drug manufacturing. These processes are featured with different formulation ingredients, printing speeds and resolutions. For instance, selective laser sintering is characterised by high resolution but low printing speed, while binder-jetting is characterised by fast printing speed but low resolution.

Personalised medicines

Across the last few decades, the pharmaceutical industry has been facing enormous challenges. The blockbuster model, by which drug companies have annual sales of over $ (United States) one billion by selling one drug, has run out of steam. The blockbuster drugs commonly target common medical problems like high cholesterol, high blood pressure, diabetes and cancer.

The rapid advance of new diagnostic and informatics approaches provide a far better understanding of the molecular basis of disease, which leads to drug development targeted far more directly at a much smaller number of patients. Personalised medicine is developed dependent on an individual's age, weight, concomitants, pharmacokinetics, and pharmacokinetic profile.

Unlike conventional drug therapies typically targeting a large patient group and considering patients are relatively homogeneous, personalised drugs fit therapy with the best response and lowest side effects to ensure better patient care. Moreover, due to the regulatory priority and market exclusivity, the emerging market focusing on specialised medicines has become ever more important for the industry.

One of the pioneering advantages of 3DP is the freedom of customised fabrication of drugs in a small batch. And the market has witnessed the success of these products. For example, although the patient population of epilepsy is large (more than 50 million), Spritam is especially targeted at the sub-patient group with swallowing difficulties. Hence, it falls into the category of a customised drug targeting the special needs of a small number of patients in a large patient group.

A long way to go

The application of 3DP in the pharmaceutical industry is still in its infancy. The industry has only captured a fraction of the potential of 3DP, but the recent approvals of 3D-printed drugs will boost its adoption in pharmaceutical manufacturing. There is an increasing number of 3D-printed drug candidates in the research and development pipeline. However, 3DP is not going to replace conventional batch manufacturing. The indications with a smaller number of patients, like orphan drugs, have the most commercial viability in the short term. To overcome the challenges and allow the technology to fully unleash its therapeutic potential, significant improvements need to be done.

The "one size fits all" drugs have been used for decades, but the future of medication will focus on customisation which fits medical treatment to the individual characteristics of each patient. There is still a long way to go to achieve the widespread benefits of 3D-printed drugs, but it will influence the entire landscape of the healthcare system in the long-term future.

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Heavy-duty launch

China is expected to launch its next generation of heavy-duty rockets in 2028 powerful enough to send a crewed spacecraft to the Moon, the country's main space contractor said recently.

The new heavy-lift launch vehicle would be capable of putting a 15- to 50-tonne spacecraft on a trajectory to the Moon, said Liu Bing, deputy designer at the China Aerospace Science and Technology. It would also be powerful enough to place a probe weighing 12 to 44 tonnes on a trajectory to Mars, Liu told reporters at a major airshow in the southern city of Zhuhai, without naming the rocket.

The country previously predicted it would complete the design and construction of a rocket with enough thrust to transport its astronauts to the Moon only by 2030.

China has been developing the super-heavy Long March 9 rocket with a lift-off weight of 4,140 tonnes and a thrust of 5,760 tonnes, state media reported in May this year. That compares with the take-off mass of the Long March 5 — currently China's biggest rocket — of about 849 tonnes and thrust of about 1,078 tonnes.

China completed the no-crew Chang'e-5 mission (*in photo*), named after the mythical Chinese goddess of the Moon, to retrieve samples from the lunar surface in December last year.

—The straits times/ann