Malaria and the sniffer dog

The legendary nose of man's best friend may find a place in the pathologist's lab

S ANANTHANARAYANAN

Malaria is considered to be the leading parasitic cause of morbidity and mortality worldwide. Despite nearly full eradication in many parts of the world, the WHO's latest World Malaria Report, says, "There were an estimated 216 million cases of malaria in 2016, an increase of five million cases over the previous year. Deaths stood at approximately 445,000, a similar number to the previous year".

While there are large scale programmes to control the disease, an important part of the drive is detection of malaria, both for treatment as well as for prevention of spread. The usual method of detection, however, is to take blood samples, which are examined in a laboratory by trained persons and a microscope. Even other methods, called "Rapid Detection Tests", which are now available, have limitations of cost and delivery at remote places.

It is in this context that Professor Steve Lindsay, department of biosciences, Durham University, UK, and his group, report that the domestic dog can be trained to detect the presence of malaria simply by sniffing the used socks of affected persons. At the annual meeting of American Society of Tropical Medicine and Hygiene, in New Orleans, US, Lindsay described his team's trials in the Upper River Region of The Gambia in West Africa, where dogs had been trained to detect the presence or absence of malaria in schoolchildren with 70 to 90 per cent accuracy.

What the finding underlines is that malaria infection leads to the release of odours, which can be detected. Giving off traces of molecules and the ability to detect them, have formed the means of communication in many parts of the natural world. That mite-sized insects can detect mating signals over distances of several kilometres is well known. While birds are known to announce readiness to mate through plumage and behaviour, in most of the animal world, the signal is one based on smell.

Other evidence has also been reported of the malaria parasite signalling its presence. Xiunan Wang and Xiao-Qiang Zhao, from University of Newfoundland, St John's, Canada, had reported a tendency of mosquitoes to prefer malaria-affected persons to source their blood meal. This was apparently the result of an adaptation of the parasite to ensure its best proliferation. As malaria affects the red blood corpuscles, blood of infected persons is easier to feed on. The mosquito appears to find it rewarding to choose malaria-infected persons and feeding time in these cases is found to be significantly reduced.

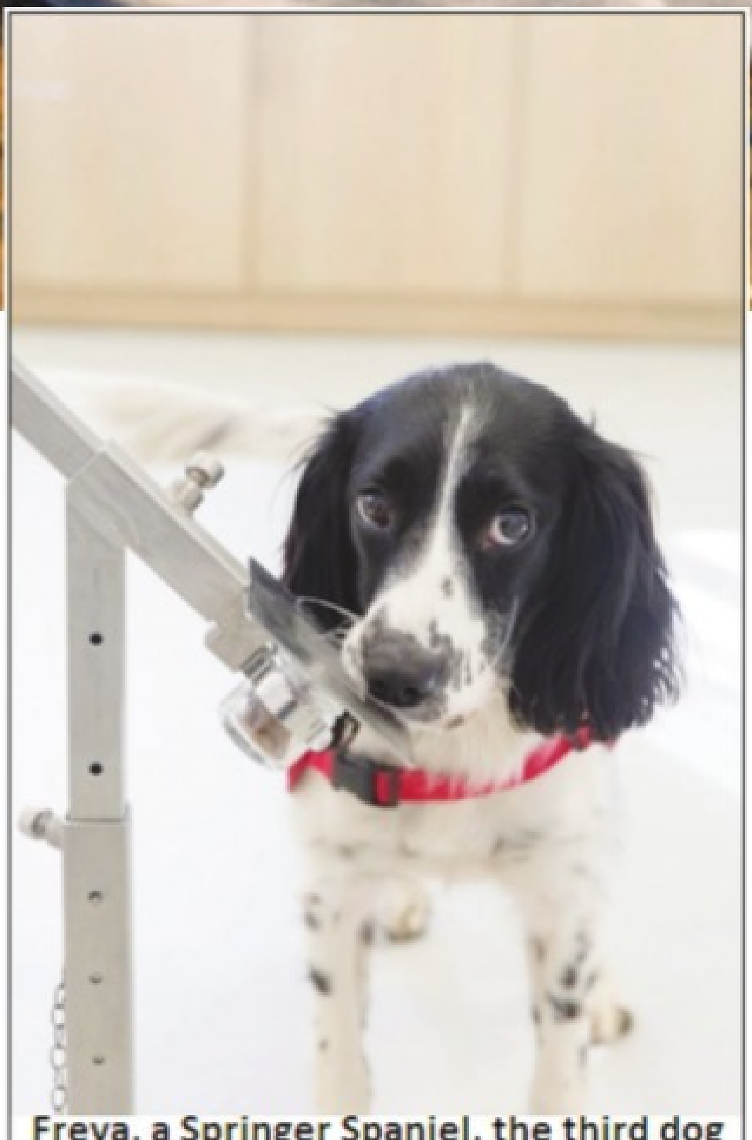
While the study of Wang and Zhao was about the factors, including ambient temperature and the frequency of mosquito bites that affect transmission dynamics, it was observed that the mechanics of how mosquitoes select where they will feed could be a means of malaria control. The mechanism is clearly olfactory, in the sense that the malaria parasite induces an odour, which can be detected by the mosquito, to emanate from the parasite's host.

While the mosquito has clearly adapted to be able to detect the odour and benefit from a meal of malaria-infected blood, the Durham University group experimented with our best known master of following scents to see if it could sniff out a case of malaria. Even the human nose is impressive in its ability to differentiate smells — it is said that we can tell apart a trillion different smells. But unlike humans, whose senses, and intelligence, have evolved beyond the sense of smell, in most animals, smell is an important part of sensing the environment.

The nasal cavity of the dog consists of membrane that is packed with folds and its surface area is about that of a human palm, some fifty times greater than the area in the human nose, which is about the size of a thumbprint. With tens of millions of more nerve endings than humans have, and an area in the brain dedicated to smell, forty times that of humans', the dog's nose is said to be a hundred thousand times more sensitive. Police dogs and tracking dogs pick up scents of individual persons days after they have been at a place. As any dog owner would tell you, a dog never ceases to amaze by responding to known persons long before they come into view or earshot. It is clear that the dog can detect and differentiate vapours or molecules in the air even at vanishingly small concentrations.

The method used to train dogs is to repeatedly expose them to mixed stimuli, with reward when they react to selected stimuli. A simple example is of training a dog to respond to its name, or to follow commands like, "sit", "stay" or "roll over". Seemingly more complex tasks, like responding to the smell of gunpowder, or drugs, also take only the same extent of training. Hence, the widespread use of dogs to detect contraband at airports or the entry to places of high security.

The Durham experimenters used the same methods to train a pair of dogs, a Labrador-Golden Retriever cross called Lexi and a Labrador called Sally, to distinguish between the scent of children infected with malaria parasites and those who were uninfected. The trained dogs were then tested with the scent of a group of apparently healthy children from West Africa. Nylon socks used by 175 children, 30 of whom had been found to be infected with malaria were shipped from Africa to the UK to see if the dogs could identify malaria in the foot odour carried by the socks.



Freya, a Springer Spaniel, the third dog trained to detect malaria at Durham

It was found that the dogs could correctly identify 21 of the 30 infected children and 130 of the 145 disease-free children. This is an impressive performance, for a first trial, of identifying the greatest part of the children in need of treatment and then, most of the children on whom no resources need be spent. Co-author Professor James Logan, head of the department of disease control, at the London School of Hygiene and Tropical Medicine, said, "Worryingly, our progress on the control of malaria has stalled in recent years, so we desperately need innovative new tools to help in the fight against it." Co-author Claire Guest said, "This is the first time we have trained dogs to detect a parasite infection and we are delighted by these early results", the press release says.

The writer can be contacted at response@simplescience.in

Sensed by a whisker

Here's how the brain regulates perception, as attested by tests on specially-trained rats

SHUBHODEEP CHAKRABARTI

Sensory encoding is the accurate and faithful depiction of the outside world using different sensors whereas perception is how the brain's computational machinery interprets those signals. Thus, there is a fundamental difference between sensory encoding and perception. Machines are far superior to the human eye when it comes to measuring reflected wavelengths of light within each scanned pixel. However, the visual areas of the brain can "interpret" these wavelengths as specific colours, hues and shades.

One major difference between machine sensing algorithms and the human nervous system is that the latter is not a one-way information channel. Based on experience, our brains construct expectations about the outside world. When sensory information enters the nervous system, it is compared with existing expectations and perceived accordingly. Thus, unexpected events, which can be potentially dangerous, are amplified whereas expected sensory input is reduced in amplitude.

There are several important clinical consequences of this phenomenon spanning the different sensory modalities. First, patients who cannot construct accurate expectations often experience hallucinations — for example schizophrenics report hearing voices because they cannot predict the sound of their own voices when they speak.

Second, in patients who have lesions in their nerves and therefore cannot sense accurately, the expectations are not met and this faulty sensory information is amplified resulting in chronic pain. For example, lesions in nerves used to convey touch signals often lead to painful sensations evoked by normally non-painful touch — a chronic condition known as neuropathic pain.

A recent study published in the journal *Nature Communications* by our group at the Hertie Institute of Clinical Brain Research at the University of Tübingen, shows how these expectations are matched to actual sensory experiences within the neural circuits of the rat brain and identifies one specific location where such computations are performed.

Rodents have an array of whiskers on their snouts with which they feel or sense objects around them (Figure A). Rats and mice can tell the difference between two sandpapers of different roughness by stroking the surface with their whiskers. Each whisker is a conical hair embedded inside the skin within a bundle of nerve endings (Figure B). Whenever a whisker contacts an object and it is bent, these nerve endings around the shaft are activated mechanically and lead to electrical impulses in the nerve. These electrical impulses, called action potentials (Figure B, inset), are then conveyed to the higher areas of the rat brain via three different relays at different hierarchical stages of the nervous system — one in the brainstem, one higher up in the thalamus and finally one in the cerebral cortex.

Each relay or "synapse" is a junction of two nerves and an action potential arriving at the end of one nerve excites the terminals of the other via electrochemical means. One aspect of the rodent nervous system, which makes it a great animal model to study, is its topography. Clusters of nerve cells, each responding to deflections of one particular whisker are distinct from one another allowing us to accurately target them with recording electrodes. These topographically arranged neuronal clusters form a map of the whiskers, which can be seen imprinted on the brains surface stained with specific markers (Figure C).

Sensory responses in the whisker-responsive neurons of the rodent cortex are affected by self-movement. The same neuron responds to a whisker deflection of the same intensity with fewer action potentials when the animal moves its whiskers. This is because the brain computes expectations based on its own actions. When the animal moves its whiskers to feel a novel object, the whisker nerve endings are activated merely because of the animals own movement.

However, this activity is expected by the nervous system and it seeks to suppress it so that the more interesting, unexpected activity such as that due to contact with the novel object can then be amplified and perceived. In doing so, the nervous system effectively "gain modulates" itself by dynamically adjusting its own sensitivity depending on context. If this was indeed the case, such gain modulation would most probably be under the control of the cerebral cortex, where such predictions are known to be computed — an idea that has not been tested until now.

We trained rats to touch objects by moving their whiskers, while recording the activity of single neurons using an array of fine electrodes connected to large amplifiers. Object contacts when the whiskers were in motion, indeed evoked fewer action potentials than identical contacts when the whiskers were at rest. We found this very early on in the rodent nervous system in the brainstem at the first relay or synapse.

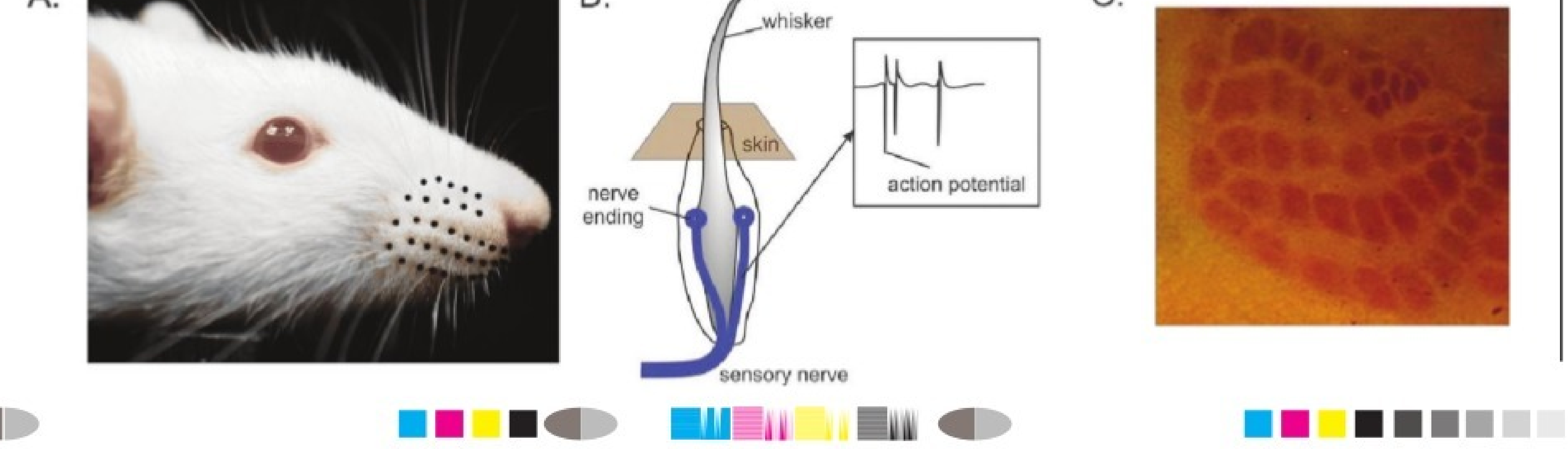
But where did this gain modulation originate? Using fluorescent dyes injected in this area we showed that these neurons received direct connections from the cerebral cortex. Could these connections be the ones mediating the gain modulation? To test this, we made big lesions in the whisker responsive area of the rodent cerebral cortex — the primary somato-sensory cortex, an area analogous to the hand representation in humans. This area is connected with movement generating regions of the brain (motor cortex) and is a possible candidate for generating expectations. Animals with lesions now showed no gain modulation at all — responses during whisker motion and rest were identical!

Our study has important implications on how we think about sensory processing. Traditionally, sensory processing has been seen as a passive process — external stimuli are encoded by nerve impulses. We show that higher brain areas like the cortex actually change how the external world is perceived by actively altering the representation of the world using direct modulation of neural activity at early synapses.

In the clinical applications mentioned earlier, the same brain area that we recorded from was shown to be involved. Schizophrenics are known to have abnormal wiring patterns in wide regions of cerebral cortex whereas in chronic pain, severing the connections of primary somato-sensory cortex to the brainstem, as we did, can suddenly abolish these painful sensations due to normal touch.

While machine sensing opens up new possibilities, it is still very far away from neural processing. Intelligent machines can only be designed when we know more about the computations occurring in the nervous system and implement those processing strategies in electronic devices. Our study is a small step in that direction.

The writer is project leader, Hertie Institute of Clinical Brain Research, Tübingen, Germany



PLUS POINTS

New species

Palaeontologists have unearthed the remains of a previously unknown species of dinosaur that lived 110 million years ago in Argentina.

The remains of three separate members of the new species — an adult and two juveniles — were discovered by a team of Spanish and Argentinian scientists at a site in Neuquen in the centre of the South American country. The new species, named *Lavocatisaurus agrioensi*, is a member of the herbivourous group of dinosaurs known as sauropods, which includes the likes of the diplodocus and brontosaurus.

Scientists said remains that belonged to the adult suggested it would have been around 12 metres in length, while both the young discovered were between six and seven metres long. "We found most of the cranial bones — the snout, the jaws, a lot of teeth, also the bones that define the eye sockets for example and, in that way, we were able to create an almost complete reconstruction," Jose Luis Carballido, a researcher at the Egidio Feruglio museum told *Agence France-Presse*, "Not only is this the discovery of a new species in an area where you wouldn't expect to find fossils, but the skull is almost complete."

Researchers who took part in the project from Zaragoza University and the National University of La Matanza said the dinosaurs likely moved around as a group and would have died together. The discovery came as a huge surprise to palaeontologists, who believe the area where the remains were found would have been a desert with scarce supply of water and limited sources of food for herbivores.

Known for their enormous size, sauropods include some of the largest animals to have ever walked the planet. Many species within the group weighed around 40 tons, while *Argentinosaurus*, thought to be the heaviest sauropod, likely weighed in excess of 80 tons.

The independent

Up for auction

From a copy of his PhD thesis to his wheelchair, several items belonging to the late British physicist Stephen Hawking are up for auction. Known for his acclaimed research on black holes, Hawking, who suffered from motor neurone disease and used an electronic voice synthesiser, died in March this year at the age of 76.

The auction titled "On the Shoulders of Giants", which also features documents penned by Isaac Newton, Charles Darwin and Albert Einstein, will feature 22 lots from Hawking's estate, including one of five known copies of his PhD thesis, "Properties of expanding universes", estimated at £100,000 to £150,000.

"Stephen Hawking was a huge personality worldwide. He had this amazing ability to connect with people," Thomas Venning, head of the books and manuscripts department at auction house Christie's London, told *Reuters*, "The whole idea... was to provide something that was accessible to his admirers so that people could connect with him and remember his extraordinary story."

Also up for sale is a copy of Hawking's best-selling book, *A Brief History Of Time*, signed with his thumbprint — estimated at between £2,000 and £3,000 — as well as awards and medals given to the scientist, priced at £10,000 to £15,000. Other documents, an invitation to a reception for "Time Travellers" as well as a motorised wheelchair Hawking used, are also being sold in the 31 October to 8 November online auction.

The auction items have already attracted interest from Asia, the US and Australia, according to Venning. "(Hawking) travelled across the world and he has fans in the US, he has fans in Asia," he said.

The straits times/ann