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The cell that makes us human

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The human mind may be special, but our brain looks much like that of any other animal. That's why the discovery of a type of neuron unique to humans and our closest relatives is causing such a stir, says Helen Phillips

JOHN ALLMAN spends a lot of time counting brain cells. He often sets out from his home turf at the California Institute of Technology in Pasadena to visit pathology labs, museums and anthropology departments around the world on the lookout for interesting brain tissue, so he can count some more. Sometimes he'll be after samples from gorillas or chimps, at other times a collection from a psychiatric hospital or from a stillborn infant. Allman practises the old-fashioned discipline of histology, and has a rare kind of patience to stare down his microscope for hours on end, often documenting tens of thousands of cells in any one brain. "Let's say it's absorbing," he admits.

In this age of brain scanners, genetic profiling and bioinformatics, Allman's absorption sounds pretty low-tech, and frankly, quite dull. What possible scientific interest could there be in counting brain cells?

His answer is surprising. He thinks he has found an important key to our humanity - an explanation for our ability to love, empathise, feel guilt or embarrassment, to understand deception and cooperation. While the definition of what makes us human may include language, our large brains and intelligence or the ability to use tools and fire, these complex social emotions set us apart from other animals too. They are judgements made not by reasoning or logic but by a type of rapid intuition which allows us to function in the most complex social environment faced by any animal. And this social intuition is special, Allman says, because, of all the traits that make us human, only these quick-fire signals seem to be carried by a recently evolved type of brain cell, unique to higher primates.

The cells that interest Allman are known as spindle cells. They were first noted by anatomists more than 100 years ago, but until recently no one had paid them much attention. Then in the late 1990s, graduate student Esther Nimchinsky, working with Patrick Hof, an expert on neurodegeneration at Mount Sinai Medical Center in New York, took an interest. She was mapping a region of the brain called the cingulate cortex - an evolutionarily ancient structure common to all mammals, which lies beneath the midline of the cerebral hemispheres. There she spotted a group of brain cells that were strikingly large, with unusually long spindle-shaped bodies. She and Hof found that the cells appeared only in the front, or anterior, part of the cingulate cortex, the ACC. While normal brains held very few of them, patients who had died of Alzheimer's disease had even fewer - only around a quarter of the usual number. With their unusual size and shape, and appearing as they often did in small clusters, these cells looked as though they might be doing something special, Nimchinsky recalls.

She subsequently found spindle cells in the same area of the brains of chimpanzees and gorillas, though not in macaque monkeys. She and Hof decided to contact Allman, an expert in primate brain evolution and anatomy. He helped them gather more brain tissue and make a huge survey of the cells in more than 50 different species - enough to be sure that the cells appeared in orang-utans but not gibbons, as well as in all the African apes: humans, gorillas, chimpanzees and bonobos. But monkeys and other primates lacked the cells, as did non-primate mammals.

In other words, only humans and our very closest relatives seem to share spindle cells. The numbers were interesting too. Orangs had just a few, humans tens of thousands. Gorillas, chimps and bonobos fell in between - the numbers seeming to reflect the animals' distance from us on the evolutionary tree.

Nimchinsky moved on, but Allman was too intrigued to let the work drop. He noticed that a handful of old anatomy studies mentioned another brain area, the orbitofrontal cortex, behind the orbits of the eyes, and along with colleagues Atiya Hakeem and Nicole Tetreault he started looking there. Within the area he found that a region named the frontoinsular, or FI, cortex was bursting with spindle cells, this time only in humans and other African apes. And that was it - the cells don't occur anywhere else. So what are these unique cells doing in just two distinct parts of the brains of only the most developed primates?

According to Christof Koch, a neuroscientist from Caltech with a particular interest in the neural basis of consciousness, there are just a few big differences that set the minds of humans apart from those of mice or monkeys: humans can talk and introspect, and they have high levels of self-awareness. "But we are hard pressed to tell the difference in the brain tissue," he says. This is what makes the spindle cells interesting. "As far as we know they are the only cell that is unique to humanoids."

Allman agrees that spindle cells might be doing something special, but what? When he began to explore what was known about these two anatomical regions and what was showing up in brain imaging studies, he realised that there might be a common theme. The anterior cingulate region has many functions: guiding attention, sensing pain and errors, and tapping into the control systems for breathing, heart rate and other internal organs. But in all these, it acts as a hub between thought, emotion and the body's response to what the brain is feeling.

Area FI also seems to have a role in emotional responses - specifically, our reactions to others. It is active when a mother hears an infant cry or when we sense the pain felt by a loved one. Sean Spence from the University of Sheffield in the UK found the same region lit up in brain scans when people were being deceived. And Andreas Bartels and Semir Zeki from University College London showed that FI as well as ACC were active when people looked at a picture of a person they loved. Tania Singer from University College London has published a study showing that when someone was judged to be a fair player, the brain response to that person's face included activity within FI. "All these responses have something in common - they all represent value judgements within a social context," Allman says. They reflect how people see you and how you respond to that. "I think [spindle] cells are the home of the complex social emotions."

But there are other brain regions, in the prefrontal cortex, which become active in some social situations yet contain no spindle cells. Can he really say that these cells have the monopoly on social emotions? For example, psychologist Josh Greene from Princeton University showed that the frontal polar region, near FI, but completely devoid of these cells, was active when people made ethically charged decisions, such as judging whether to save someone's life but endangering others, or when punishing those who did not comply with rules. This might be seen as a strong argument against a vital role for spindle cells in complex social emotions.

But Allman points out that the sorts of social situations that trigger neural activation outside FI and ACC tend to be more deliberate: they take the past and future into account, or involve complex calculations. He suggests that our brains have two separate systems. One is more deliberating, thinking about issues of fairness, punishment, moral judgements and the like. The second, faster, system mediated by spindle cells controls more intuitive behaviour during social interactions. If you love someone, you know instantly how to react to them. You don't have to think. This is where spindle cells are important, Allman believes. "The main thing [spindle cells] do is to adjust your behaviour in a rapid real-time interaction in a complex social environment," he says.

It certainly looks as though spindle cells are built for speed. Their most striking feature is that they are huge. The body is up to 0.1 millimetres long, and four times the volume of the surrounding cells. And they have a very wide and long axon and dendrites - the branching extensions that act as the wiring in the brain. "Velocity increases as axon size increases," Koch says, "so we can probably say that the output zips along at high speed."

Such thinking rings true to primatologist Louise Barrett from the University of Liverpool in the UK. "What is unique about humans is the speed at which we run," she says. Speed is vital for juggling more complex social information of the type that we deal with, she says. Antonio Damasio of the University of Iowa, the author of three books about emotions, agrees that relating spindle cells to emotions is "entirely reasonable". Clearly the cells don't work in isolation, he points out. But there is no doubt that the areas where spindle cells are found are important for social emotions and most other emotions. "However, the interpretation must be regarded as speculative, for the time being," he adds.

One reason this sounds an incredible claim is that it seems a big job for a relatively small number of cells. At most there are just over 100,000 spindle cells in our brains, a tiny fraction of the billions of brain cells. "That doesn't sound like a lot of neurons to carry this freight, to be such an important player in social cognition," says Roger Bingham, who works on the evolution of the mind at the University of California at San Diego. But it's not unheard of, he points out. Signals such as moods, reward and pleasure are also carried by a small number of cells that have a widespread influence all over the brain.

The anatomy backs the idea that a few cells can be very influential. The cortex of the brain is built up of neat layers of cells running parallel to the brain's undulating surface. Each layer has a specific role: one takes in information fed from our senses; another sends feedback; another relays information to the next brain region in the circuit. Spindle cells are always in layer 5, the layer that sends the final signal, the result of all the calculations and activity in a particular region, onto other brain regions. This means that they carry the weight of all the important activity of the region. Allman suggests the signal they convey to other parts of the brain may be very simple: something like "I feel good about this" or "I don't feel good about this". This is an important component of social intuition, he says, and it may also extend to non-social situations as a feeling of luck or a hunch. "It is so simple that I think it is entirely reasonable that it could be performed by about 100,000 neurons," he says.

Although Allman has not been able to measure any of the electrical properties of spindle cells, he has been able to study some of their chemical properties. He and his colleague Karli Watson found receptors on the cells for the neurotransmitters serotonin, dopamine and vasopressin. These transmitters have known links with behaviours such as reward value, bonding, love and mood, which reinforces the brain imaging findings.

A decade ago, for example, Thomas Insel, director of the US National Institute of Mental Health in Bethesda, Maryland, discovered that vasopressin and a related hormone, oxytocin, were vital for the formation of pair bonding in voles. Both hormones are released during mating. Blocking their activity prevents bonding in animals that have mated, and giving these hormones encourages unmated animals to bond. "The relevant circuits have either oxytocin or vasopressin receptors," he says. "It appears that dopamine pathways in the brain are specifically involved."

Insel admits that he has wondered whether looking for vasopressin receptors in the human brain might tell us which circuits are important for human social bonding too. We often attribute love and bonding to our heart, but maybe our feelings for loved ones are actually carried by the spindle cells. "I think this is a fascinating hypothesis, but one that will be difficult to prove or disprove," he says.

One way to test the idea that spindle cells are vital for quick-fire social emotions would be to look at brains that you would not expect to have such social skills, and see what sort of cell populations they have. For example, people with autism are often extremely capable in predictable environments where rules, logic and calculations work, but in a complex, ever-changing social setting they often fail to behave in appropriate ways. So are spindle cells found in autistic people's brains?

It is rather early to say, according to Allman. But he thinks that during the development of autistic brains the spindle neurons may fail to migrate to their normal positions. Hof also has some intriguing results suggesting that the spindle cells in schizophrenic brains appear abnormal too - though here other cell types may also be affected. And then there is the early discovery that spindle cells are particularly vulnerable to neurodegeneration in Alzheimer's disease. Humans are the only primates that suffer such age-related neurodegenerative illnesses, he points out. Exactly why spindle cells are vulnerable will be an important question in understanding and treating these devastating diseases.

Allman explains it at an evolutionary level: "Because this class of neurons has recently evolved, natural selection has had just a short time to work on the circuits that they are involved in and therefore they may be more vulnerable to dysfunction," he says. But Hof is also trying to understand the protein chemistry and unique structures that make the cells vulnerable. Meanwhile, Allman is busy seeking tissue from brains with all kinds of neuropsychiatric disorders. He is considering a number of disorders, he says, including obsessive-compulsive disorder and anorexia, which he thinks have all the hallmarks of an overactive spindle system.

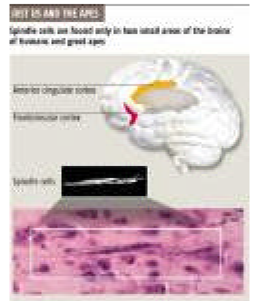
As well as helping us understand brain dysfunction, research into spindle cells also offers an intriguing insight into the evolution of the human mind. Allman suspects that spindle cells have been around for some 10 million years, most likely appearing in the common ancestor of African apes and orang-utans. If he is correct, and they are the home of complex social emotions, then some of the mental traits we consider to be most distinctly human actually have deep origins.

This makes perfect sense to Barrett and her colleague Robin Dunbar, who have identified big differences between the social structures of great apes and monkeys. They believe that the superior abilities of apes in general cognitive tasks and in social settings have their origins in their so-called fission-fusion societies, where animals live as part of a social group, but one that is not together all of the time.

"Great apes have a much more dispersed social system," Barrett says. They may spend time on their own, but they also know all the other individuals around. "When in a dispersed system, you have to keep in mind the animals that are not there, and keep track of them through time," she says. The increased complexity in what they call the "social environment" may have driven the evolution of bigger brains and some of the complex skills we think of as uniquely human.

Bingham agrees. Evolutionary psychologists have concentrated their efforts to understand human nature on considerations of the social pressures on the minds of our ancestors, he says. But the origins of human characteristics such as guilt, remorse, love and empathy began much earlier than we might think. Brains evolved to deal with an uncertain environment, he says, and for apes, problems of the environment are largely social cognition problems: trying to work out what the other player is thinking, believing, and how they will act.

"You can see how resentment, a sense of fair play, righteous anger and other complex social emotions come into our everyday lives," Bingham says. "We come by all these sentiments and responses over evolutionary time. Finally we are actually getting to look inside the black box to see where it happens."



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