

FEATURE

To Unlock the Brain's Mysteries, Purée It

A Vanderbilt neuroscientist has discovered an unusual but shockingly fruitful way to study our most enigmatic organ.

By Ferris Jabr

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One day in June 2012, at São Paulo's international airport, Suzana Herculano-Houzel hauled two heavy suitcases onto an X-ray-machine conveyor belt. As the luggage passed through the scanner, the customs agent's eyes widened. The suitcases did not contain clothes, toiletries or any of the usual accouterments of travel. Instead, they were stuffed with more than two dozen curiously wrapped bundles, each enclosing an amorphous blob suspended in liquid. The agent asked Herculano-Houzel to open her bags, suspecting that she was trying to smuggle fresh cheese into the country; two people had been caught doing exactly that just moments before.

"It's not cheese," Herculano-Houzel said. "It's only brains."

She was a neuroscientist, she explained, and she had just returned from an unusual — but completely legal — research expedition in South Africa, where she collected brains from a variety of species: giraffes, lions, antelopes, mongooses, hyenas, wildebeests and desert rats. She was taking the organs, sealed in containers of antifreeze, back to her lab in Rio de Janeiro. The customs agents reviewed her extensive collection of permits and documentation, and they eventually let her pass with suitcases in tow.

In the last 12 years, Herculano-Houzel, now a researcher and professor at Vanderbilt University in Nashville, has acquired the brains of more than 130 species. She has brains from commonplace creatures — mice, squirrels, pigeons — and more exotic ones, like Goodfellow's tree kangaroo and the Tasmanian devil. She has brains from bees and an African elephant. She prefers to obtain whole brains if possible, and she goes to great lengths to protect the organs during transport.

A brain is a precious thing, containing many of science's greatest unsolved mysteries. What we don't know about the brain still eclipses what we do. We don't know how the brain generates consciousness. We aren't sure why we sleep and dream. The precise causes of many common mental illnesses and neurological disorders elude us. What is the physical form of a memory? We have only inklings. We still haven't cracked the neural code: that is, how networks of neurons use electrical and chemical signals to store and transmit information. Until very recently — until Herculano-Houzel published an important discovery in 2009 — we did not even know how many cells the human brain contained. We only thought we did.

Before Herculano-Houzel's breakthrough, there was a dominant narrative about the human brain, repeated by scientists, textbooks and journalists. It went like this: Big brains are better than small brains because they have more neurons, and what is even more important than size is the brain-to-body ratio. The most intelligent animals have exceptionally large brains for their body size. Humans have a brain seven times bigger than you would expect given our overall size — an unrivaled ratio. So, the narrative goes, something must have happened in the course of human evolution to set the human brain apart, to swell its proportions far beyond what is typical for other animals, even for our clever great-ape and primate cousins. As a result, we became the bobbleheads of the animal kingdom, with craniums spacious enough to accommodate trillions of brain cells: 100 billion electrically active neurons and 10 to 50 times as many supporting cells, known as glia.

By comparing brain anatomy across a large number of species, Herculano-Houzel has revealed that this narrative is seriously flawed. Not only has she upended numerous assumptions and myths about the brain and rewritten some of the most fundamental rules about how brains are constructed — she has also proposed one of the most cohesive and evidence-based frameworks for human brain evolution to date.

But her primary methods are quite different from others' in her field. She doesn't subject living brains to arrays of electrodes and scanners. She doesn't divide brains into prosciutto-thin slices and carefully sandwich them between glass slides. She doesn't seal brains in jars of formaldehyde for long-term storage. Instead, she demolishes them. Each organ she took such great care to protect on her trans-Atlantic journey was destined to be liquefied into a cloudy concoction she affectionately calls "brain soup" — the key to her groundbreaking technique for understanding what is arguably the most complex congregation of matter in the universe. In dismantling the brain, she has remade it.

The history of studying the brain is a history of learning how to perceive it, literally and figuratively. Just as technological advances have allowed us to better examine the moon, stars and planets, they have significantly improved our ability to chart and inspect the thick constellations of cells in our own heads. The prevailing metaphor for the brain has long been a piece of biological machinery, but our

conception of that machine has evolved in parallel with our technological prowess. At first, the brain was viewed as the body's coolant system, a hydraulic pump for "animal fluids." Then it was a collection of self-winding springs or an "enchanted loom," then a clock, an electromagnet, a telephone switchboard, a hologram and, most recently, a biological supercomputer.



Suzana Herculano-Houzel holding a wildebeest brain in her lab at Vanderbilt University.
Jeff Minton for The New York Times

Despite all the advances we've made, there are still many fundamental aspects of the brain that we do not understand at all. This is mainly because the brain is a many-layered mystery, demanding intense scrutiny at vastly different scales, from the molecular to the perceptual. But it's also because neuroscience has sometimes neglected, rushed or botched what should be its most elementary tasks, chasing holy grails before establishing primary principles. Case in point: We are well into the 21st century, and we are only now getting an accurate census of the brain's cellular building blocks.

In part because the scientific portrait of the brain remains so patchy, it has long been embellished with numerous myths and misconceptions. For example, there's no truth to the idea that the brain is half android and half artist, with a left hemisphere dedicated to logic and analytical thinking and a right hemisphere for intuition and creativity. You don't have a primitive reptilian brain tucked inside your more sophisticated mammalian tissues. You can't increase brainpower by eating nuts, blueberries, fish and other so-called brain foods. Entire books have been written to counter such falsehoods.

Misinformation about the brain is not isolated to the general public; it is surprisingly prevalent in academia too. By the time Herculano-Houzel was old enough to pursue graduate studies in science, she had long been inoculated with a strong dose of skepticism. When she was growing up in Brazil, her parents emphasized that "it was a good thing to not take somebody's word, no matter how respected they were," she recalls, "and rather ask: 'Why? How do you know that?'" It was not until she earned a Ph.D. in neuroscience in Europe and returned to Rio de Janeiro in 1999, however, that she confronted neuromythology head on.

Instead of pursuing postdoctoral studies — which she thought would be too intellectually restricting — she persuaded the city’s recently opened Museum of Life to offer her a job giving presentations on the brain to the public. One of her first projects was a survey regarding general beliefs about the brain: E.g., did consciousness depend on the brain? Did drugs physically alter the brain? She was shocked to learn that 60 percent of college-educated people in Rio de Janeiro believed that humans used only 10 percent of their brains — a longstanding fallacy. In truth, the brain is highly active across its entirety just about all the time, even when we are spacing out or sleeping. She couldn’t let it go. Where did such a prevalent falsehood come from? How did it spread?

She started looking for clues in research papers and popular science writing. In the foreword to the first edition of Dale Carnegie’s “How to Win Friends and Influence People,” the American psychologist William James is misquoted as declaring that “the average man develops only 10 percent of his latent mental ability.” In the ’30s and ’40s, another pioneering psychologist, Karl Lashley, discovered that he could scoop out large portions of a rat’s brain without seriously impairing its ability to solve a maze. Herculano-Houzel also recalled that early editions of the textbook “Principles of Neural Science,” along with countless studies, claimed that the human brain contained at least 10 times as many glial cells as neurons. Glia are now known to be every bit as important as neurons, facilitating electrical and chemical communication, clearing cellular detritus, protecting and healing injured brain cells and guiding the development of new neural circuits. But until the mid- to late 20th century, scientists mostly regarded glia as passive scaffolding for neurons. Perhaps the widely cited fact that glia outnumbered neurons by at least 10 to one helped cement the notion that only 10 percent of the brain really mattered. But where were the studies establishing the oft-repeated glia-to-neuron ratio?

After an exhaustive search, Herculano-Houzel concluded that there was no scientific basis for the claim. She and her collaborator Christopher von Bartheld, a professor at the University of Nevada School of Medicine, published a paper last year summing up their detective work. In the 1950s and ’60s, a few scientists proposed that glia were about 10 times as common as neurons, based on studies of small brain regions, ones that happened to have particularly high glia-to-neuron ratios. In a decades-long game of telephone, other researchers repeated these estimates, extrapolating them to the entire brain. Science journalists parroted the numbers. Soon this misconception spread to textbooks and educational websites run by the government and respected scientific organizations. Even the latest edition of “Principles of Neural Science” states that the brain as a whole contains “two to 10 times more glia than neurons.” The truth is that not a single study has ever demonstrated this. “I realized we didn’t know the first thing about what the human brain is made of, much less what other brains were made of, and how we compared,” Herculano-Houzel says.

So she decided to find out herself. For decades, the standard method for counting brain cells was stereology: slicing up the brain, tallying cells in thin sheets of tissue splayed on microscope slides and multiplying those numbers by the volume of the relevant region to get an estimate. Stereology is a laborious technique that works well for small, relatively uniform areas of the brain. But many species have brains that are simply too big, convoluted and multitudinous to yield to stereology. Using stereology to take a census of the human brain would require a daunting amount of time, resources and unerring precision.

In a study from the 1970s, Herculano-Houzel discovered a curious proposal for an alternative to stereology: Why not measure the total amount of DNA in a brain and divide by the average amount of DNA per cell? The problem with this method is that neurons are genetically diverse, the genome is a highly dynamic structure — continuously unraveling and reknitting itself to amplify or silence certain genes — and even small errors in measuring quantities of DNA could throw off the whole calculation. But it gave Herculano-Houzel a better idea: “Dissolve the brain, yes! But don’t count DNA. Count nuclei!” — the protein-rich envelopes that enclose every cell’s genome. Each cell has exactly one nucleus. “A nucleus is a nucleus, and you can see it,” she says. “There is no ambiguity there.”

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By 2002, Herculano-Houzel had moved from the Museum of Life to a new science-communications job at the Federal University of Rio de Janeiro, where she also had access to lab space and the freedom to pursue research of her choice. She began experimenting with rat brains, freezing them in liquid nitrogen, then puréeing them with an immersion blender; her initial attempts sent chunks of crystallized neural tissue flying all around the lab. Next she tried pickling rodent brains in formaldehyde, which forms chemical bridges between proteins, strengthening the membranes of the nuclei. After cutting the toughened brains into little pieces, she mashed them up with an industrial-strength soap in a glass mortar and pestle. The process dissolved all biological matter except the nuclei, reducing a brain to several vials of free-floating nuclei suspended in liquid the color of unfiltered apple juice.

To distinguish between neurons and glia, Herculano-Houzel injected the vials with a chemical dye that would make all nuclei fluoresce blue under ultraviolet light, and then with another dye to make the nuclei of neurons glow red. After vigorously shaking each vial to evenly disperse the nuclei, she placed a droplet of brain soup on a microscope slide. When she peered through the eyepiece, the globular nuclei looked like Hubble photos of distant stars in the black velvet of space. Counting the number of neurons and glia in several samples from

each vial, and multiplying by the total volume of liquid, gave Herculano-Houzel her final tallies. By reducing a brain, in all its daunting intricacy, to a homogeneous fluid, she was able to achieve something unprecedented. In less than a day, she accurately determined the total number of cells in an adult rat's brain: 200 million neurons and 130 million glia.

In the early years of Herculano-Houzel's research, especially once she graduated from rats to primates, she encountered substantial resistance from her peers. Here was a young, essentially unknown scientist from Brazil not only proposing a radically different way of studying the brain but also contradicting centuries of conventional wisdom. "At first I shared the same opinion as everyone else," says Andrew Iwaniuk, an evolutionary neuroscientist at the University of Lethbridge in Alberta, Canada. "This is insane. This can't possibly work. What do you mean you are blending an entire brain and coming up with the number of neurons?" As Herculano-Houzel's data set expanded, however, reservations began to recede. In the last few years, several independent teams of scientists have validated the brain-soup technique with carefully controlled studies, winning the confidence of most researchers. "The technique works — no doubt about that," Iwaniuk says. "It's hundreds or thousands of times faster than using traditional methods. And that means we can rapidly compare so many different species and see what might make the human brain special — or not."

Rat brains were just the beginning. "Once I realized I could actually do this," Herculano-Houzel told me, "there was a whole world of questions out there just waiting to be examined." Which is to say, there was a whole planet of brains waiting to be dissolved.

By 2016, Herculano-Houzel had migrated to Vanderbilt University. When we walked through the doors to her new lab, one of the first things I noticed was a row of four large white freezers covered with souvenir magnets: a toadstool-red crab with jiggling legs, the Loch Ness monster sporting a plaid bonnet and a bear chasing a human stick figure with the caption "Canadian fast food!" "That's one of my airport pastimes — the gaudier the better," Herculano-Houzel told me with a characteristically boisterous laugh. Her personality, much like her approach to science, is defined by exuberance. During our conversations, she punctuated her speech with vigorous head shakes and staccato guffaws, leaning halfway across the table when she really got excited. Unlike many of her peers, Herculano-Houzel does not shy away from a little showmanship; a TED Talk she gave has been viewed nearly two and a half million times. One neuroscientist I spoke to referred with mild disapproval to her "self-aggrandizement."

She swung one of the freezers open, revealing shelves crowded with Tupperware boxes. Each container was labeled with a bit of masking tape inked with a numerical ID: Box 19, Box 6, Box 34. "What's in here?" I asked. "Oh, all sorts," she said. "About 200 different brains. Birds and mammals." One particularly large brain sat in its plastic bin as casually as a sliced cantaloupe. As I leaned in for a closer look, its distinctive exterior came into view: a labyrinth of flesh, now fallow and cold, that once fizzed with electric current and pulsed with freshly pumped blood. "Here you have different carnivorous species," she continued. "Lion, leopard, dogs, cats, raccoons. There are ostrich brains. A few primates. A bunch of giraffes — their spinal cords as well. Four meters' worth of spinal cord."

At this point, Herculano-Houzel has published studies on the brains of more than 80 species. The more species she has compared, the clearer it has become that much of the dogma about brains and their cellular components is simply wrong. First of all, a large brain does not necessarily have more neurons than a small one. She has found that some species have especially dense brains, packing more cells into the same volume of brain tissue as their spongier counterparts. As a rule, because their neurons are smaller on average, primate brains are much denser than other mammalian brains. Although rhesus monkeys have brains only slightly larger than those of capybaras, the planet's largest rodents, the rhesus monkey has more than six times the number of neurons. Birds appear to have the densest brains of all, but their brains are not particularly large. An emu, one of the biggest birds alive today, has a brain that weighs about as much as an AA battery. Were there a bird with a brain the size of a grapefruit, however, it would probably rule the world.

The brain-soup technique further revealed that the human brain, contrary to the numbers frequently cited in textbooks and research papers, has 86 billion neurons and roughly the same number of glia — not 100 billion neurons and trillions of glia. And humans certainly do not have the most neurons: The African elephant has about three times as many, with a grand total of 257 billion. When Herculano-Houzel focused on the cerebral cortex, however — the brain's wrinkled outermost layer — she discovered a staggering discrepancy. Humans have 16 billion cortical neurons. The next runners-up, orangutans and gorillas, have nine billion cortical neurons; chimpanzees have six billion. The elephant brain, despite being three times larger than our own, has only 5.6 billion neurons in its cerebral cortex. Humans seemed to possess the most cortical neurons — by far — of any species on earth.

A cross-section of a preserved human brain looks like a slice of gnarled squash, with an undulating cream-colored interior outlined by an intensely puckered gray rind. That rind — composed of layers of densely packed neurons and glia — is the cerebral cortex. Its deep grooves and ridges significantly increase its total surface area, providing more room for cells within the confines of the skull. All mammals have a cortex, but the extent to which the cortex is wrinkled depends on the species. Squirrels and rats have cortices as smooth as soft-serve, whereas human and dolphin brains look like heaps of udon noodles. Over the years, some researchers have proposed that the more corrugated the cortex, the more cells it contains, and the more intelligent the species. But no one had precise cell counts to back up those claims.

The cerebral cortex is the difference between impulse and insight, between reflex and reflection. It is essential for voluntary muscle control, sensory perceptions, abstract thinking, memory and language. Perhaps most profound, the cerebral cortex allows us to create and inhabit a simulation of the world as it is, was and might be; an inner theater that we can alter at will. "The cortex receives a copy of everything else that happens in the brain," Herculano-Houzel says. "And this copy, while technically unnecessary, adds immense

complexity and flexibility to our cognition. You can combine and compare information. You can start to find patterns and make predictions. The cortex liberates you from the present. It gives you the ability to look at yourself and think: This is what I am doing, but I could be doing something different.”

The sheer density of the human cortex dovetails with an emerging understanding of interspecies intelligence: It’s not that the human mind is fundamentally distinct from the minds of other primates and mammals, but rather that it is dialed up to 11. It’s a matter of scale, not substance. Many mental abilities once regarded as uniquely human — toolmaking, problem-solving, sophisticated communication, self-awareness — turn out to be far more widespread among animals than previously thought. Humans just manifest these talents to an unparalleled degree. Herculano-Houzel thinks the simplest explanation for this disparity is the fact that humans have nearly twice as many cortical neurons as any other species studied so far. How, then, did our species gain such a huge lead?

The standard explanation for our unrivaled intelligence is that humans bucked the evolutionary trends that restricted other animals. Somehow, perhaps because of a serendipitous genetic mutation millions of years ago, the human brain inflated far beyond the norm for a primate of our body size. But Herculano-Houzel’s careful measurements of dozens of primate species demonstrated that the human brain is not out of sync with the rest of primatkind. In both mass and number of cells, the brains of all primates, including humans, scale in a neat line from smallest to biggest species — with the exception of gorillas, orangutans and chimpanzees. The great apes, our closest evolutionary cousins, are the anomalies, with oddly shrunken brains considering their overall heft. While contemplating this incongruity, Herculano-Houzel remembered a book she read a few years earlier: “Catching Fire: How Cooking Made Us Human,” by the Harvard anthropologist Richard Wrangham.

Wrangham proposed that the mastery of fire profoundly altered the course of human evolution, to the extent that humans are “adapted to eating cooked food in the same essential way as cows are adapted to eating grass, or fleas to sucking blood.” Cooking neutralized toxic plant compounds, broke down proteins in meat and made all foods much easier to chew and digest, meaning we got many more calories from cooked foods than from their raw equivalents. Because our digestive systems no longer had to work as hard, they began to shrink; in parallel, our brains grew, nourished by all those extra calories. The human brain makes up only 2 percent of our body weight, yet it demands 20 percent of the energy we consume each day.

Herculano-Houzel realized that she could extend and modify this line of thought. In the wild, modern great apes spend about eight hours a day foraging just to meet their minimal caloric requirements, and they routinely lose weight when food is scarce. In the course of their evolutionary history, as they developed much larger bodies than their primate ancestors, with larger organs to match, their brains most likely hit a metabolic growth limit. Great apes could no longer obtain enough calories from raw plants to nourish brains that would be in proportion with their overall mass.

Herculano-Houzel tested this insight with math. Based on their body size, gorillas and orangutans should have brains at least as large as ours, with neuron counts to match. Knowing how much energy a neuron needs on average, however, and how much time an ape can spend foraging, Herculano-Houzel calculated that modern great apes are physiologically restricted to brains with about 30 billion neurons. There simply aren’t enough hours in the day, or enough calories in raw plants, to push them over that threshold. “That’s not something I thought about,” Wrangham says. “It’s an ingenious way of looking at things.”

Cooking liberated our ancestors from this same physiological straitjacket and put us back on track to develop brains as large as expected for primates our size. And because primates have such dense brains, all that new brain mass rapidly added a huge number of neurons. It took 50 million years for primates as a group to evolve brains with around 30 billion neurons total. But in a mere 1.5 million years of evolution, the human brain gained an astounding 56 billion additional neurons. To use the metaphor of our time, cooking tripled the human brain’s processing power.

There is something almost comical about this revelation. For so long, we have struggled to keep the human brain perched on its pedestal. We have insisted that although we are the product of evolution just like any other animal, our evolutionary journey was special — that we inherited decently large brains from our ape ancestors and transformed them into the most formidable thinking machines on the planet. As it turns out, quite the opposite is true. The evolutionary path of the human brain is not one of inordinate growth, but rather a long-overdue game of catch-up.

Even if we now have more cortical neurons than any other species, the true significance of that discrepancy remains unclear. Consider that the elephant, which has three times fewer cortical neurons than humans, is one of the smartest animals ever studied: It crafts tools, recognizes itself in the mirror and even seems to have some understanding of death. Likewise, the octopus — an invertebrate with no cerebral cortex, a meager 100 million neurons in its brain and 300 million more in its arms — is one of the most intelligent species in the ocean, capable of remembering individuals, opening complex puzzle boxes and escaping “escape-proof” tanks. Honeybees have minuscule brains, yet their talents for collaboration and communication exceed those of many more densely brained creatures. Then there are organisms like plants, which, despite having no neurons whatsoever, are exquisitely sensitive to their environments, adapting to changes in light and moisture, recognizing kin and eavesdropping on one another’s chemical alarm signals.

Ultimately, the brain-soup technique’s central strength — its reductionism — is also its weakness. By transforming a biological entity of unfathomable complexity into a small set of numbers, it enables science that was not previously possible; at the same time, it creates the temptation to exalt those numbers. In her book, “The Human Advantage,” Herculano-Houzel stresses the distinction between cognitive

capacity and ability. We have about the same number of neurons as humans who lived 200,000 years ago, yet our respective abilities are vastly different. At least half of human intelligence derives not from biology but from culture — from the language, rituals and technology into which we are born. Perhaps that is also why parrots, dolphins and apes raised by scientists in intellectually demanding environments often develop a degree of intelligence not seen in their wild counterparts: Culture unlocks the brain's latent potential.

For centuries, we have regarded the brain as a kind of machine: a ludicrously convoluted one, but a machine nonetheless. If we could only pick it apart, quantify and examine all its components, we could finally explain it. But even if we could count and classify every cell, molecule and atom, we would still lack a satisfying explanation of its remarkable behavior. The brain is more than a thing; it's a system. So much of intelligence is neither within the brain nor in its environment, but vibrating through the space in between.

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