CHARTS SHOW HOW YOUR BRAIN EXPANDS AND SHRINKS WITH AGE

Physicians could one day use them as a routine clinical tool, researchers say.

By Max Kozlov

When neuroscientist Jakob Seidlitz took his 15-month-old son to the paediatrician for a check-up last week, he left feeling unsatisfied. There wasn't anything wrong with his son — the youngster seemed to be developing at a typical pace, according to the height and weight charts the physician used. What Seidlitz felt was missing was an equivalent metric to gauge how his son's brain was growing. "It is shocking how little biological information doctors have about this critical organ," says Seidlitz, who is based at the University of Pennsylvania in Philadelphia.

Soon, he might be able to change that. Working with colleagues, Seidlitz has amassed more than 120,000 brain scans — the largest collection of its kind — to create the first comprehensive growth charts for brain development (R. A. I. Bethlehem *et al*. *Nature* https://doi.org/hpkn; 2022). The charts show visually how human brains expand quickly early in life and then shrink slowly with age. The sheer magnitude of the study, published in *Nature* on 6 April, has stunned neuroscientists, who have long had to contend with reproducibility issues in their research, in part because of small sample sizes. Magnetic resonance imaging (MRI) is expensive, meaning that scientists are often limited in the number of participants they can enrol in experiments.

"The massive data set they assembled is extremely impressive and really sets a new standard for the field," says Angela Laird, a cognitive neuroscientist at Florida International University in Miami.

Even so, the authors caution that their database isn't completely inclusive — they struggled to gather brain scans from all regions of the globe. The resulting charts, they say, are therefore just a first draft, and tweaks would be needed to deploy them in clinical settings.

If the charts are eventually rolled out to paediatricians, great care will be needed to ensure that they are not misinterpreted, says Hannah Tully, a paediatric neurologist at the University of Washington in Seattle. "A big brain is not necessarily a well-functioning brain," she says.

Because brain structure varies significantly from person to person, the researchers had to aggregate a huge number of scans to create growth charts with statistical significance. That's no easy task, says Richard Bethlehem, a neuroscientist at the University of Cambridge, UK, and a co-author of the study. Instead of running thousands of scans themselves, which would take decades and be prohibitively costly, the researchers turned to already-completed neuroimaging studies.

Bethlehem and Seidlitz sent e-mails to researchers all over the world asking if they would share their neuroimaging data for the project. The duo was amazed by the number of replies, which they attribute to the COVID-19 pandemic giving researchers less time in their laboratories and more time than usual with their e-mail inboxes.

In total, the team aggregated 123,894 MRI scans from 101,457 people, who ran the gamut from fetuses 16 weeks after conception to 100-year-old adults. The scans included brains from neurotypical people, as well as people with a variety of neurocognitive differences, including autism spectrum disorder. The researchers used statistical models to extract information from the images, and ensure that the scans were directly comparable, no matter what type of MRI machine had been used.

The end result is a set of charts plotting several key brain metrics by age. Some metrics, such as grey-matter volume and mean cortical thickness (the width of the grey matter) peak early in a person's development, whereas the volume of white matter (found deeper in the brain) tends to peak by around age 30 (see 'Brain change'). The data on ventricular volume (the amount of cerebrospinal fluid in the brain), in particular, surprised Bethlehem. Scientists knew that this volume increases with age, because it is typically associated with brain atrophy, but Bethlehem was shocked by how rapidly it tends to grow in late adulthood.

A first draft

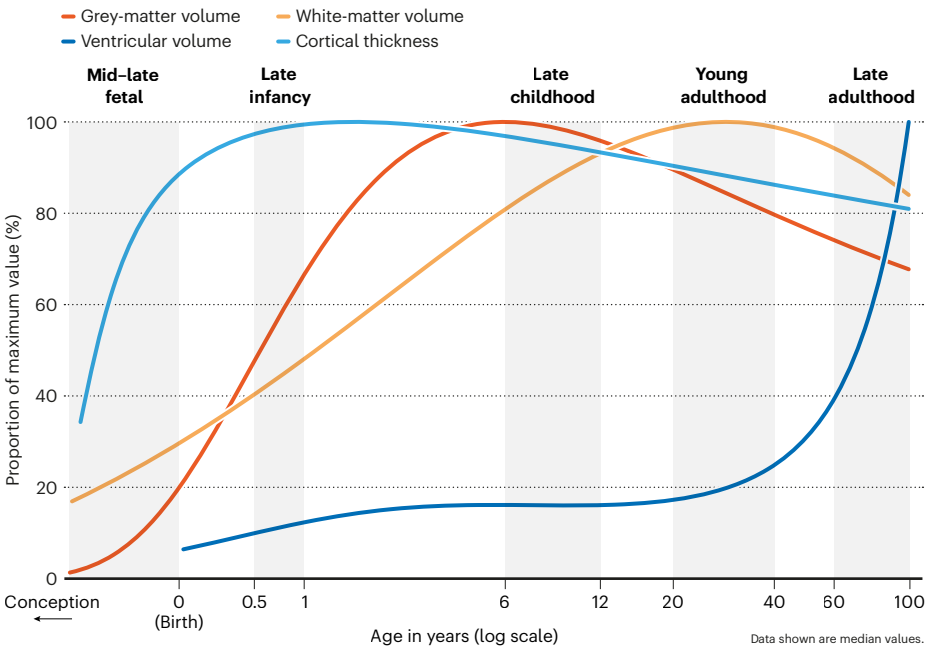
The study comes on the heels of a bombshell paper published in *Nature* on 16 March showing that most brain-imaging experiments contain too few scans to reliably detect links between brain function and behaviour, meaning that their conclusions might be incorrect (S. Marek *et al*. *Nature* **603**, 654–660; 2022). Given this finding, Laird expects the field to move towards adopting a framework similar to the one used by Seidlitz and Bethlehem.

To amass so many data sets is akin to a "diplomatic masterpiece", says Nico Dosenbach, a neuroscientist at Washington University in St. Louis, Missouri, who co-authored the 16 March study. He says this is the scale on which researchers should operate when aggregating brain images.

Despite the size of the data set, Seidlitz,

BRAIN CHANGE

Researchers analysed more than 120,000 brain scans to assemble the most comprehensive growth chart of the brain so far. White- and grey-matter volume and mean cortical thickness (the width of the grey matter) increase rapidly early in development, whereas ventricular volume (the amount of cerebrospinal fluid in the brain) increases rapidly later in life.



SOURCE: R. A. I. BETHLEHEM *ET AL*. *NATURE* HTTPS://DOI.ORG/HPKN (2022)

Bethlehem and their colleagues acknowledge that their study suffers from a problem endemic in neuroimaging studies — a remarkable lack of diversity. The brain scans they collected come mainly from North America and Europe, and disproportionately reflect populations that are white, university-aged, urban and affluent. The study includes only three data sets from South America and one from Africa — accounting for around 1% of all the brain scans used in the study.

Billions of people worldwide lack access to MRI machines, making diverse brain-imaging data difficult to come by, Laird says. But the authors haven't stopped trying. They have launched a website where they intend to update their growth charts in real time as they receive more brain scans (see go.nature.com/3rctwfd).

Big data sets, big responsibility

Another challenge was determining how to give proper credit to the owners of the brain scans used to construct the charts. Some of the scans came from open-access data sets, but others were closed to researchers. Most of the closed-data scans hadn't yet been processed in a way that would allow them to be incorporated into the growth charts, so their owners did extra work to share them. These scientists were then named as authors of the paper.

Meanwhile, the owners of the open data sets received only a citation in the paper — which doesn't hold as much prestige for researchers seeking funding, collaborations and promotions. Seidlitz, Bethlehem and their colleagues processed these data. In most cases, Bethlehem says, there was essentially no direct contact with the owners of these data sets.

There are a number of reasons that data sets might be closed: for instance, to protect the privacy of health data. But this doesn't make it fair that the researchers who opened their data sets didn't get authorship, Bethlehem and Seidlitz say. They contend that authorship guidelines from journals, including *Nature* — which say that each author is expected to have made "substantial contributions" to, for example, the analysis or interpretation of data — are an obstacle. (*Nature*'s news team is editorially independent of its publisher.)

A *Nature* spokesperson responds that the issue was "considered carefully by the editors and authors according to our authorship policies" and that "all data sets were appropriately credited per our data citation policy".

Ultimately, these concerns can be traced back to how researchers are evaluated by the scientific enterprise, says Kaja LeWinn, a social epidemiologist at the University of California, San Francisco. She says that stakeholders — including funders, journals and research institutions — need to re-evaluate how brain science can be properly recognized and rewarded, especially as these types of large-scale study become more common.

INFECTED IMMUNE CELLS HOLD CLUES TO SEVERE COVID

The virus SARS-CoV-2 can infect immune cells, prompting a massive inflammatory response.

By Smriti Mallapaty

Immune cells infected with SARS-CoV-2 can trigger a massive inflammatory response that contributes to severe COVID-19, suggest two papers.

Since the early days of the pandemic, research has suggested that inflammation leads to significant respiratory distress and organ damage, hallmarks of severe COVID-19. But scientists have struggled to pinpoint what triggers the inflammation.

The latest studies implicate two types of white blood cell — monocytes in the blood and macrophages in the lungs — which, once infected with the virus, trigger inflammation. The studies also provide conclusive evidence that the virus can infect and replicate in immune cells, and reveal the receptor it exploits to enter those cells. Evidence for such infections has been mixed until now.

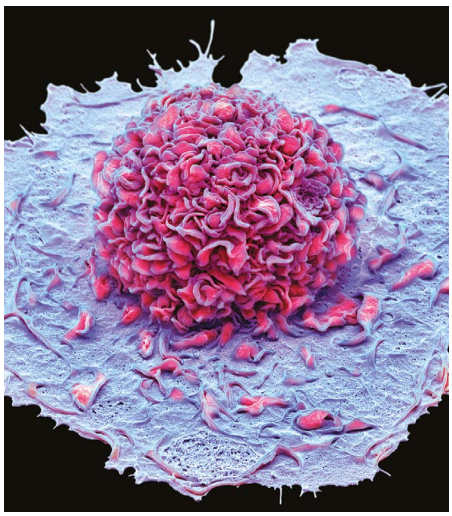
The studies offer a plausible explanation for how severe COVID-19 progresses, says Malik Peiris, a virologist at the University of Hong Kong. "I don't think it is the only or most important pathway, but it is certainly interesting."

Still, infected immune cells could offer a potential target for drug development, says Jian Zheng, an immunologist at the University of Iowa in Iowa City.

In a paper published in *Nature* on 6 April, Judy Lieberman, an immunologist at Boston Children's Hospital in Massachusetts, and her colleagues looked at blood samples from people with COVID-19 (C. Junqueira *et al*. *Nature* https://doi.org/hppt; 2022). They found that about 6% of monocytes — 'early responder' immune cells that patrol the body for foreign invaders — were undergoing a type of cell death associated with inflammation, known as pyroptosis. To see so many cells dying is unusual, she says.

When the researchers looked at the dying cells, they found they were infected with SARS-CoV-2. The team suggests the virus was probably activating inflammasomes, large molecules that trigger a cascade of inflammatory responses that end in cell death.

The researchers also looked at another type of immune cell, macrophages, in the lungs of people who had died of COVID-19. Because macrophages collect cellular garbage, including viral debris, it has been difficult to show whether they were infected with SARS-CoV-2 or just sopping up this debris. The team found that about one-quarter of macrophages had activated inflammasomes, and a fraction of those had indeed been infected with the virus. Other infected lung cells, from tissue called the epithelium, did not display the same response.



STEVE GSCHMEISSNER/SPL

SARS-CoV-2 can infect macrophages (pictured) in the lungs.

The results align with those of the second study, posted on the preprint server bioRxiv by Esen Sefik, an immunologist at Yale University School of Medicine in New Haven, Connecticut, and her colleagues, and yet to be peer reviewed (E. Sefik *et al*. Preprint at bioRxiv https://doi.org/hppw; 2022). They found that the virus could infect and replicate in macrophages in human lung cells and in a mouse model of the human immune system. The macrophages showed the same inflammatory response as described by Lieberman, and eventually died.

The macrophages' response could be their way of stopping SARS-CoV-2 from replicating, says study co-author Richard Flavell, an immunologist also at Yale. When inflammasomes were activated, the virus stopped replicating in the cells. When the researchers blocked inflammasomes, the macrophages started producing infectious virus.

But Stanley Perlman, a virologist at the University of Iowa, says studies will be needed to work out how important infected immune cells are in inducing severe COVID-19, compared with other possible mechanisms.