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Health

Why the brain's microbiome could hold the key to curing Alzheimer's

The surprising discovery that your brain has its own microbiome is raising an intriguing possibility – that some dementias might be reversible

By David Robson

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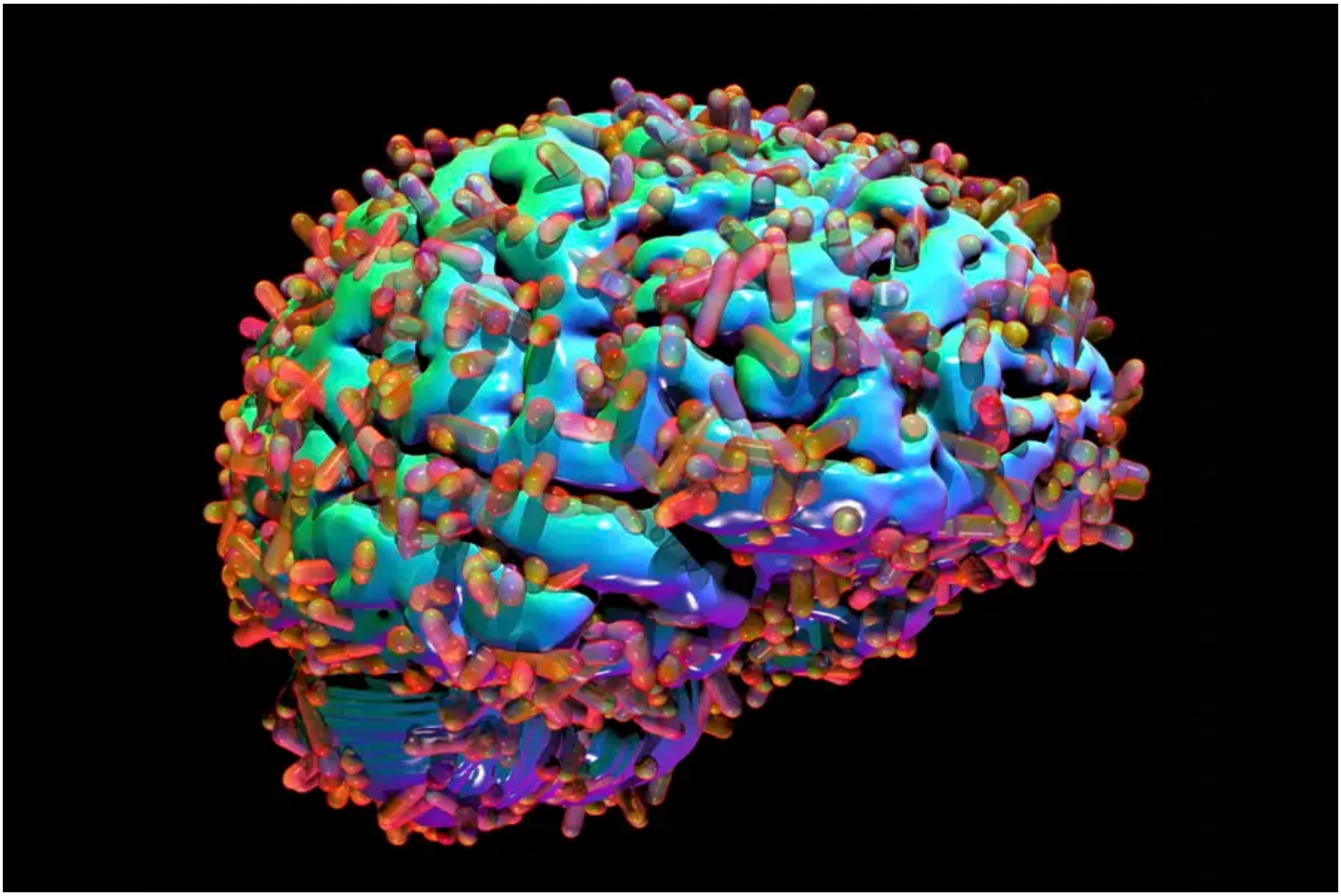

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IT SEEMED like a classic case of Alzheimer's disease. For three years, a man in his 70s had experienced serious cognitive decline: he frequently forgot the names of family members and was no longer able to drive or leave home by himself. Further deterioration seemed inevitable. But then his doctors checked a sample of his cerebrospinal fluid 🔗

https://pubmed.ncbi.nlm.nih.gov/15505372/ and noticed a fungus called *Cryptococcus neoformans*. When they put him on a course of antifungal medication, the results were startling. Within two years, he had regained his driving licence and returned to work as a gardener.

Neuroscientists have long suspected that certain infections can increase the risk of dementia. For instance, both *Porphyromonas gingivalis* /article/2192409-gum-disease-and-alzheimers-your-questions-answered/, the bacteria behind gum disease, and the herpes simplex virus /article/2242749-common-herpes-virus-causes-signs-of-alzheimers-disease-in-brain-cells/, which causes cold sores, have been linked with Alzheimer's https://pubmed.ncbi.nlm.nih.gov/37283269/. But cases of "reversible dementia" are starting to inspire enormous interest in the idea that our brains are teeming with microorganisms – and that an imbalance in this "brain microbiome" may predispose people to neurodegenerative disease.

Until recently, the brain was thought to be devoid of microbes, not least because of the blood-brain barrier, a specialised membrane that keeps pathogens and toxins in the blood out of the brain. So the idea of a brain microbiome was controversial. However, a new study seems to clinch the case. Richard Lathe https://www.ed.ac.uk/infection-medicine/our-staff/associate-members/professor-richard-lathe at the University of Edinburgh, UK, and his colleagues analysed data from post-mortem brains https://www.biorxiv.org/content/biorxiv/early/2023/02/12/2023.02.06.527297.full.pdf stored in four brain banks in the UK and US. They found a wide variety of microbes, with different types and amounts in different brain regions. Lathe estimates that this brain microbiome contains some 100,000 species, comprising a subset of around one-fifth the gut microbiome. Roughly 1000 "core" species make up 90 per cent of the population.

The researchers also found that, in people with Alzheimer's disease, certain microbes were over-represented. These included species of *Cryptococcus* and *Candida* fungi, *Streptococcus* and *Bacillus* bacteria, as well as a currently unidentified alga. Although the study hasn't yet been published in a peer-reviewed journal, it chimes with research https://doi.org/10.3389/fcimb.2023.1123228 by Jeffrey Lapides https://drexel.edu/medicine/faculty/profiles/jeffrey-lapides/ and his colleagues at Drexel University College of Medicine in Pennsylvania. They examined post-mortem brain tissue from 32 individuals and found three distinctive microbial species that were associated with the development of Alzheimer's.

Such findings are intriguing, but there are many unanswered questions. Is a healthy microbiome essential for a healthy brain, as is the case in the gut? Do particular microbes cause neural degeneration or are they a consequence of it? And, if they are to blame, how: do certain species cause harm, is it the overall balance of species that tips someone into illness or do our brains suffer from the crossfire between two competing species, as Lapides suspects? "It could be that the chemical results of that fight are toxic," he says. We don't even know how microbes get into neural tissue, given the blood–brain barrier.

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Clues are starting to emerge, though. Take *Candida albicans*, a fungus commonly found in our gut where it is kept under control by "friendly" bacteria. Aimée Parker 🔗 https://quadram.ac.uk/people/aimee-parker/ at the Quadram Institute in Norwich, UK, and her colleagues discovered that mice with a weakened gut microbiome were more

likely to have *C. albicans* in their brain 🔗 https://doi.org/10.3389/fnagi.2022.828429. In humans, it is possible that long-term antibiotics treatment could set this in motion by upsetting the gut microbiome. Then, when the fungus reaches the blood-brain barrier, research shows it can spew out chemicals that loosen the barrier membrane, allowing the fungus to enter neural tissue 🔗 https://pubmed.ncbi.nlm.nih.gov/37819761/. This appears to trigger the production of a chemical called amyloid beta, which prompts the brain's immune cells, known as microglia, to combat fungal growth. If this process goes awry, the amyloid beta might build up into the plaques associated with Alzheimer's, suggests Parker.

As yet, we have just a faint pencil sketch of the brain's microbiome. There is still much to be discovered – including treatments that specifically target unbalanced microbiomes. Then, many more dementias may be reversible.

This article is part of a special series on the brain, in which we explore:

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