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Microglia pruning brain synapses captured on film for the first time

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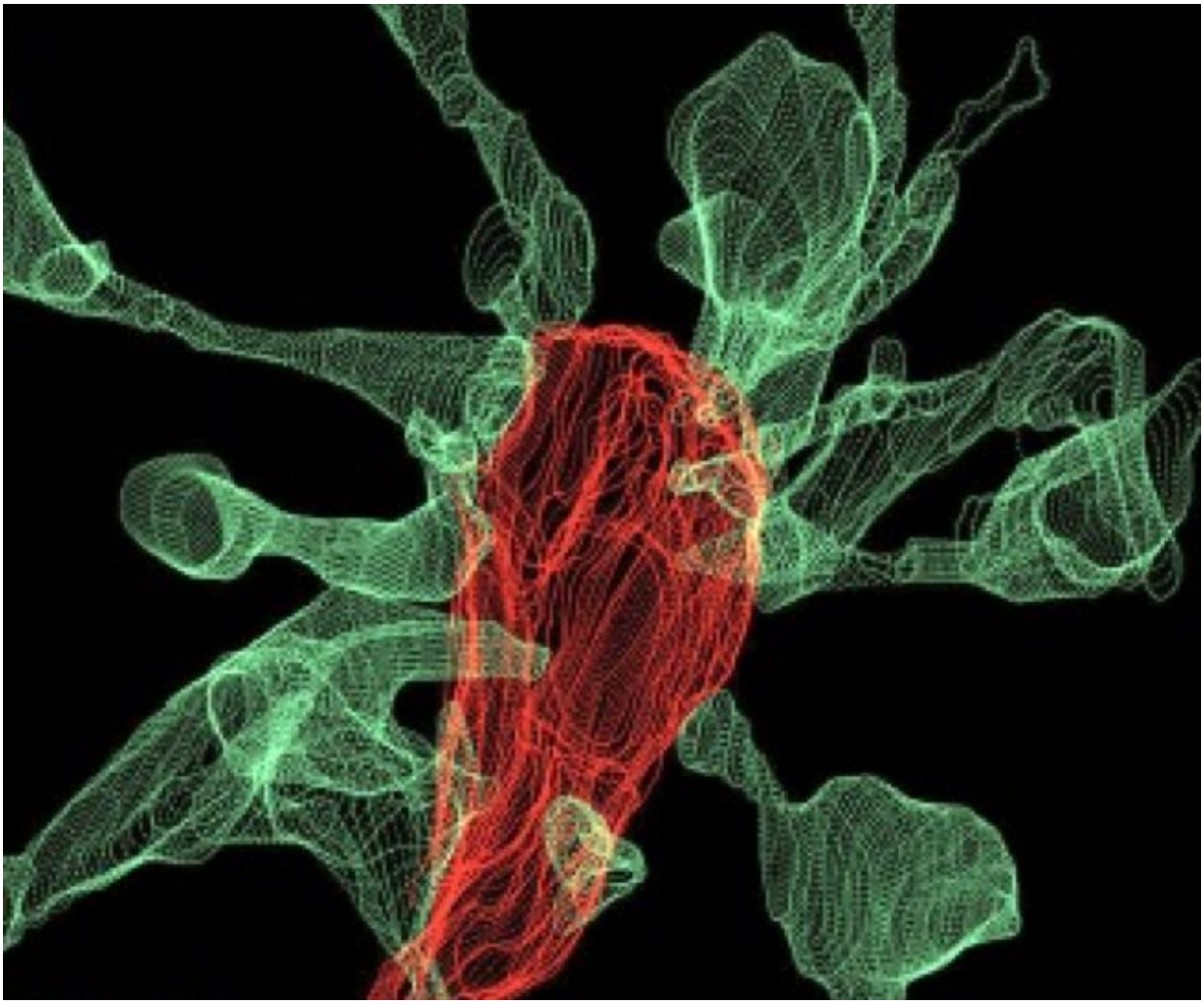

Multiple synapse heads send out filopodia (green) converging on one microglia (red), as seen by focused ion beam scanning electron microscopy (FIBSEM). Credit: L. Weinhard, EMBL Rome

For the first time, EMBL researchers have captured microglia pruning synaptic connections between brain cells. Their findings show that the special glial cells help synapses grow and rearrange, demonstrating the essential role of microglia in brain development. *Nature Communications* will publish the results on March 26.

Around one in 10 brain cells are microglia. Cousins of macrophages, they act as the first and main contact in the central nervous system's active immune defense. They also guide healthy brain development. Researchers have proposed that microglia prune synapses as an essential step during early circuit refinement. But until now, no one had observed this activity.

Microglia make synapses stronger

Laetitia Weinhard from the Gross group at EMBL Rome set out on a massive imaging study to observe this process in action in the mouse brain, in collaboration with the Schwab team at EMBL Heidelberg. "Our findings suggest that microglia are nibbling synapses as a way to make them stronger, rather than weaker," says Cornelius Gross, who led the work.

Around half of the time, microglia contact a synapse, and the synapse head sends out thin projections called filopodia to contact them. In one particularly dramatic case—as seen in the accompanying image—15 synapse heads extended filopodia toward a single microglia as it picked on a synapse. "As we were trying to see how microglia eliminate synapses, we realised that microglia actually induce their growth most of the time," Laetitia Weinhard explains.

It turns out that microglia might underly the formation of double synapses, in which the terminal end of a neuron releases neurotransmitters onto two neighboring partners instead of one. This

process can support effective connectivity between neurons. Weinhard says, "This shows that microglia are broadly involved in structural plasticity and might induce the rearrangement of synapses, a mechanism underlying learning and memory."

Perseverance

Since this was the first attempt to visualise this process in the brain, the current paper entails five years of technological development. The team tried three different state-of-the-art imaging systems before succeeding. Finally, by combining correlative light and electron microscopy (CLEM) and light sheet fluorescence microscopy—a technique developed at EMBL—they were able to make the first movie of microglia eating synapses.

"This is what neuroscientists have fantasised about for years, but nobody had ever seen before," says Cornelius Gross. "These findings allow us to propose a mechanism for the role of microglia in the remodeling and evolution of brain circuits during development." In the future, he plans to investigate the role of microglia in brain development during adolescence and the possible link to the onset of schizophrenia and depression.

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