First wireless map of worm's nervous system revealed

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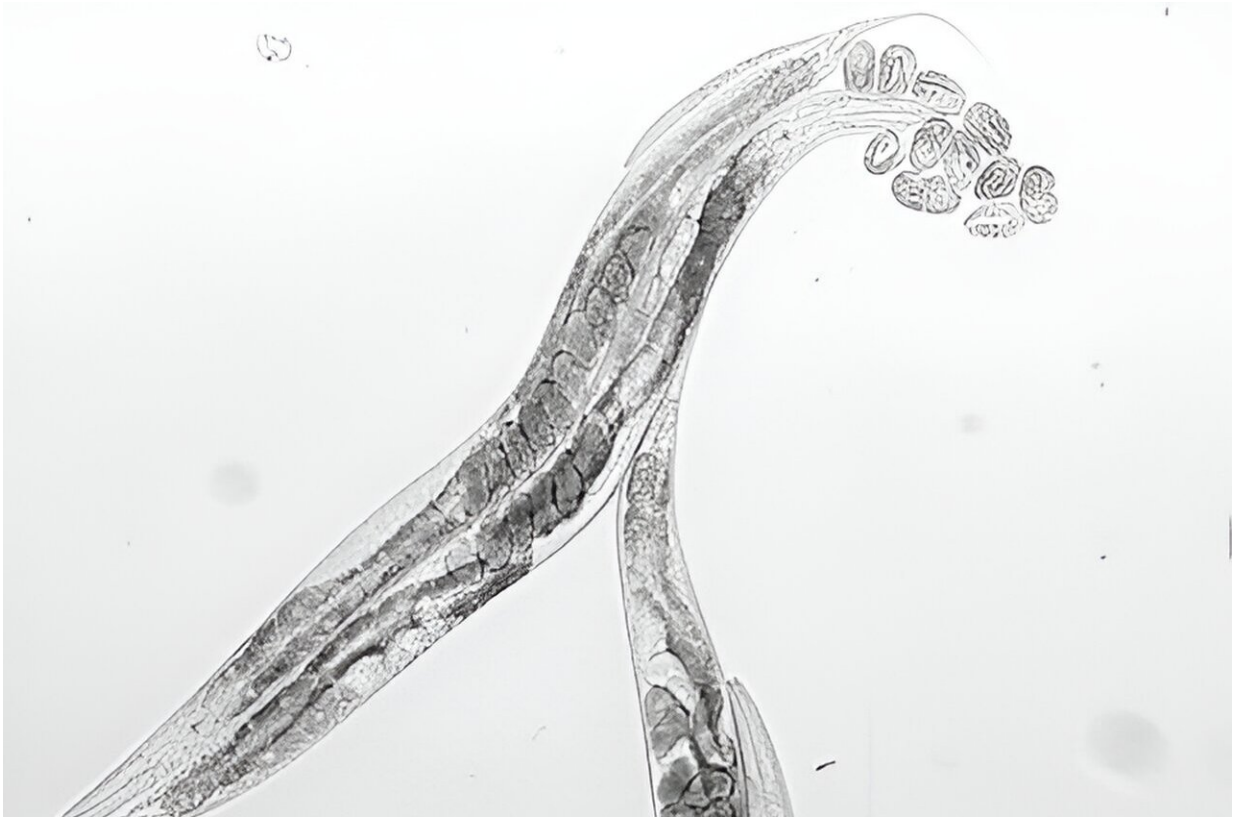

C. elegans. Credit: Kdfj/Wikimedia Commons, CC BY-SA

Researchers have built the first ever map showing how every single neuron in the nervous system of a tiny worm communicates wirelessly. This huge step forward in understanding how neurons communicate

through extremely short proteins called neuropeptides will help scientists understand how our emotions and mental states are controlled, as well as widespread neuropsychiatric conditions like eating disorders, OCD and PSTD.

The map, which details 31,479 neuropeptide interactions between the worm's 302 neurons, shows where each neuropeptide, as well as each receptor for those peptides, acts in the animal's nervous system. Neuropeptides allow communication between neurons that are not immediately next to each other, so their networks can be thought of as a wireless connectome. A connectome is a map of the neurons which make up an organism's brain and the detailed circuitry of neural pathways within it.

Researchers are making rapid progress in building connectomes for simple organisms, but until now, no-one had managed to build a map of a neuropeptide network in any animal.

Dr. William Schafer and Ph.D. student, Lidia Ripoll-Sánchez, both of the Medical Research Council Laboratory of Molecular Biology in Cambridge in the U.K., led the work, together with Petra Vértes of Cambridge University and Isabel Beets from KU Leuven in Belgium. Their study is published in *Neuron* today (Nov. 6).

The worm they studied is called C. elegans. It's harmless, around 1mm long, and lives in soil. C. elegans has a very simple anatomy, but it shares many of the essential biological characteristics that are central problems of human biology.

Dr. Schafer said, "Neuropeptides and their receptors are among the hottest new targets for neuroactive drugs. For example, the diabetes and obesity drug Wegovy targets the receptor for the peptide GLP-1. But the way these drugs act in the brain at the network level is not well-

understood.

"The structure of neuropeptide networks suggests that they may process information in a different way to synaptic networks. Understanding how this works will not only help us understand how drugs work but also how our emotions and mental states are controlled.

"The idea of mapping these wireless networks has been one of our goals for a long time, but only now have the right combination of people and resources come together to make this actually possible."

Neuropeptides play a critical role in lasting biological responses. These diverse neuropeptides play important roles in mood, sexual behavior, learning and memory, sleep and addiction. They function throughout the nervous system, but can also act on other types of tissue as hormones. Oxytocin is one example: it acts on various circuits in the brain that affect bonding between parents and children, but it also causes contraction of the muscles of the uterus during childbirth. Even when neuropeptides act in the brain, they can allow communication between neurons that are not connected by the physical junctions, called synapses, used by classical neurotransmitters.

Since most neurons seem to make both neuropeptides and neuropeptide receptors, the communication pathways formed by neuropeptides make up large neural networks. These networks are extensive, complex, and critical to the functioning of the brain. As such, they are important for understanding the neuronal basis of behavior.

Ripoll-Sánchez said, "Basic mechanisms of neuropeptide signaling are shared in all animals: neuropeptides are released from dense core vesicles in cells and diffuse to neurons unconnected to the releasing cell by wired synapses.

"The worm's nervous system is anatomically small, but at the molecular level its neuropeptide systems are highly complex, showing significant parallels to larger animals, and its synaptic connectome shows many features that are conserved in bigger brains. We expect the neuropeptide connectome of C. elegans will serve as a prototype to understand wireless signaling in larger nervous systems."

The researchers built the map by combining biochemical, anatomical and gene expression datasets, using them to determine which neurons can communicate with each other using specific neuropeptide signals. Once they built this network, they used graph theory to analyze its structure and identify key topological features as well as neurons with important roles in linking different parts of the network.

As well as generating the first comprehensive map of neuropeptide signaling in a whole animal, the researchers found that the wireless neuropeptide network in C. elegans has a different structure from wired connectomes. They are denser, more decentralized, and have different key neurons, or hubs. The network also connects parts of the nervous system that are isolated from the wired synaptic connectome.

Jo Latimer, Head of Neurosciences and Mental Health at the Medical Research Council, said, "This is another exciting and significant body of work by colleagues at the MRC Laboratory of Molecular Biology and others, adding to the connectome work of LMB researchers earlier this year. Not only have they worked out which neuropeptides act where in the animal's nervous system, they have discovered that the network is complex, but clearly organized, with an information processing circuit within it.

"This is a further important step forward in understanding how brains and nervous systems work, and this increased understanding may have the potential to lead to the future development of targeted therapies for a

range of conditions."

The next step will be to see whether the principles by which neuropeptide networks in worms are organized also apply in bigger brains. The researchers are currently working with other collaborators to map wireless neuropeptide networks in animals such as fish, octopuses, mice, and even humans.

More information: Lidia Ripoll-Sánchez et al., The neuropeptidergic connectome of C. elegans, *Neuron* (2023). DOI: 10.1016/j.neuron.2023.09.043. www.cell.com/neuron/fulltext/S0896-6273(23)00756-0

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