Mapping the Human Brain: The Connectomes of *C. Elegans* and Fruit Fly Larva

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There are more neurons in your brain than stars in the Milky Way. With billions of neurons and trillions of connections, or synapses, between them, the human brain is extraordinarily complex. Scientists have long been seeking to create a connectome of the brain, the complete diagram of neurons and synapses in an organism's nervous system (Kwon, 2020). It would provide a "map" of the brain, to be used as a tool for more efficient, precise, and focused neuroscientific research, as well as a deeper understanding of the anatomy and neural network of the brain. However, building a human connectome, or any organism's connectome at all, is incredibly difficult. The more developed and complex the organism, the more its brain can be influenced by the environment, making each individual's brain very different from others'. Researchers thus needed to focus on much simpler organisms to begin the process of mapping the neural network of the brain.

Scientists decided to research the organism *Caenorhabditis Elegans*, or simply *C. Elegans*, to learn more about the brain. This non-parasitic, millimeter long nematode worm has only 959 somatic cells, around 300 of which are neurons ("What is…," n.d.). It is one of the most widely used model organisms in biological studies, and it was the first multicellular organism to have its genome completed (Meneely, Dahlberg & Rose, 2019). It is one of the smallest, most primitive organisms in existence that still shares many of the same biological features as humans ("What is…," n.d.). Researchers can record activity from the entire brain simultaneously, allowing them to obtain a better picture of how neural dynamics generate functions and behaviors (Randi & Leifer, 2020). By visualizing the entire brain at once, room for error or speculation can be eliminated. For example, there are no unobserved neurons that might have created an unexplained behavior (Randi & Leifer, 2020).

In 1986, a team of scientists led by Sydney Brenner published a nearly complete draft of the connectome of the 302 neurons in a hermaphrodite (male and female reproductive organs) *C. Elegans* (Jabr, 2012). This impressive feat was painstakingly done through the slicing and photographing of the *C. Elegans*' body with an electron microscope. Using this model, scientists were able to analyze and understand multiple things. They quickly distinguished motor neurons, sensory neurons, and interneurons ("connecting" neurons), and the different connections between them (Jabr, 2012). The connectome is extremely useful in analyzing which neurons serve what purpose. By knowing which neurons to stimulate, and what other neurons they connect to, more specific, efficient studies can be done on the organism's behavior.

In a study investigating quiescence, a sleep-like, lethargic state, scientists were able to identify specific neurons that stayed active, such as the sleep-inducing neuron RIS (Nichols et. al, 2017). Also, many investigations studying the neural circuits responsible for movement have been done using *C. Elegans*, supported by the connectome. For example, in the 1980s, Martin Chalfie used the connectome to identify which cells "were connected to which" in his experiment on forward and backward movement patterns of the worm (Jabr, 2012).

Nevertheless, this connectome wasn't perfect, and lacked an important component. In 2012, a team headed by Scott Emmons published the connectome of a male *C. Elegans*, which has 383 neurons. This connectome featured synaptic weights, meaning some neuronal connections were stronger than others (Jabr, 2012). This feature of a connectome is extraordinarily important, because these differences in strength contribute to the brain plasticity needed for learning and memory. Interestingly, *C. Elegans*, a nematode worm, shares some of the same features in its nervous system that contribute to learning and memory acquisition and storage. Rather than something completely new and seen only in complex organisms such as ourselves, these properties can be found in very primitive species. Some neuroscientists also stipulate that genes control the tightest connections between neurons (Jabr, 2012). Many disease-associated genes in humans have orthologs, genes that retain the same function in two species sharing a common ancestor, in *C. Elegans* (Liang, McKinnon, & Rankin, 2020). This makes *C. Elegans* a very useful organism to study neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease in. Using its connectome will allow for more targeted research to be done on these important topics.

Furthermore, a full connectome of the brain of the larva of *Drosophila melanogaster*, a fruit fly, was completed in 2023 by researchers at the University of Cambridge. It shows the over

3,000 neurons and over 500,000 synapses in the organism's brain (NIH, 2023). They found that certain neurons could have multiple pathways from sensory input neurons to the output neurons, and that this so-called "recurrent architecture" was more prevalent in neurons related to learning (NIH, 2023). Neurons with a high number of connections were more likely to be connected to either the learning center of the fly's brain, or the opposite brain hemisphere, suggesting the importance of the connection of the hemispheres, and also of learning, even for this small fly.

As the analyzing of the connectome pairs with behavioral studies in these organisms, neuroscientists will obtain a deeper understanding of how neurons work together to form circuits to execute different behaviors. Nonetheless, this connectome is only the beginning. A connectome acts as a roadmap for neuroscientists, a way for them to understand where to begin their research on different neurons and their functions. But, scientists then need to perform additional experiments on the actual mechanisms behind different behaviors.

Although we might never complete the connectome of the trillions of synapses in the human brain, scientists have already achieved success working with *C. Elegans* and fruit flies. These brain "maps" will help them create targeted, specific experiments on human behaviors and diseases, leading to many more discoveries on the human brain.

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