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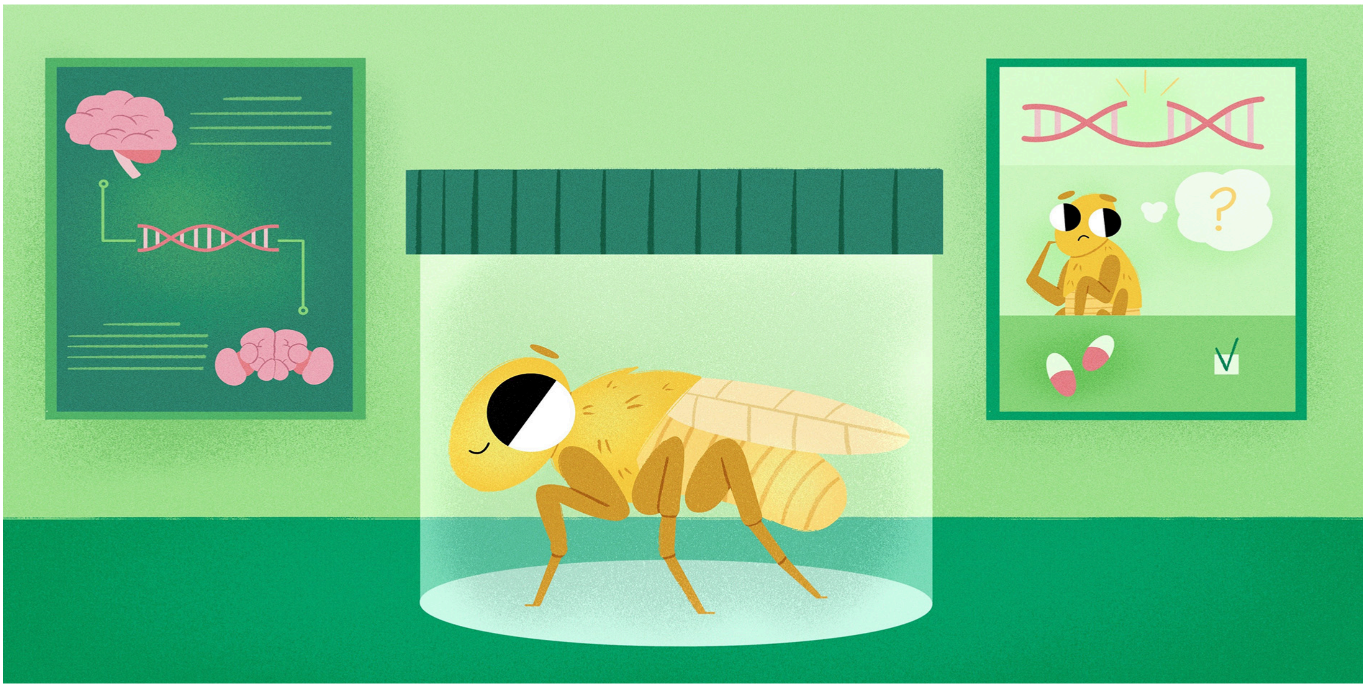

WHAT CAN FLIES TEACH US ABOUT BRAIN DISEASES?

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AGE: 13


SOPHIE
AGE: 13


SURABI
AGE: 15

Diseases that affect the brain are one of the leading causes of disability worldwide. Many doctors and scientists are trying to work out how these diseases arise and how they can be treated. Unfortunately, the brain is an extremely complicated organ, so this goal is very challenging. One way of simplifying this challenge is to look at simpler brains. For example, a human brain has about 100,000 times more brain cells than a fruit fly brain, but it works in a similar way. Although a fruit fly may seem very different from a human, we still have a lot in common. For example, we both have brains that control how we move our bodies. Scientists are using fruit fly brains to study a wide range of brain diseases that affect human patients. Fly brains can be used to understand how a disease happens, and they can even be used to test drugs to discover new medicines. This article gives an overview of how scientists are using flies to help understand and treat brain disorders.

WHAT IS A MODEL?

When a scientist wants to understand how something works, they have two main ways of approaching the problem. The first way is to try to study the thing itself, observing it closely, and taking careful measurements. However, in some cases, direct observation may not be possible because the phenomenon that the scientist is interested in may be too rare or difficult to measure. In these cases, scientists turn to **models** to simplify the problem into a version that they can more easily study. For example, if you wanted to understand how an airplane wing works, but you did not live anywhere near an airport, you could build a simple model from paper and throw it out the window. You may not think this is a very good representation of an actual airplane, with its complicated engines and electrical components, however, if you were only interested in how its wings moved through the air, then the model version may be good enough to help you come up with some ideas.

MODELS

A simpler version of a complicated system that scientists can easily perform experiments on. This leads to better understanding of the complex system.

We can use similar models to understand the brain. The human brain is one of the most complicated structures in existence, consisting of over 100 billion cells that are connected in intricate patterns, and in constant communication with the rest of the body. Furthermore, most humans do not want their brains to be removed from their heads and studied—even in the name of science! Far from being put off by the difficulties presented by the brain's complexity and inaccessibility, the field of **neuroscience** is one of the most active fields in modern science. Neuroscientists study the brain because brain function is a fundamental scientific mystery, and also because if scientists and doctors want to treat diseases of the brain, they need to understand how it works. Some scientists do study the brain directly using sophisticated technologies like magnetic resonance imaging scanners. However, many researchers prefer to use simpler models, on which experiments can be more easily conducted.

NEUROSCIENCE

The scientific field that addresses questions relating to the nervous system.

FLIES AS A MODEL FOR BRAIN STUDIES

Models for neuroscience studies can take many forms. Some can exist entirely within a computer, in which approximations of brain function are built purely from mathematical principles. Many scientists choose to study mice because mice and humans are both mammals, so we share many similarities. However, it is **unethical** to do unlimited experiments on mice, and the mouse brain is still very complicated! Therefore, scientists can turn to simpler animals such as fruit flies. The fly brain contains around 200,000 brain cells compared to humans' 80 billion [1]—therefore, fly brains are much simpler. Despite its small size, the fly brain can coordinate complicated behaviors, and many of the basic principles of its function are the same as those of the human brain.

UNETHICAL

If an experiment is unethical it does not adhere to the moral standards of society. This may be because it causes undue suffering to an animal.

MUTATIONS

Changes in the DNA sequence of a gene that may cause disease.

GENE

A section of the DNA that affects a physical characteristic, like hair or eye color.

Many diseases are caused by **mutations**—changes in the DNA sequence. Around 75% of the **genes** that are responsible for diseases in humans are also found in flies [2]. One of the reasons that scientists love to use flies is that they can make mutations in fly genes very easily. Therefore, by making equivalent mutations in the fly DNA, scientists can create models of human diseases. When they study these mutations, scientists can often see that the flies experience the same (or similar) symptoms as humans (Figure 1). Scientists have been studying flies for over 100 years, and they understand the fly brain better than almost any other animal.

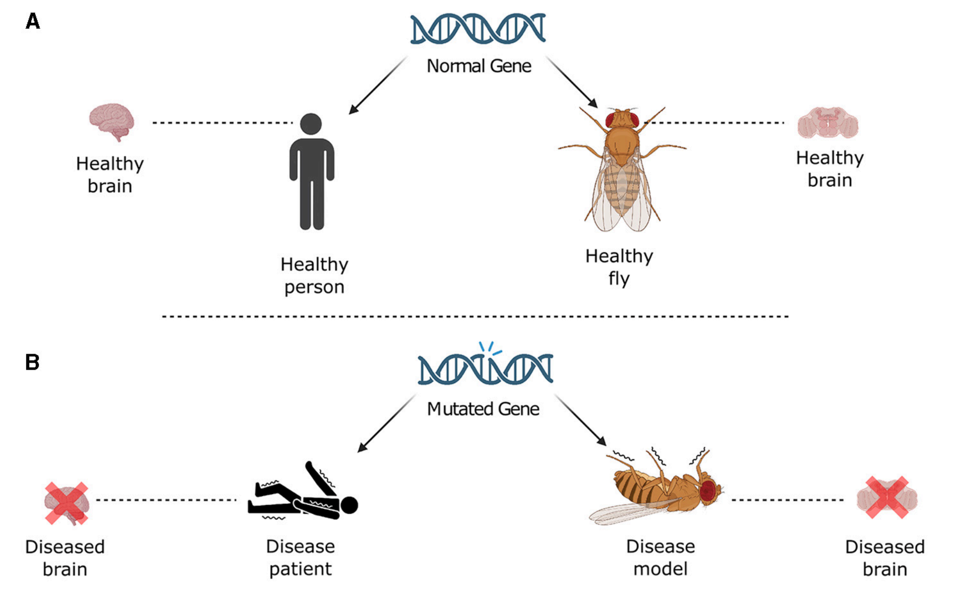

Figure 1

Figure 1

(A) Normal genes contribute to the proper functioning of the brain in both humans and flies. **(B)** Mutations result in disrupted brain function, leading to disease. In this case, both the fly and the human are experiencing similar symptoms in the form of a seizure.

The lifecycle of a fly—the time it takes to develop from an egg to a mature adult—is only 10 days. This means that scientists can breed lots of experimental subjects in a very short time. The longest an adult fly can live is around 100 days. This makes them especially useful to model diseases that get worse as people get older, as experiments looking at "middle aged" flies will take only a few weeks, while they would take months or years using other model animals like mice or rats.

TESTING BEHAVIOR IN MODEL FLIES

Once scientists have made a model by changing the fly's DNA to include a disease-causing mutation, the next step is to see what effect the mutation has on the fly. Diseases affecting the brain can cause a wide range of symptoms. Some, such as Alzheimer's Disease, affect a person's ability to make new memories and recall old ones, while other diseases, such as Parkinson's Disease, affect the ability to move [3]. Diseases may shorten people's lifespans, affect their moods, or disrupt their sleep. Because scientists have been studying flies for so long, they understand fly behavior very well, and they can design experiments to test whether a mutation affects a fly's normal behavior.

When scientists choose what sort of model to use to study a disease, it is important to think about what sort of experiments they will need to do. For example, if a disease primarily affects people's ability to speak, scientists might not be able to learn much from a fly model. On the other hand, flies exhibit many behaviors that are similar to ours, though usually simpler. They sleep, can form memories and recall them days later, and of course they can move around. If a brain disease affects any of these behaviors, scientists can test whether the behavior is altered in the fly model.

There are many types of experiments to test a fly's ability to move. These experiments can be simple and "high throughput", which means scientists can test a lot of flies very rapidly. For example, experiments might involve testing how long it takes a fly to climb a certain distance [4]. Other experiments could be more complicated, which means they are slower to perform and fewer flies can be tested quickly, but they give scientists much more information. For example, scientists can take high-speed videos of flies walking to view them in slow motion, and use a computer program to analyse changes in fly movements too small for the scientists to see with their eyes (Figure 2). Experiments will always be performed on a test subject and a **control**, which is used to establish a baseline to compare the test subject to. In this case, the control would be a healthy fly with normal movement, so scientists can see whether the mutation changes movement when compared to a healthy fly.

CONTROL

An experimental group in which no changes are made. Controls are used to compare to a test condition to see if it produces any effect.

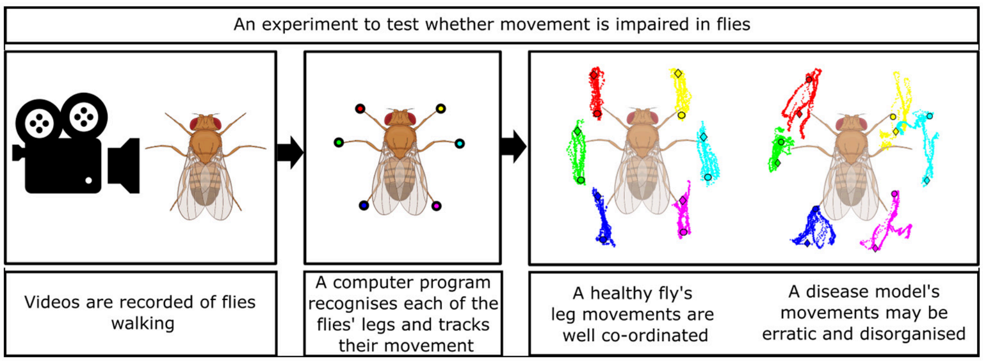

Figure 2

Figure 2

Scientists can record videos of flies walking in slow motion, to study how well their walking is coordinated. This can help them to test whether mutating a fly gene can affect its brain.

Once scientists have established that a mutation has an effect on the animal—whether this is impaired movement, inability to sleep normally, or inability to form new memories—the next step is to understand *how* this is happening. Understanding how mutations cause problems gives insight into how the brain works and how scientists and doctors might go about treating the disease. One way to understand the effects of a mutation is to investigate the structure

NEURONS

One of the main cell types of the brain. Neurons communicate with other cells using electrical signals.

and function of the brain. The most important cells in the brain that talk to each other *via* electrical signals are called **neurons**. Neurons form complicated networks, in which one neuron may connect to and communicate with thousands of others. Each neuron has a unique shape and form, allowing it to perform its specific job. Using high-powered microscopes, scientists can investigate whether neurons in the brain of a disease model fly have an abnormal shape compared to healthy controls. Abnormal neurons might affect the function of the brain network, and because everything we do depends on these brain networks working correctly, these abnormal neurons might be the cause of altered behaviors. If there is a difference in the shape of a neuron, it may be because the neuron failed to form correctly in the young developing brain (which is why some diseases are present from birth), or it may be because the neuron initially formed correctly, but then began to degrade and die later on (which is why some diseases do not occur until people are older, and get worse with age).

Together, experiments like these can tell scientists a lot about how a mutation causes a disease, and how they might treat it. For example, in Parkinson's disease, certain neurons die off more quickly than usual as people get older, which affects the brain's ability to control movement. Some people with Parkinson's have mutations in a gene called *PRKN*. Scientists made fly models with the same mutations in the fly version of the *PRKN* gene, and tested their behavior. The flies could move normally when they were younger, but as they aged, their ability to climb and fly got worse much more quickly than usual. This helped prove that the mutation in *PRKN* was causing Parkinson's disease, and scientists are continuing to research how it does so and why it kills certain neurons [3].

USING FLIES TO FIND NEW MEDICINES

When people get sick, sometimes their illnesses can be treated with medicines. Medicines often change something in the person's body to make them feel better. Medicines can work by helping an illness to improve, or by minimizing the symptoms that make a person feel bad—for example, you may take a painkiller when you have a common cold or a headache. For many diseases, there are already medicines available that a doctor can prescribe. However, for some diseases there are few or no medicines available. In these cases, scientists and doctors are trying to discover new medicines that can help these patients. Unfortunately, it can be very difficult and take a long time to discover new drugs that can become safe medicines.

This is where flies come in! Research on flies is relatively fast and cheap compared to some other scientific techniques, because scientists can generate lots of flies in a small amount of time, and their food and upkeep are very affordable. Fly models of disease can be fantastic tools to find new medicines for people with brain diseases that may not have many drug treatments currently available [5]. Testing new drugs on flies can be the first step to find out if a drug may be helpful for a patient. For example, if a drug improves the way a fly can walk, then it is possible the drug may have a similar effect in patients with the disease that scientists are modeling (Figure 3). Again, these experiments can be "high throughput"—since flies are cheap and quick to grow, scientists can test lots of drugs on flies in a short space of time. Any drugs that look like they rescue some features of a brain disease in the fly can be taken forward for more testing, to ensure they are effective and safe before being given to humans. The ultimate aim of this kind of research is to find new drugs that might help patients with diseases to feel much better.

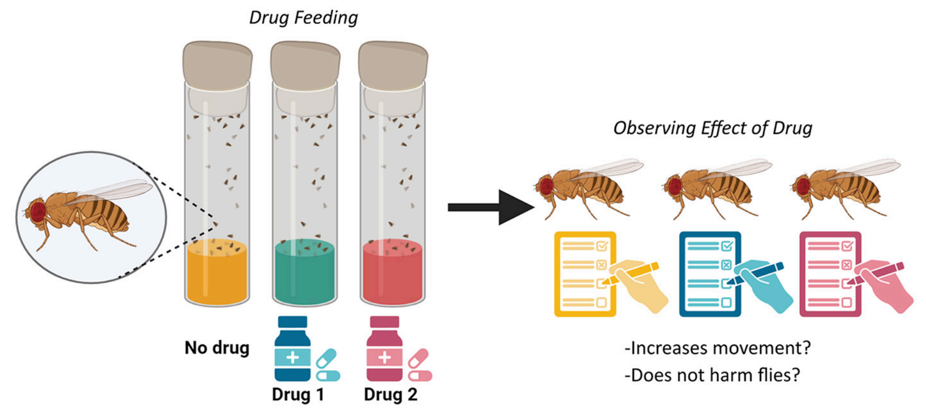

Figure 3

Figure 3

Flies can be used to test the effects of drugs to see if they might make good medicines. Drugs are added to the fly food, then the flies that ate the drug are examined for effects, compared to control flies that had no drug treatment.

THE FUTURE FOR FLIES IN RESEARCH

The effort to understand and develop treatments for brain diseases is an ongoing process. Many years more research will be required to fully understand the nervous system and its disorders, but with a large variety of tools at their disposal, scientists are making great progress. We hope that we have convinced you that, although they are tiny, flies are an important resource for tackling these problems.

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ALEX, AGE: 13
Alex, a 13-year-old student in 7th grade from New York, is interested in science. He reads and independently studies various topics that fascinate him across different scientific fields.

ANISHA, AGE: 13
My name is Anisha and I am 13 years old. I am in seventh grade. Some of my hobbies are that I do choral singing and I am a ballroom dancer. Science is definitely one of my passions that I deeply enjoy and want to pursue in my future.

SOPHIE, AGE: 13
Sophie is an outstanding student from New York. She is very interested in ecology and environmental conservation.

SURABI, AGE: 15
My name is Surabi. I am 15 years old. I am a sophomore. I am a competitive dancer and a volleyball player. I want to become a doctor.

AUTHORS

ABIGAIL D. WILSON
Dr Abigail Wilson is a research fellow based at the Institute of Neurology at University College London (UK). Her current research aims to advance our understanding of disease mechanisms in neurological movement disorders such as dystonia, and to identify new treatments to improve symptoms of the disease. This research uses *Drosophila*, or fruit flies, to model human diseases. Before her work at UCL, Abigail researched cardiovascular diseases at the University of Oxford—her Ph.D. focused on the causes of sudden cardiac death. Her hobbies include long-distance running and skiing.

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Simon Lowe is a research fellow working the UCL Institute of Neurology in London. He studied psychology and philosophy at Oxford University before doing a master's degree in neuroscience at King's College London. His Ph.D. was at Bristol University, where he started using fruit flies to model human diseases, studying the mechanism of Alzheimer's disease and Down syndrome. He is interested in how mutations in our DNA can alter the way our brains develop, how this can cause diseases, and how we can go on to treat them. Outside of science he likes rock climbing, kayaking, and playing the guitar.

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James Jepson is a professor of neurogenetics at the UCL Queen Square Institute of Neurology. After his D.Phil. at Oxford University, he moved to America to study genes influencing complex behaviors in the fruit fly, *Drosophila*, then established his own group at UCL. His lab focuses on using *Drosophila* to study movement and neurodevelopmental disorders. He also tries to be a good dad to his young son, and enjoys chess, tai chi, mindfulness, and science fiction novels—when time permits.

GABRIEL N. AUGHEY
Gabriel Aughey initially studied biochemistry in Cardiff, before completing a Ph.D. in genetics at the University of Oxford, and postdoctoral research at Imperial College London. He is currently a research fellow at University College London. He is interested in how changes in gene expression contribute to nervous system development and neurological diseases, and he likes working with flies to answer these questions. In his spare time, he enjoys hiking, running, and cycling on and off road. *g.aughey@ucl.ac.uk