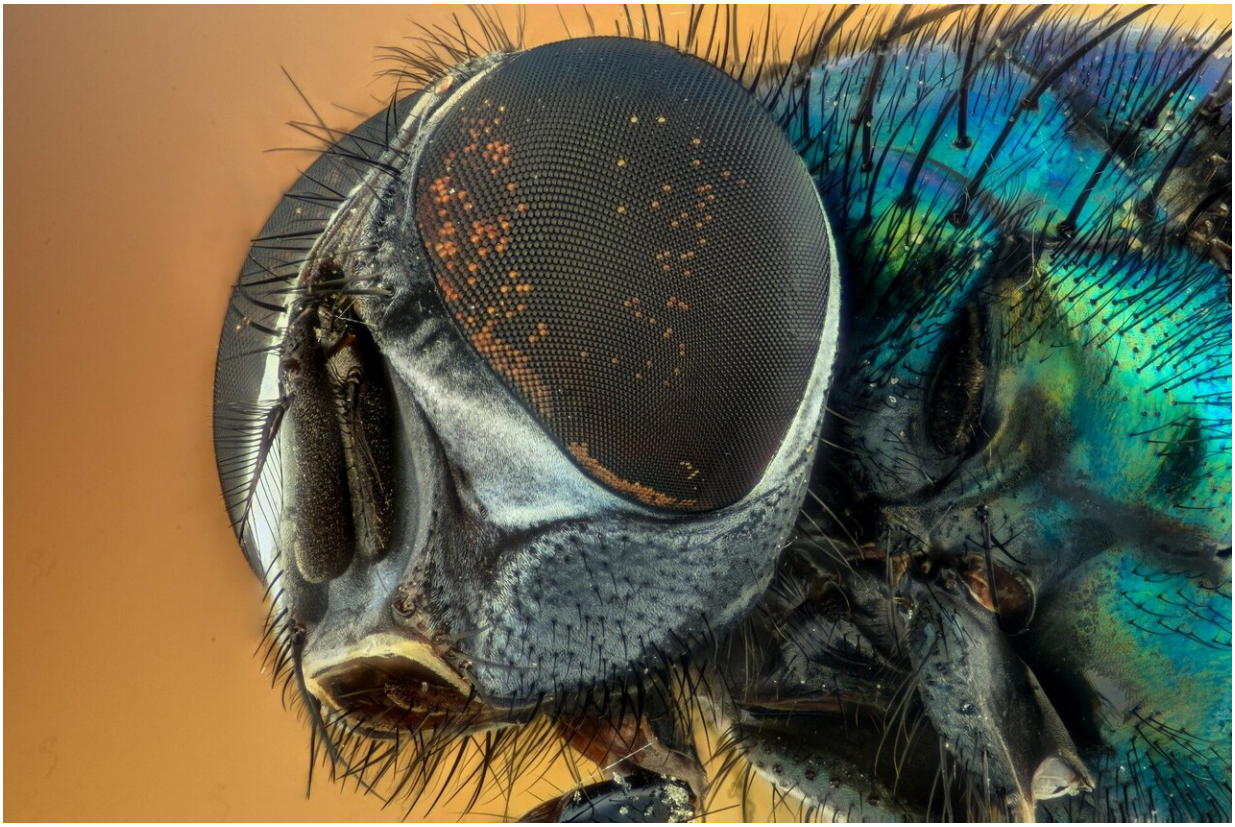
Q&A: Dissecting movement disorders through the eyes of a fly

October 12 2020



Credit: CC0 Public Domain

Every time we move, electrical impulses are channeled along neuronal highways, jumping from nerve cell to nerve cell until they reach a muscle, causing it to contract. Because muscle movement depends on

neuronal function, neurodegenerative diseases can sometimes result in debilitating symptoms like tremors or rigidity.

Neurodegenerative diseases, which include Alzheimer's and Parkinson's disease (PD), affect millions worldwide. Importantly, a group of these diseases, known as movement disorders, are essentially incurable, significantly affecting a patient's quality of life.

Sherry Aw, Independent Fellow and group leader at A*STAR's Institute of Molecular and Cellular Biology (IMCB), leads a research group that studies the biology behind movement disorders. Using the fruit fly (Drosophila melanogaster) as a disease model, her group aims to understand the pathology behind these disorders and devise new therapeutic and diagnostic strategies. In this interview with A*STAR Research, Aw shares about her work and how she plans to dissect the science behind movement disorders like PD.

Why did you choose to study neuroscience, and in particular, neurodegenerative diseases?

My interest in neuroscience began from a place of curiosity: despite great advances in understanding neurophysiology, there is still so much to discover about how the brain functions. Even now, we still do not really understand how the brain does what it does as a whole.

It was later during my post-doctoral training at Professor Stephen Cohen's lab at IMCB that I developed a more specific interest in neurodegenerative diseases. In particular, I study a class of neurodegenerative diseases called movement disorders, which, broadly speaking, are diseases that lead to loss of control over voluntary movement. Not only are these conditions highly debilitating for the patient, but they are also of growing socioeconomic impact in aging

societies like ours. There are also no disease-modifying cures for most of these disorders at the moment, which can be partially attributed to our lack of understanding at the level of their basic biology.

Broadly, what key problem(s) are you trying to solve with your research?

Movement disorders are characterized by difficulties in controlling voluntary movements, resulting in certain signs like hand tremors. For example, patients with spinocerebellar ataxia 3 (SCA3), a rare genetic movement disorder, suffer from worsening coordination of their gait, hands, speech and eye movements.

However, the specific changes in movement control are distinct between one condition and another. For example, while SCA3 is associated with excessive, involuntary movement like jerkiness and poor coordination, Parkinson's disease (PD) leads to rigidity and slowness of movement. These different behaviors likely arise from the different types of neuronal circuitry affected. Hence, we aim to characterize these vulnerable neuron types and dissect their underlying neurogenetic and molecular mechanisms.

Why are fruit flies a suitable model for studying human movement disorders?

Despite the obvious differences between the two species, the fruit fly has helped to illuminate numerous conserved mechanisms of human brain function and neurodegenerative diseases. We use the fruit fly as a disease model for human movement disorders because very fundamental principles of neuronal function are conserved from fly to human, not just at the molecular and cellular levels, but even up to the level of neuronal circuitry.

We found these similarities in a previous study using a fully automated machine learning-based program that we developed for tracking the movements of fruit fly leg movements, called Feature Learning-based LImb segmentation and Tracking (FLLIT). In that study, we showed for the first time that there is a close resemblance between the gaits of fly PD and SCA3 models compared to human patients with those respective diseases. Importantly, these findings suggest that the motor neuronal circuitry is well-conserved between flies and humans. Since the fruit fly possesses a million times fewer neurons than humans, studying these questions in the fruit fly model allows us to investigate the complex mechanisms underlying these movement disorders in a more simplified model.

What are some of the research questions you are tackling now?

Using FLLIT, we reported the first measurement of leg tremors in flies and discovered that those with SCA3 exhibited strong tremors when walking. Currently, we intend to follow up on these findings to elucidate the molecular and cellular mechanisms behind these tremors. Specifically, we are trying to understand how dysfunctions in the underlying neuronal circuitry in flies with SCA3 can lead to tremors.

Other than that, we are also working to optimize a microRNA sensor that we developed, called Pandan. MicroRNAs are a promising group of biomarkers for many diseases, including neurodegenerative diseases. However, current methods for microRNA detection require advanced training and costly equipment. By enhancing the sensitivity and specificity of Pandan, our microRNA sensor could potentially be used as a low-cost clinical diagnostic tool for movement disorders and other diseases in the future.

What are some of the implications your research will have for neurodegenerative diseases?

We hope that by understanding the basic mechanisms underlying movement disorders, we will be able to identify new therapeutic and diagnostic strategies against neurodegenerative diseases. For example, our research could potentially unravel the biochemical pathways whose dysfunctions contribute to specific movement disorders, enabling us to identify novel candidate genes that can serve as the basis for new clinical therapeutics.

Going forward, what other related research questions will you be pursuing?

I believe our work will evolve in two directions. First, we hope to expand and validate the neurogenetic mechanisms that we are discovering in flies using mammalian animal models over the next five to ten years. Second, we aim to put a greater focus on translational research, especially in the area of drug development. For example, we are using FLLIT to study the cellular mechanisms that underlie tremors, which are very prevalent but poorly understood. We plan to apply our method towards behavioral phenotype-based drug screening, in order to identify potential druggable targets that underlie movement disorders.

Provided by Agency for Science, Technology and Research (A*STAR), Singapore