Fruit fly models of schizophrenia, a philosophical account

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A thesis to partially fulfil the requirements of a Masters by Research

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Abstract

Drosophila melanogaster – the common fruit fly - has been a model organism in science for over one hundred years. Thanks to a shared ancestor hundreds of million years ago, a surprisingly large number of features are common between fruit flies and humans. This conservation of features allows researchers to model how mechanistic breakdown or malfunction can lead to diseases in humans. There has been great success in research in Parkinson's disease using the Drosophila to model the relevant features of the disease. This past success has led to a call for other diseases, such as schizophrenia, to be modelled in Drosophila. How these models succeed, why mechanistic explanations are preferred in neuroscience will be explored to give an account of when we can expect success from such an enterprise. By modelling the mechanisms that cause disease, in model organisms, scientists can explore how these neuroanatomical and neurochemical features lead to specific changes that can explain symptoms of human sufferers. Drosophila are a vessel for studying the *in vivo* action of mechanisms of interest. The knowledge of the molecular action of the mechanism is refined by testing the action of the mechanism in other model organisms. Drosophila are the ideal starting point to explore mechanistic causes of disease *in vivo*.

Introduction: How can a fruit fly model for a human?

Bane of kitchen bins across the globe, *Drosophila melanogaster*, the fruit fly, has a surprising role in science. Scientists use Drosophila as a sophisticated, organic tool for uncovering and understanding the mechanisms behind human diseases.[1] Drosophila are used as models for many different biological phenomena, and as stand-ins for humans in the exploration of genetic disorders and other diseases.[2] Drosophila*'s* century as a tool of science, and its central role in many important discoveries has led to the nickname the 'golden bug'.[3]

This thesis will explore questions of how we are able to use Drosophila to model human neurological disease through two case studies: the successful example of Parkinson's disease, and the more challenging proposition to model schizophrenia using the fruit fly. I will use the positive case of Parkinson's disease to illustrate the epistemological and practical underpinnings of Drosophila research into neurological disease. The case of schizophrenia provides a lens to explore the complications of these modelling exercises.

Model organisms have been used in science to explore many biological phenomena; there are today 13 official model organisms listed by the U.S. National Institute of Health (NIH).[4] Initially explored as objects of interest; some organisms are now used to explore mechanisms and features that are common between species.[5] Model organisms are frequently used for what they can reveal about humans. They can model human diseases thanks to the commonality of features and anatomical functions between the two organisms.[6] The perseveration of genes, neurotransmitters, cell development and many

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[1] Robert E. Kohler, *Lords of the Fly: Drosophila Genetics and the Experimental Life* (Chicago and London: The University of Chicago Press, 1994).
[2] Berrak Ugur, Kuchuan Chen, and Hugo J. Bellen, "Drosophila Tools and Assays for the Study of Human Diseases," *Disease Models & Mechanisms* 9, no. 3 (2016).
[3] Gerald M. Rubin and Edward B. Lewis, "A Brief History of Drosophila's Contributions to Genome Research," *Science* 287, no. 5461 (2000).
[4] National Institute of Health, "Model Organisms for Biomedical Research. Bethesda, Md," National Institute of Health, http://www.nih.gov/science/models/ ; Sabina Leonelli and Rachel A. Ankeny, "What Makes a Model Organism?," *Endeavour* 37, no. 4 (2013).
[5] Rachel A. Ankeny and Sabina Leonelli, "What's So Special About Model Organisms?," *Studies in History and Philosophy of Science* 42, no. 2 (2011).
[6] Ugur, Chen, and Bellen.

other mechanisms, despite divergent evolution means that Drosophila are homologous to humans and other species in various ways.[7]

Through the discussion of Parkinon's disease, I will make a case for understanding model organisms as tools for exploring mechanisms. By relying on the homology of species, and the shared mechanistic features, scientists can understand the mechanisms behind disease. Researchers can engineer the Drosophila to contain the mechanisms and then explore their actions. The sophisticated tools available to scientists and researchers mean that Drosophila can be genetically engineered to carry genes and mutations, and the effects of these can be observed.[8] A homology, such as a gene correlated with Parkinson's disease, can be introduced into Drosophila and its molecular action studied *in vivo*. How this builds knowledge about human disease and functioning will be discussed as well as the complications of such research.

I will begin by defining model organisms, and briefly discuss the history of the Drosophila and its use as a model in biology and sub-disciplines. Through the development of advanced genetic engineering techniques, Drosophila have been crafted into a tool for exploring the mechanisms that give rise to phenomena.[9] This will inform the discussion of why philosophers argue we should prefer these kinds of mechanistic explanations over other forms of explanation.

I will define mechanistic explanations through exploring the Drosophila model of Parkinson's Disease. This example will illustrate the role of the Drosophila as a model for mechanisms of interest. It will also explore some of the components of mechanistic definitions; parts, causal relationships, and arrangement.

After outlining the case of Parkinson's Disease and Drosophila I will move to a broader discussion of how research moves from identifying a phenomenon (a disease and its symptoms) to idealising disease to a mechanistic explanation. The role of mechanisms in

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[7] Arnon Levy and Adrian Currie, "Model Organisms Aren't (Theoretical) Models," (2014).

[8] Peter A. Lawrence, *The Making of a Fly: The Genetics of Animal Design* (Cambridge, Mass., USA;Oxford [England];: Blackwell Science, 1992).

[9] Marcel Weber, *Philosophy of Experimental Biology* (New York: Cambridge University Press, 2004).

scientific explanation has been the topic of much discussion in philosophy of science, and I will consider the argument that we should prefer mechanistic explanations because of their predictive and explanatory power.

By discussing idealisation I will further my claim that model organisms are the vessel for investigating the object of interest; the mechanism that explains and predicts the phenomena under investigation. This idealisation and exploration of the mechanisms of disease is incredibly fruitful, and has a proven record of furthering our understanding of human diseases. However, it is a mistake to think of the Drosophila as a model of the disease, they are an *in vivo* experimental set-up to investigate, manipulate and understand the idealised *mechanism*, thought to give rise to the disease.

I will discuss the translation of knowledge from fruit fly to human and claim that we should understand model organisms as vessels for exploring the mechanisms behind human disease. This task relies on shared material practise and the employment of model organisms that have a long history of use in biology, leading to a wealth of knowledge about them.[10]

Having considered these questions, I will turn to a case where it the search for a mechanistic explanation of disease is much more problematic than the Parkinson's disease case; schizophrenia research. There have been several papers calling for Drosophila models of schizophrenia. While this research is in its infancy, it is important to understand the limitations as well as the ways it can succeed. I will lay out some of the problems of diagnosis and boundaries in developing a Drosophila model of a complex disease of the mind such as schizophrenia.

Scientists are interested in the ways these mechanisms affect the functioning of the organisms, and the relationship between mechanism and neurological features. It is not possible to have a Drosophila model of schizophrenia. The fruit fly can be a vessel for exploring the role of genes, stress, environment, and other factors on neurological functioning but Drosophila cannot display the symptoms of schizophrenia. It is problematic

[10] Leonelli and Ankeny.

to think that we can develop an insect model of a complex, debilitating, and often devastating disease such as schizophrenia. The symptoms of schizophrenia cannot be exhibited by the fruit fly, they lack a mental landscape complex enough to suffer from delusions, hearing voices and the other symptoms of schizophrenia as described by the DSM (Diagnostic and Statistics Manual of mental health disorders by the American Psychiatric Association).[11] There are some potential behavioural correlates that could guide researchers in identifying the disease in insects but these are not robust enough to serve as biomarkers.[12] I will briefly discuss these candidates for diagnosis.

Where success can be expected, is in the ability of Drosophila to quickly screen the genes and mutations implicated in the development of the disease and lay the foundations for further exploration in more complex organisms such as rodents. Beginning with Drosophila allows scientists to work with an organism that is cheaper to house and feed, easier to work with and has a much shorter generation span than many other animal organisms. This ease of use makes Drosophila the ideal place to begin unravelling the mechanistic causes of disease.

Research methods

This Masters' thesis is a philosophical exploration of neuroscientific research that utilises *Drosophila melanogaster* as a model for schizophrenia. In the tradition of philosophical inquiry, I will explore the epistemology, ontology, methods, power of prediction and explanation, and the underlying premises of, specifically, mechanistic explanation of the causes of schizophrenia derived from work with *Drosophila melanogaster*. The focus of the

[11] D. S. M. Task Force American Psychiatric Association and Association American Psychiatric, *Diagnostic and Statistical Manual of Mental Disorders: Dsm-5*, 5th ed. (Washington, D.C: American Psychiatric Association, 2013).

[12] Richard J. Gardner et al., "Neural Oscillations During Non-Rapid Eye Movement Sleep as Biomarkers of Circuit Dysfunction in Schizophrenia," *European Journal of Neuroscience* 39, no. 7 (2014); C Gottesmann, "The Dreaming Sleep Stage: A New Neurobiological Model of Schizophrenia?," *Neuroscience* 140, no. 4 (2006); Claude Gottesmann and Irving Gottesman, "The Neurobiological Characteristics of Rapid Eye Movement (Rem) Sleep Are Candidate Endophenotypes of Depression, Schizophrenia, Mental Retardation and Dementia," *Progress in neurobiology* 81, no. 4 (2007); Sue Llewellyn, "In Two Minds? Is Schizophrenia a State 'Trapped'between Waking and Dreaming?," *Medical hypotheses* 73, no. 4 (2009); David Pritchett et al., "Evaluating the Links between Schizophrenia and Sleep and Circadian Rhythm Disruption," *Journal of Neural Transmission* 119, no. 10 (2012); Bart van Alphen and Bruno van Swinderen, "Drosophila Strategies to Study Psychiatric Disorders," *Brain research bulletin* 92 (2013).

paper will be on two case studies, an example of a past success, the use of as a model for Parkinson's disease, and a discussion of present day work to develop a model of schizophrenia.

I will draw on the successful work done to uncover the genetic mechanisms that cause Parkinson's Disease. Past success and the ability of researchers to work with, and manipulate Drosophila, will form a case study of the development of mechanistic explanations of a human disease. The contrasting case study will be the current work to develop a Drosophila model of schizophrenia, a task that has only just begun, and is relying on the same kinds of mechanistic understanding of disease. I will develop a hypothesis about the cross-species search for mechanistic explanations. This hypothesis will be tested against both cases, one where there has been clear success in Parkinson's research, and the contested case, the search for the mechanisms that underlie schizophrenia. These cases will be examined on their broad methodological assumptions, focussing on reconstructing the specific details when necessary, as is the practise in the philosophy of science. The conclusion will be normative recommendations of when it seems that we can depend on cross-species models of disease.

Research using Drosophila as a model for schizophrenia is currently in its infancy, and there will undoubtedly be rich information gained from such pursuits. Given the difficulty in describing a set of ubiquitous symptoms of schizophrenia in humans, such an undertaking must be approached with a clear commitment to how we understand the disease and its mechanisms. It will be possible to examine virtually all empirical research, as well as proposals and discussion papers on the topic to create a case study of this work. The empirical research selected focuses on the mechanistic causes of disease; the way that discrete functions and processes, bounded by physical and chemical laws, malfunction and give rise to disorder and disease. I will examine these case studies through the lens of philosophy of science and its understanding of mechanistic explanation.

2 Chapter One: Background information

In this chapter I will define frequently used terms, and discuss why the fruit fly has such an esteemed and prominent place in recent scientific history. I will sketch a brief overview and definition of model organisms and Drosophila. The change in classification of an organism from experimental to model will be discussed from a historical perspective - focussing on material practise, and a philosophical perspective.

2.1 Model organisms

I will begin by defining homology and analogy, and move to a definition of a model organism. Homology describes the shared features of organisms in different taxa, preserved from a common ancestor. A common example of homology is the bones in the forearms of vertebrates: whale flippers, bat wings, human forearms, dog front legs, and other vertebrates possess homologous structures inherited from a tetrapod ancestor.[13] An example of a homologous trait between Drosophila and humans are circadian rhythms that regulate sleep and wake cycles.[14] Drosophila have highly homologous sleep and wake mechanisms, mushroom bodies, and dopamine to humans.[15] In both humans and Drosophila, sleep/wake cycles regulate not only periods of activity and rest, but also attention and memory using homologous neurotransmitters, and brain structures.[16] Conserved through hundreds of millions of years of divergence from our common ancestor; homologous mechanisms will be discussed further in this section 1.2.3 as an explanation of why we can use Drosophila to model human diseases. Analogous as used in this paper, describes functional analogy; anatomy, systems, and features that perform the same function within Drosophila and humans but are not inherited from a common ancestor. An example of an analogous feature are wings, bat wings, bird wings, insect wings perform the

[13] Jessica Bolker, "The Use of Natural Kinds in Evolutionary Developmental Biology," *Biological Theory* 7, no. 2 (2013).
[14] Maximilian Michel and Lisa C. Lyons, "Unraveling the Complexities of Circadian and Sleep Interactions with Memory Formation through Invertebrate Research," *Frontiers in Systems Neuroscience* 8 (2014); Joan C. Hendricks and Amita Sehgal, "Why a Fly? Using Drosophila to Understand the Genetics of Circadian Rhythms and Sleep," *Sleep* 27, no. 2 (2004).
[15] Laurent Seugnet et al., "D1 Receptor Activation in the Mushroom Bodies Rescues Sleep-Loss-Induced Learning Impairments in Drosophila," *Current Biology* 18, no. 15 (2008).
[16] Ibid.

same function in flying creatures, despite morphological and anatomical differences. Model organisms are defined as non-human organisms used in science as stand-ins for humans.

Model organisms have been used in science for many thousands of years. Naturalists, collectors, and others spent countless years in the field studying organisms, and collecting specimens. Providing the clues to Darwin's theory of evolution, overviews of anatomical features, and cell development, animals have been at the forefront of science for many years. Model organisms as a class of material practice has a long history in science.[17] The use of many creatures to develop theories about development, anatomy and other biological features was an obvious way to understand biological features in humans.

In the early twentieth century, scientists achieved great leaps in our understanding of genetics, anatomy and other biological phenomena using model organisms.[18] Model organisms have been used in research for as a substitute for humans, or for interest in their own features. Particular creatures were chosen due to their availability, and their unique and interesting features. Organisms have taught us about anatomy, reproduction, cell metabolism, sleep, psychology, and countless other biological phenomena.[19] The success of model organisms in science is clear and is due to the knowledge these organisms have provided across many fields.[20]

2.1.1 Models for human diseases

In many fields of research, model organisms are stand-ins for human systems, diseases, and anatomical features.[21] The choice of model organism will be influenced by many factors and considerations, including the homology of the organism to other species and the ease of use.[22] There are animal models suited for studying embryology, cell development,

[17] S. Blair Hedges, "The Origin and Evolution of Model Organisms," *Nature Reviews Genetics* 3, no. 11 (2002).
[18] Kohler.
[19] MK Davidson, JR Lindsey, and JK Davis, "Requirements and Selection of an Animal Model," *Israel journal of medical sciences* 23, no. 6 (1987).
[20] Robert Gerlai, "Learning from Flies," *Trends in Neurosciences* 24, no. 9 (2001).
[21] Hedges.
[22] Richard M. Burian, "How the Choice of Experimental Organism Matters: Epistemological Reflections on an Aspect of Biological Practice," *Journal of the History of Biology* 26, no. 2 (1993).

evolution, behaviour, and many other physiological and biological features and systems.[23] Organisms classified as model organisms are ones initially used in field experiments and laboratories.[24] Entering the laboratory over the twentieth century, these organisms are well understood, and are found to have features that make ideal as stand-ins for other species.[25] Some organisms are ideal for studying various physiological functions*, C elegans* (nematode worm) for behaviour and development, and rodents for immunology.[26] Primates were once popular in psychological and other research but are now rarely used because of ethical concerns over their treatment.[27] *E Coli* has been used to model economic theory, with competition between slightly different strands for scant or abundant resources allowing scientists to observe the patterns that form over multiple different generations under differing conditions.[28]

While there are model organisms that are used to explore general biological systems and features, mostly their value is as a stand-in for humans and they are most often used in various branches of medicine, including neuroscience. [29] Models are selected for their high fidelity to the human system, mechanism, or function of interest.[30] Model organisms are utilised for practical reasons; they are cheaper to house, feed and breed than more complex organisms.[31] There are few if any ethical objections to the use of insects in experiment, as opposed to the use of more complex creatures such as mammals, particularly primates and humans.[32]

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[23] Hedges.

[24] Ibid.

[25] Pierre-Luc Germain, "From Replica to Instruments: Animal Models in Biomedical Research," *History and Philosophy of the Life Sciences* 36, no. 1 (2014).

[26] Hedges.

[27] Akira Sawa, "Chapter 1 - Genetic Animal Models for Schizophrenia: Advantages and Limitations of Genetic Manipulation in Drosophila, Zebrafish, Rodents, and Primates," in *Progress in Brain Research*, ed. Akira Sawa (Elsevier, 2009).

[28] Eshel Ben-Jacob, "From Snowflake Formation to Growth of Bacterial Colonies Ii: Cooperative Formation of Complex Colonial Patterns," *Contemporary Physics* 38, no. 3 (1997).

[29] Leonelli and Ankeny.

[30] Germain.

[31] Rowland H. Davis, "The Age of Model Organisms," *Nature Reviews. Genetics* 5, no. 1 (2004).

[32] Ibid.

Model organisms are an incredible tool for understanding human disease. Their history of use, incredible wealth of knowledge and ease of use make them sophisticated tools for understanding the mechanistic causes of disease.[33] The homology of organisms needs to considered when selecting a model for a particular target, such as a human disease.[34] Model organisms achieve the status of model when extensive study and use has revealed how they are homologous and analogous to humans.[35] This history of use increases the certainty about the shared characteristics between target and model.[36] Continuing success has ensured the use of model organisms in biology, and in particular in the search for mechanistic explanations of human diseases.

2.1.2 Epistemic niches

With a wealth of knowledge and an entrenched material practise built up around them, model organism carve an epistemic niche as models in science.[37] This term describes the unique place Drosophila and other organisms have in the production of scientific knowledge.[38] Niche is a term from evolutionary biology to describe the ecological conditions that an organism needs to survive.[39] Niches provide a habitat and environment for different species to thrive. An example of this is the place in a wooded habitat for creatures that burrow and scavenge for insects in the undergrowth. Niches are filled by countless species in different environments.

Describing the Drosophila as filling an epistemic niche acknowledges the laboratory as a place where model organisms are enlisted to uncover knowledge filling a knowledge niche, while also physically adapting to life in the laboratory.[40] The laboratory changes the

[33] William Bechtel, "Mechanism and Biological Explanation," *Philosophy of Science* 78, no. 4 (2011); Levy and Currie.
[34] Germain.
[35] Hedges.
[36] Leonelli and Ankeny.
[37] Jessica Bolker, "Models in Context: Biological and Epistemological Niches," in *Entangled Life: Organism and Environment in the Biological and Social Sciences*, ed. Gillian Barker, Eric Desjardins, and Trevor Pearce (Dordrecht: Springer, 2013).
[38] Ibid.
[39] Ibid.
[40] Ibid.

organism, they are carefully selected for stable characteristics. Any stray outside flies are removed, and their every need catered for; they are fed housed, bred, and kept safe from the outside world.[41] Model organisms, and their ease of use, and the ability to extrapolate knowledge to other organisms, gives them a privileged place in experimental biology and other disciplines.[42] Their longevity in research programs allows them to be used as practical and pragmatic ways to explore biological phenomena.[43] The place for organisms in many branches of medicine, biology, and their sub-disciplines have been filled by a handful of model organisms.[44] One of the most commonly used is Drosophila.

There are many epistemic questions that arise from the use of an insect or other organism to stand-in for a human. Meunier has claimed the epistemic question regarding model organisms is *how* they model for other species.[45] The question of how these organisms, focussing on Drosophila, are able to stand-in for, or model for other organisms is the key to understanding them as vehicles for mechanisms of interest. I will now give a brief outline of the Drosophila's history in science, how their physical features, and rapid technological development in genetics allowed Drosophila a place as an *in vivo* vessel for exploring mechanisms.

2.2 Drosophila as a model organism

The focus of this paper is on *Drosophila melanogaster*, the fruit fly, and its place in modelling neurological disorders. In this section I will give a brief overview of the history of Drosophila as a model organism, and how scientists are able to use such an insect as a model of human diseases. I will discuss the success of the fruit fly as a model for Parkinson's disease, and how this success is driving the search for a Drosophila model of schizophrenia. There will be a brief discussion of schizophrenia research and our present understanding of the disease. This background information will inform the discussion in subsequent sections.

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[41] Ibid.

[42] Ibid.

[43] Leonelli and Ankeny.

[44] Bolker, "Models in Context: Biological and Epistemological Niches."

[45] Robert Meunier, "Stages in the Development of a Model Organism as a Platform for Mechanistic Models in Developmental Biology: Zebrafish, 1970-2000," *Studies in history and philosophy of biological and biomedical sciences* 43, no. 2 (2012).

2.2.1 Morgan

The humble fruit fly, used by Morgan, in what came to be known as his “Fly Room”, was the first animal to display stable Mendelian inheritance patterns but it was not the first choice of organism, rather it was one of many used in laboratories at the time.[46] The fruit fly, however, was the first to confirm Mendel’s theory and allowed Morgan and his cohort to uncover and map sex-linked trait inheritance.[47] This was in part due to its physical features; huge larval chromosomes visible with relatively little magnification, stable trait transmission, ready availability, and a short generation time.[48] Morgan confirmed the work done by Mendel in his garden many years before, and laid the groundwork for understanding the physical mechanism responsible for sex-linked trait transmission.[49] The Drosophila was first made popular thanks to its ability to quickly generate mutant strains allowing the exploration of sex-linked trait transmission.[50] Since that time, the ease of use, fecundity, and body of knowledge of the Drosophila has given the fruit fly a special place in scientific research.

Drosophila have several physical features that made it an ideal organism for studying trait transmission; they are fecund, easy to house, breed and feed.[51] Their rapid breading cycle; females are fertile from 12 days, can live for up to 45 days, and will generally lay 50 -70 eggs per day, allows for fast paced research.[52] Their visible phenotypes such as bristles, wing structure and eye colour turned out to be ideal characteristics to further research into sex-linked trait inheritance.[53] Their size, diet and history of use mean they are cheap to house, and there are thousands of strains of mutant flies whose features, genes and potential disease application are readily available to be used.[54]

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[46] Leonelli and Ankeny.

[47] C. Kenneth Waters, "How Practical Know-How Contextualizes Theoretical Knowledge: Exporting Causal Knowledge from Laboratory to Nature," *Philosophy of Science* 75, no. 5 (2008).

[48] Kohler.

[49] Ibid.

[50] Ibid.

[51] Meunier.

[52] Kohler.

[53] Leonelli and Ankeny.

[54] Robert E Kohler, "Drosophila: A Life in the Laboratory," *Journal of the History of Biology* 26, no. 2 (1993).

2.2.2 A 70s resurgence

Falling out of favour for the middle part of the twentieth century, Drosophila experienced a revival in the 1970s thanks to the development of new technology to study DNA and genetics.[55] Again, their physical features, and ease of use, made them an ideal organism for this research.[56]

The newest genetic engineering technology, CRSPR 9, allows scientist an incredibly sophisticated tool to manipulate the fruit fly for use as a model.[57] Their genome was the among first organism's to be fully mapped in 1998.[58] Modelling with an organism is committed to understanding human features by way of a proxy. There has been undoubted success using organisms to stand-in for humans. I will now discuss the relationship between the model, Drosophila, and the target, humans.

2.2.3 Drosophila and our ancestors

Scientist are able to use organisms to understand human disease thanks to the perseveration of many processes, genes, and systems across millions of years of divergent evolution.[59] Basic cellular and genetic functions are preserved between species, even if their common ancestor was hundreds of millions of years ago. Drosophila and humans share a common ancestor approximately 400 – 600 million years ago, the *Urbilateria* and have homologous features passed on through countless generations.[60] Little is known about the exact morphology of the *Urbilateria*, but its axial symmetry and primitive digestive systems, as well as cellular metabolism, development and more are conserved in its descendants.[61]

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[55] Ibid.; Weber.

[56] Ibid.

[57] Mauro Agostino Zordan and Federica Sandrelli, "Circadian Clock Dysfunction and Psychiatric Disease: Could Fruit Flies Have a Say?," *Frontiers in Neurology* 6 (2015).

[58] Carla M. Sgrò and Linda Partridge, "Laboratory Adaptation of Life History in Drosophila," *The American Naturalist* 158, no. 6 (2001).

[59] Gerlai.

[60] Levy and Currie.

[61] Ibid.

This preservation through shared phylogeny is key to understanding how we can use animals to model human disease.[62]

The shared phylogenetic ancestor and the preservation of processes and genes across millions of years of evolution allows these organisms to model human diseases. These disorders cause homologous or analogous symptoms and allow scientists to view the actions of pathogens and mutations in a whole organism.[63] It is possible to genetically manipulate fruit flies to display approximately 75% of human genetic disorders.[64] By understanding the ways in which the model, the fruit fly, and the target, a human, are similar scientists can apply their knowledge of disease aetiology, potential treatments, and biomarkers in a simpler organism. This conservation of mechanisms, and the ability of scientists to use Drosophila as a vessel for observing mechanistic actions, is the key to their success.[65]

2.2.4 Representatives of a class

Another use of model organisms is as a representative of a broader class of organisms. Knowledge about one species is transported to another based on their shared phylogeny. Scientists uncover phenomena that are initially found in the organism of interest; based on a taxonomic relationship and an understanding of the mechanism behind the phenomena, which can then be applied to other organisms.[66] This has been discussed by Germain, and Levy and Currie.[67] This inference from model to target is based on the relationship between species from the perspective of evolution; it assumes that once a particular characteristic has evolved and conferred an advantage, it is passed on relatively unchanged despite diverging evolutionary paths.[68] The genes that are responsible for the development of organisms, growth, neural structures and other features are shared amongst many

[62] Germain; Levy and Currie.
[63] Germain.
[64] Kohler.
[65] Germain.
[66] Hedges; Levy and Currie.
[67] Germain; Levy and Currie.
[68] Hedges; ibid.; Davis.

organisms.[69] Therefore species that have a common ancestor will share some of their genetic properties.[70] Model organisms despite being an infinitesimally tiny portion of the biosphere have been able to create maps that show evolution and divergence that are applied to all organisms[71].

Their ability to represent other organisms is based on their phylogenetic relatedness, as discussed by Levy and Currie:

> *"…the model organism fulfills a stand-in role of sorts. A coarse-grained uniformity across a range of organisms, coupled to a specific result from the model organism, are jointly taken to imply that the specific result from the model is likely to hold more broadly. Here, the model organism is treated as a specimen, and what we have called circumstantial evidence justifies treating it as representative of a broader class."*[72]

Levy and Currie present an argument that model organisms should be viewed as specimens of a broader class sharing important features with other members of that class. Scientists can infer from a Drosophila to a human because of the uniformity of organisms that share a common ancestor.[73] Through scientific research and experimentation we are able to infer how the results of an experiment with one organism will apply to other organisms.[74] Shared ancestry - phylogenetic relationships – between target and model organisms means some shared causal mechanisms, allowing researchers to use one organism to represent many.[75] By their account this means work with model organisms is experimental.[76] I agree with this understanding of the role of model organisms in science and claim that this preservation of mechanisms facilitates the use of a fruit fly as model of human disease.

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[69] Levy and Currie.
[70] Ibid.
[71] Hedges.
[72] Levy and Currie, 9.
[73] Ibid.
[74] Ibid.
[75] Hedges.
[76] Levy and Currie; Germain.

The above explanation demonstrates why Drosophila engineered to model human diseases are valuable tools in science.[77] By introducing specific genetic features into Drosophila, and measuring and observing what results because of these changes, scientists can infer to broadly similar organisms.[78] Drosophila are engineered to share the mechanisms of interest, specific genes and/ or mutations that introduce another homology between organisms. This allows the homologous structure to be studied in a model organism.[79] Though the mechanism of interest is present in a fruit fly and not a human, the changes caused by the actions of these genes in Drosophila can then extrapolated to humans.[80] The epistemic and experimental history of the fruit fly in the laboratory, allows scientists to genetically engineer the Drosophila with great precision, only altering the genes of interest.[81] Previous work, and an understanding of the homologous and analogous features of the Drosophila, gives scientists the ability to infer from fruit fly to human.[82] Genetically engineering Drosophila to carry specific genes allows researchers to use Drosophila to explore the action of the gene *in vivo*.

Gaula states:

> *"Experiments are useful when one has an imperfect understanding of some basic causal mechanism of the system under study. They are useful in these contexts precisely because the laboratory "stuff" is the same as the non-laboratory "stuff".*"[83]

Guala here is making a similar claim to Levy and Currie. The success of model organisms is due to the shared features across diverse species. The targeted mechanisms under investigation are not similar, they are homologous. Whether fruit flies in a laboratory, or human patients, Drosophila models of disease carry homologous mechanisms of interest; the same "stuff".

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[77] Levy and Currie.
[78] Ibid.
[79] Ibid.
[80] Ibid.
[81] Ibid.; Waters.
[82] Levy and Currie.
[83] Francesco Guala, "Models, Simulations, and Experiments," in *Model-Based Reasoning* (Springer, 2002), 69.

This inference between organisms is discussed by Barker et al:

> *"Animal models in biomedical research are often conceived of as Causal Analogical Models (CAMs). The idea behind a CAM is quite intuitive. If two physical systems share a number of causal properties, then researchers can study one system (the model) and infer how another (target) system will respond to similar interventions (taking into consideration identified differences)."*[84]

The above quote is referring to rodents, it is equally applicable to work with Drosophila. Some of the causal mechanisms in Drosophila are homologous in organisms with a shared phylogeny.[85] Despite obvious physical differences, humans and fruit flies share a surprisingly high number of causal mechanisms that regulate many physiological aspects of both species.[86] Factoring in known differences, scientists can infer from the model to the target.[87] Drosophila is engineered by scientists to explore mechanisms, how the mechanisms affect the fruit fly can be inferred to humans.[88] These shared mechanisms are the key to working with model organisms.[89]

2.3 Idealisation

"If the human brain were simple enough for us to understand, we would still be so stupid that we couldn't understand it."[90]

It is necessary to idealise. If we were working with a system that was as complex as the one we were attempting to learn about then we would be no closer to clarity than we are today. Which components are being idealised, when utilising Drosophila as a model for human disease, and how the idealised components relate to the target will be discussed in this

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[84] Gillian Barker, Eric Desjardins, and Joaquin Madrenas, "Thinking Outside the Mouse: Organism-Environment Interaction and Human Immunology," in *Entangled Life: Organism and Environment in the Biological and Social Sciences*, ed. Gillian Barker, Eric Desjardins, and Trevor Pearce (Springer Science & Business Media, 2013), 169.

[85] Ibid.

[86] Lawrence.

[87] Guala; Barker, Desjardins, and Madrenas.

[88] Ibid.

[89] Barker, Desjardins, and Madrenas.

[90] Jostein Gaarder and Paulette Møller, *Sophie's World: A Novel About the History of Philosophy* (London: Weidenfeld & Nicolson, 1995), 74.

section. I will make an argument that we should classify the Drosophila, as a vessel for an idealised mechanism. The mechanism is idealised and then explored using the Drosophila, the target of the experiment is the mechanism and its actions, and not the fruit fly as a whole. This work, is a part of a modelling exercise involving other model organisms, and ultimately the human targets.

All science requires some level of idealisation and simplification. This allows scientists to strip away the factors that may confound results and complicate the work being done.[91] Stripping away the irrelevant features of a system and creating experimental set-ups that can be controlled, repeated and manipulated to reveal the important relationships and understand the features that are relevant to the phenomenon being explored is intrinsic to science.[92] Removing complicating factors by imagining perfect planes, and friction free surfaces allows for repeatability and robust claims.[93] To remove the mess and noise and study the phenomenon of interest is the aim of science. Knowledge is furthered by increasingly fine-grained explanations that are shaped by history and their past success, more robust claims hold and are expanded.

2.3.1 Simpler brains

The human brain possesses more than 200 billion neurons, and is incredibly complex organ, rich with mechanisms, abilities and components.[94] The Drosophila brain, with its relatively modest 200 million connections is a much simpler brain than that of humans yet is surprisingly similar in some ways.[95] Drosophila share circadian rhythms and they appear to suffer from something akin to jet-lag when these are interrupted or disturbed.[96] Sleep

[91] Nancy Cartwright, *The Dappled World: A Study of the Boundaries of Science* (Cambridge University Press, 1999).
[92] Ian Hacking, *Representing and Intervening: Introductory Topics in the Philosophy of Natural Science*, vol. 5 (Cambridge Univ Press, 1983).
[93] Cartwright.
[94] van Alphen and van Swinderen.
[95]
[96] Chiara Cirelli and Daniel Bushey, "Sleep and Wakefulness in Drosophila Melanogaster," *Annals of the New York Academy of Sciences* 1129 (2008).

appears to regulate memory formation and attention in the Drosophila as well as in other organisms.[97]

Weber uses the example of nerve signalling to illustrate mechanistic accounts in science. Changes in neurochemistry transmit a signal along nerves; providing an explanatory account of the action potential of cells, and how these function in an organism. This is a straightforward, mechanistic account of a vital function in neuroscience. It also reduces an observable phenomenon, to a mechanistic account. It translates a sensation felt by a whole organism to a molecular story of the physical interaction between chemicals, cells, and other parts of the nerve.

> *"It may very well be that other examples are further removed from the explanatory ideal that the mechanism of action potentials exemplifies. But, I claim, this kind of explanation – explanation that really takes biological systems down to physicochemical laws – is the goal of much twentieth- and twenty-first-century biological research. Where biologists have not yet reached it, they are trying to move closer to this ideal."*[98]

This is a strong claim by Weber. I would contest that much of neuroscience is more complex than simply understanding physiochemical laws, but I agree that the goal of modern biology is best characterised as a search for mechanistic explanations. Weber has also raised the idea of mechanistic explanation as an ideal that will be explored further through this thesis.

2.3.2 Is Drosophila an idealised brain?

The Drosophila performs several tasks as a model and as an experimental organism in neuroscience, and has been described as a "simplified brain" or "miniature brain" by some researchers.[99] Should we view Drosophila as an idealised brain? This is implicit in the view of

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[97] Robert Stickgold and Matthew P. Walker, "Memory Consolidation and Reconsolidation: What Is the Role of Sleep?," *Trends in Neurosciences* 28, no. 8 (2005).

[98] Weber, 29.

[99] Bruno Van Swinderen and Rozi Andretic, "Dopamine in Drosophila: Setting Arousal Thresholds in a Miniature Brain," *Proceedings: Biological Sciences* 278, no. 1707 (2011); Hendricks and Sehgal; van Alphen and van Swinderen.

Drosophila as a miniature brain.[100] It is a much simpler neural network than that of humans, and it does share many of the same neurological and neurochemical features, but does this mean we can understand the Drosophila brain as simplified or idealised?[101] I will argue that although the brain of the Drosophila is simpler than that of a human's, it cannot be understood as "idealised". Experimental apparatus may be idealised and environmental factors controlled for, but the Drosophila are the vehicle for the study of the idealised molecular mechanism thought to control or affect the phenomenon under investigation. The Drosophila is not a miniature human brain, nor is the brain idealised. The idealised component of the research is the mechanism.

I argue that we cannot consider the Drosophila brain to be a simplified, or idealised brain, as these are living organisms, not models in the sense that other concrete models are.[102] This presents a challenge to not only the researchers in these programmes, but also to philosophy of science and whether work with Drosophila is experimental or modelling.[103] Viewing Drosophila as possessing a miniature human brain is a misrepresentation of the relationship between the model and the target. The target of neuroscientific research into schizophrenia is a human patient with the disease. Drosophila in these experiments are not a simplified or miniature schizophrenic patient, they are an organism that shares a phylogenetic relatedness and homological neurochemistry, and similar enough biology and anatomy to observe the actions of a mechanism.[104]

Drosophila can be used as a model for circadian rhythms, and that is the model component in this work – the circadian circuitry.[105] Research into many other neurological disorders and the success of utilising the Drosophila in these areas provides a potential insight into how parts of a fruit fly can model parts of a human. The Drosophila model is a part of a wider

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[100] Swinderen and Andretic.

[101] Ibid. Jasmine M. McCammon and Hazel Sive, "Addressing the Genetics of Human Mental Health Disorders in Model Organisms," *Annual review of genomics and human genetics* 16, no. 1 (2015).

[102] Melinda Bonnie Fagan, "Generative Models: Human Embryonic Stem Cells and Multiple Modeling Relations," *Studies in History and Philosophy of Science Part A* 56 (2016). Michael Weisberg, *Simulation and Similarity: Using Models to Understand the World* (OUP USA, 2013).

[103] Fagan.

[104] Levy and Currie.

[105] Hendricks and Sehgal.

programme that tests, models, and idealises disease to better understand it and lead to improved diagnosis, treatment, and management of the symptoms.

The place of the Drosophila is to allow scientists to idealise and experiment *in vivo* on various components of neurochemistry and neurobiology to understand the effect of different malfunctioning mechanisms on the whole organism. The mechanisms that are being experimented on are the idealised components of the experiment, not the whole organisms. The idealised components of the fly may be genetic, chemical, anatomical or a combination of these and other things, but the fly itself is a sophisticated piece of laboratory equipment that allows for *in vivo* experimentation on the idealised parts. This idealisation sheds light on how we are to understand the Drosophila's role in modelling mechanistic aspects of schizophrenia, which is discussed in chapter three. By using a simpler organism that shares enough analogous and homologous features, we can create a model of parts of brains and their relationship to some aspects of behaviour.

2.4 When does an experimental organism become a model?

There are two ways to answer the question of when an organism is a model rather than an experimental organism. The first approach is to look to its use, its role in science, and its inclusion as a preferred model organism by institutions; a historical and social account. The second approach is though philosophy of science, looking for epistemic and ontological differences between uses of the same organism. I will begin with discussing the definition of a model from the perspective of scientific practise.

2.4.1 Answer from history

One way to define the difference between an experimental organism and a model is based on the history of work with that organism. How widespread its use is in science, its history as a tool of science, the infrastructure that is built around it, and resources such as the Fly Base (home to over 10,000 strains of Drosophila).[106] Institutions such as the U.S. National Institutes of Health (NIH) create lists of model organisms for biomedical research, officially

[106] Bloomington Drosophila Stock Center - Indiana University, "Bloomington Drosophila Stock Center," Indiana University, http://flystocks.bio.indiana.edu/Browse/browse.htm.

ordaining the Drosophila as a biomedical model organisms.[107] This inclusion as an official model organism recognises the utility and longevity of the Drosophila as a model for human diseases and molecular actions of some mechanisms. The NIH carries weight when scientists are deciding on the best organisms for their research.[108] Funding is more likely to be allocated to research that uses a recognised model organism, and the work is easily translated to other laboratories that share the materials and practise.[109]

Scientists working in communities agree on standards to compare competing theories.[110] Researching within established paradigms creates accepted ways to create knowledge and test theories through experiments and models.[111] These communities shape what is counted as knowledge and what is considered to be disproven through experimentation.[112] Through cooperation, a vast base of epistemic and material resources are created and shared.[113] There are standards and norms for working within these spaces, which is reflected through the roles organisms play in experiment, and their use as models for disease.[114] Consensus on which organisms are models is reached through social, epistemic, and physical use.[115]

2.4.2 Philosophical responses

Philosophers of science have mixed positions on the difference between a model organism and an experimental one. One distinction between model and experiment is; a model is a representation of something else, and an experiment is a direct investigation of a specific phenomenon. By this definition, a search for mechanistic causes of disease, is an

[107]Sabina Leonelli and Rachel A. Ankeny, "Re-Thinking Organisms: The Impact of Databases on Model Organism Biology," *Studies in History and Philosophy of Biol & Biomed Sci* 43, no. 1 (2012).
[108] "What Makes a Model Organism?."
[109] Ankeny and Leonelli.
[110] Leonelli and Ankeny, "What Makes a Model Organism?."; Ankeny and Leonelli; Bolker, "Models in Context: Biological and Epistemological Niches."
[111] Leonelli and Ankeny, "What Makes a Model Organism?."
[112] Kevin Lattery, "The Epistemology of Experimental Systems in Biological Research" (Ph.D., University of Minnesota, 1999).
[113]Ankeny and Leonelli.
[114] Leonelli and Ankeny, "What Makes a Model Organism?."
[115] Hans-Jörg Rheinberger, *An Epistemology of the Concrete: Twentieth-Century Histories of Life* (Duke University Press, 2010).

experiment. It is investigating a phenomenon – mechanism - and its action within an organism. However, some claim that it is a modelling exercise, as the ultimate target is how the mechanism affects a human. While the ultimate target is human sufferers of the disease, the investigation is into the molecular actions of a mechanism. Weber has proposed a new category to describe work done with Drosophila and other model organisms as experimental modelling. I will consider this position and reject it in favour of the argument by Germain, Levy and Currie that many uses of model organisms are experimental and not modelling exercises.

Determining the difference between a modelling exercise and experiment is important to the epistemic and/or ontological status of the scientific practice. It seems there is an epistemic and ontological difference between models and experiments. I will argue that Drosophila models are vehicles for experimenting on the mechanisms behind neurological diseases. I will begin by discussing the ontology of modelling versus experiment and then consider the epistemological differences.

2.4.3 Ontological and epistemic distinctions

Ontological distinctions between model organisms and experimental ones, hinges upon the type of work they are used for. The two categories represent two different uses of animals in science. A model organism performs a certain type of work; standing in for other organisms. An experimental organism is studied to understand that organism alone, not what it reveals about other organisms, although that may be possible, it is not the aim. This is the categorisation posited by Levy and Currie, they explicitly argue that the work with model organisms is experimental.[116] They ground this argument in natural kinds; the interest in model organisms is in the shared mechanisms, ones that are homologous between two species.

Their claim is that the homology between organisms, means that scientists are not using a substitution but rather investigating a concrete feature that is the same stuff in both target and model, a natural kind. A natural kind refers to an instance of phenomena or object that

[116] Levy and Currie.

is the same no matter where it is. It is possible to research electrons and conclude that the results will hold for all electrons that exist in the universe. Science frequently relies on natural kinds in its work. The use of Drosophila relies on the homology of the mechanism under investigation, a natural kind. It is the same material stuff in the Drosophila as it is in organisms that share these mechanisms. The homology may arise naturally or as the result of genetic engineering. This differentiates the work done by model organisms, from other models as it is the same stuff under investigation rather than an analogous material or mechanism.[117]

The material relationship between the target of inquiry and the experiment is crucial ontologically, as it means that work is either being done with a proxy or without. This relationship gives weight to the epistemic outcomes of the work done. A reliance on natural kinds is one example of the key differences epistemically, between a simulation, or a model and an experiment. The knowledge that is created is about the mechanism and its interaction with an organism. The organism is the vessel for exploring the mechanism which is homologous in model and target. The study is of the mechanism and its actions. The knowledge of the action of that mechanism holds, dis-analogies arise at levels above the mechanism of interest. If its actions are altered by differences between organisms, it is a result of other mechanisms interacting with it.

A wealth of physical resources, and a large body knowledge is one way of differentiating model organisms from experimental ones.[118] The knowledge allows scientists to understand what changes more clearly arise from manipulation; they have a stable population to compare to, and previous knowledge to draw on. Performing work with an organism that has a greater number of unknown properties, scientists face questions about how outcomes may relate to changes.[119] This approach seems to back up the idea that there is an important epistemic difference between model organisms and experimental organisms.[120]

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[117] Germain.

[118] Leonelli and Ankeny, "What Makes a Model Organism?."

[119] Ibid.

[120] Health; Leonelli and Ankeny, "What Makes a Model Organism?."

Model organisms have clear social, epistemic, and physical structures that differentiate them from experimental organisms.[121]

Distinguishing the mechanism from the organism changes the classification from a modelling exercise to an experimental one. The action of the mechanism is under investigation, its molecular effects can then be corroborated in other organisms, and the mechanism studied for potential treatment and diagnosis.[122] The changes in the medium, the organism the mechanism is in, are important for understanding the action of the mechanism. Transporting the mechanism of interest to different mediums, enhances the knowledge of the actions of the mechanism. The difference in medium and changes in biological and chemical environments are a vital component of this work. The differences in medium will reveal changes in action. A change in action, could mean the mechanism is not the driving force of disease in other organisms, or that there is more than one mechanism at play. This distinguishes model organisms from other modelling exercises, such as the construction of a proxy system to test theories about the causal relationships between structures in San Francisco Bay-Delta.[123] It is not theoretical modelling extrapolated to an analogous system; it is the study of a homologous structure.

Experimental modelling, the term coined by Weber to capture the different epistemic characteristics of research using model organisms in biology, is a compromise between the two categories. Reflecting the difficulty in clearly demarcating experiments from models in many biological sciences. He claims that experiments idealise a phenomenon to investigate the causal relationships that exist within that system. He asserts that model organisms serve as proxies for causal processes in other species, the phenomenon is not under direct investigation, but is providing generalizable knowledge.

> *"Thus, we have identified an important difference between experimental models and ordinary experiments: while ordinary experiments seek to establish a causal dependence in a particular system, experimental models provide knowledge of causal processes that generalizes to systems*

[121] Ankeny and Leonelli.

[122] Germain.

[123] Weisberg.

> *where biologically and chemically quite different kinds of causes are at work."*[124]

This is a different understanding of the case studies of Parkinson's disease and schizophrenia discussed in this paper. The biological and chemical causes under investigation are not "quite different".[125] The mechanism is homologous, it is the "same stuff".[126] There are uses of Drosophila and other model organisms that fall into "experimental modelling" as characterised with Weber. Model organisms are used to investigate mechanisms and systems where the material is not homologous. One example of this is drug testing. Scientists use organisms used to test different therapeutic treatments, particularly pharmacological ones. The actions of these drugs are dependent on features of the organism that are chemically and biologically quite different.

Indeed, differences between organisms and the consequent differing effects of drugs have caused tragic results in the past.[127] Treatments that were safely administered to model organisms were then given to humans with disastrous results because of key differences between the species not captured in the testing stages.[128]

I agree with Levy's and Currie's categorisation of the relationship between model and target; placing the emphasis of the work on the mechanism and not the organism. The organism is the experimental set-up for investigating the mechanism. The model is of the action of the mechanism in the organism, not the organism.

Having discussed the role of mechanisms in understanding Drosophila models, I will now explore what mechanistic explanations are, and why we should prefer them.

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[124] Marcel Weber, "Experimental Modeling in Biology: *In Vivo* Representation and Stand-Ins as Modeling Strategies," *Philosophy of Science* 81, no. 5 (2014): 764.
[125] Ibid.
[126] Guala.
[127] Isabella W. Y. Mak, Nathan Evaniew, and Michelle Ghert, "Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment," *American Journal of Translational Research* 6, no. 2 (2014); Ganesh Suntharalingam et al., "Cytokine Storm in a Phase 1 Trial of the Anti-Cd28 Monoclonal Antibody Tgn1412," *New England Journal of Medicine* 355, no. 10 (2006).
[128] .Ibid.

3 Chapter two: Mechanisms, Parkinson's disease, and Drosophila

In this chapter I will define mechanistic explanations using the example of Parkinson's Disease. I will outline how the genetic manipulation of Drosophila to express genes correlated with Parkinson's Disease advanced our knowledge of the disease, revealing its molecular parts and causes. This will lay the ground for a broader discussion of mechanistic explanation in biological sciences.

3.1 Shared mechanisms

There are calls for Drosophila to model for increasingly complicated human neurological diseases such as schizophrenia and autism.[129] The success of the organism in modelling other neurological disease, in particular Parkinson's Disease drives researchers to model increasingly complicated disorders using the Drosophila. This research is predicated on the understanding many types of neurological disease as the result of a breakdown, or breakdowns in mechanisms that regulate neurological activity and the resulting behaviour of an organism. The mechanistic model of disease in neuroscience is widely used and applied. Many parts of neuroscientific research are focussed on uncovering and explaining the mechanisms, both anatomical and neurochemical, which regulate our behaviour. Within philosophy of science, there is a school of thought that claims we should prefer these kinds of mechanistic explanations.[130] This preference is based on the predictive power of mechanistic explanation.

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[129] Katsuo Furukubo-Tokunaga, "Modeling Schizophrenia in Flies," (Netherlands: Elsevier Science & Technology, 2009); van Alphen and van Swinderen.; Shinya Yamamoto and Elaine S Seto, "Dopamine Dynamics and Signaling in Drosophila: An Overview of Genes, Drugs and Behavioral Paradigms," *Experimental Animals* 63, no. 2 (2014); Akira Sawa, "Genetic Animal Models for Schizophrenia: Advantages and Limitations of Genetic Manipulation in Drosophila, Zebrafish, Rodents, and Primates," *Progress in brain research* 179 (2009). Stéphane Jamain et al., "Identification of the Human Kif13a Gene Homologous to Drosophila Kinesin-73 and Candidate for Schizophrenia," *Genomics* 74, no. 1 (2001).

[130] Nina Atanasova, "Mechanistic Explanations and Animal Model Simulations in Neuroscience," *Journal of Experimental & Theoretical Artificial Intelligence* 24, no. 4 (2012); William Bechtel, "Can Mechanistic Explanation Be Reconciled with Scale-Free Constitution and Dynamics?," *Studies in history and philosophy of biological and biomedical sciences* 53 (2015); "The Challenge of Characterizing Operations in the Mechanisms Underlying Behavior," *Journal of the experimental analysis of behavior* 84, no. 3 (2005); "Constructing a Philosophy of Science of Cognitive Science," *Topics in cognitive science* 1, no. 3 (2009); "Mechanism and Biological Explanation."; John Bickle, "Reducing Mind to Molecular Pathways: Explicating the Reductionism Implicit in Current Cellular and Molecular Neuroscience," *Synthese* 151, no. 3 (2006); Melinda Bonnie Fagan, "The Joint Account of Mechanistic Explanation," *Philosophy of Science* 79, no. 4 (2012); Carl F Craver,

The search for mechanistic correlates and causes of disease requires idealisation of the disease and the mechanisms. How this idealisation can create a cross-species model will be discussed extensively. As in the case of Parkinson's disease, this can be characterised as a quest for mechanistic explanations of the disease, which will be discussed in the next section. Throughout this paper, I will make a case that the Drosophila is an *in vivo* experiment, where the model is the neural circuitry, neurotransmitters, and mechanisms under investigation, and not the whole organism. This *in vivo* experiment is the result of shared knowledge across many disciplines, and multiple model organisms that explore the molecular actions of mechanisms.

3.2 Mechanism and explanations

Mechanistic explanations explain phenomena through description of the causal relationships between relevant parts over time.[131] Within biology scientists look for and describe the physical and chemical parts bound by causal relationships, to explain the phenomenon of interest.[132] These kinds of explanations have been identified by philosophers as characterising much of the work in the biological sciences, providing a causal account of the relationships between parts that give rise to a phenomenon.

The success of work with Drosophila produces mechanistic explanations of functions common to the fruit fly, and to humans. The Drosophila serves as a vehicle for understanding the molecular causes of diseases. By allowing scientists to perform *in vivo* experiments on idealised targets, such as genes and mutations, Drosophila has entrenched itself in the material practise of many scientific disciplines. The humble fruit fly has now been enlisted into countless research programs around the world. There are breeding centres that carry over 10,000 strains, manipulated to exhibit certain features, or developed

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Explaining the Brain: Mechanisms and the Mosaic Unity of Neuroscience (Oxford University Press, 2007); Melinda Bonnie Fagan, "Stem Cells and Systems Models: Clashing Views of Explanation," *Synthese* 193, no. 3 (2016); David Michael Kaplan and Carl F. Craver, "The Explanatory Force of Dynamical and Mathematical Models in Neuroscience: A Mechanistic Perspective*," *Philosophy of Science* 78, no. 4 (2011); Friedemann Pulvermüller, Max Garagnani, and Thomas Wennekers, "Thinking in Circuits: Toward Neurobiological Explanation in Cognitive Neuroscience," *Biological Cybernetics* 108, no. 5 (2014).

[131] Craver.

[132] Ibid.

as a model of human disorders.[133] These flies are the vessels to explore the mechanisms that explain and predict biological phenomena.

I will be following Craver's definition of mechanistic explanation. As argued by Craver, there are good reasons to understand explanations in neuroscience as straightforwardly mechanistic.[134] They are constitutive causal models that follow the set of conditions laid out below:

> *(E1) mere temporal sequences are not explanatory (temporal sequences);*
> *(E2) causes explain effects and not vice versa (asymmetry);*
> *(E3) causally independent effects of common causes do not explain one another (common cause);*
> *(E4) causally irrelevant phenomena are not explanatory (relevance); and*
> *(E5) causes need not make effects probable to explain them (improbable effects).*
> *Good explanations explain effects with causes.* [135]

Mechanistic explanations must explain the causal relationships between parts over time but not rely only temporal sequences. Effects cannot explain causes. There is no place for phenomena that is not causally relevant to be explanatory. The improbability of an effect does not change the causal relationship between cause and effects

Mechanisms are not necessarily linear.[136] There may be feedback loops, positive or negative that form part of the mechanistic explanation.[137] Within neuroscience, feedback loops are present in many mechanisms, due to the nature of neurotransmission and the maintenance of homeostasis in the brain.[138] The interest of scientists modelling Parkinson's Disease is the molecular action of the mechanism in an organism. I will now discuss mechanistic explanations using the Drosophila model of Parkinson's disease as a case study.

3.3 Parkinson's disease and mechanistic explanation

The explanation of Parkinson's disease takes the form of a mechanistic explanation. It

[133] University.
[134] Craver.
[135] Ibid., 26.
[136] Ibid.
[137] Ibid.
[138] Ibid.

explains and predicts the effects of protein build-up, the presence Lewy bodies, and the manifestation of the symptoms in human sufferers. The relationship between genes, physical changes in the brain, and symptoms is explained through spaciotemporal understanding of the causal relationships between neurotransmitters, proteins, and neurons.[139] Parkinson's disease also has recognisable symptoms that can be easily seen in a fruit fly.[140] Memory impairment, palsy and other symptoms can be straightforwardly observed in an insect.[141]

The model of Parkinson's disease in Drosophila contains mechanistic explanation of the disease. The organism contains the objects of interest; the neurons, genes, and proteins that govern their behaviour. The relationship between parts, has been causally explained. Lewy bodies are made from protein; these proteins form Lewy bodies as they build up in the brains of people carrying the mutation. The build-up of proteins, eventually leads to Parkinson's disease. The production of these proteins is caused by the mutation in certain genes leading to an impairment in mitochondrial DNA (mitDNA) reuptake of the proteins that form Lewy bodies and interfere with neuronal activity and neurotransmission. The proteins then cause damage to neurons, and inhibit the ability of neurons to transmit and receive dopamine.

This is a mechanistic explanation. We have the phenomenon – Parkinson's disease, that is explained by the relationship between parts of the brain, and the changes that arise over time. The explanation is predictive, as by understanding the impairment and damage in neurons and the loss of dopamine receptors, we can predict changes to behaviour regulated by dopamine. Key to this understanding is research using Drosophila. By using the Drosophila to model the mechanisms of interest, scientists are relying on a mechanistic explanation of brain processes and the associated behaviour or symptoms displayed by the fruit fly. A mechanistic and interventionist approach is implied in the strategies laid out by van Alphen and van Swinderen to explain the causes of schizophrenia, inspired by the

[139] Ibid.

[140] José A. Botella et al., "Modelling Parkinson's Disease in Drosophila," *Neuromolecular medicine* 11, no. 4 (2009).

[141] Ibid.

success with Parkinson's disease.[142] This approach uses mechanistic explanations to describe features of the neuroanatomy, neurochemistry, and neurobiology of the organism.[143] Interventions are then made to see what kinds of things may affect the mechanism being examined - van Swinderen and van Alphen suggest a strategy to investigate the particular genetic features that may be responsible or implicated in schizophrenia based on the success with Parkinson's disease.[144]

This reflects the nature of the search for mechanisms in neuroscience, as is explicit in many other papers that include statements such as:

> *"...confirming genetic linkage for intermediate phenotypes may also be useful for revealing mechanistic information for pathology."*[145]
>
> "*However, recent advances in Drosophila neurogenetics and the accumulation of human psychiatric genetics data will aid the identification of novel risk factors, molecular and genetic components, and cellular processes that underlie each of the pathophysiology of psychiatric disorders, ultimately generating novel mechanism-based treatments.*"[146]

The above quotes demonstrate that categorising the search for treatments and prevention of many human diseases begins by identifying the mechanisms that cause the disease. The mechanisms can be studied in Drosophila and a better understanding of their molecular actions developed, with the hope of developing specific treatments that target the causal mechanisms behind diseases.

There is a limit to the explanatory power of mechanisms. Many scientists would stop short of claiming to have the power to explain all the complex brain states that arise because of mechanistic failure. There are hypotheses and correlations, but an emotional reaction such as anger in a mentally unwell patient is most likely the result of hugely complicated and

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[142] Melinda Bonnie Fagan, "Interventionist Omissions: A Critical Case Study of Mechanistic Explanation in Biology," *Philosophy of Science* 83, no. 5 (2016). Anjana S. Narayanan and Adrian Rothenfluh, "I Believe I Can Fly!: Use of Drosophila as a Model Organism in Neuropsychopharmacology Research," *Neuropsychopharmacology* 41, no. 6 (2016).

[143] .

[144] van Alphen and van Swinderen.

[145] McCammon and Sive, 175.

[146] Katsuo Furukubo-Tokunaga, "Chapter 12 - Modeling Schizophrenia in Flies," in *Progress in Brain Research*, ed. Akira Sawa (Elsevier, 2009), 113.

interwoven brain functions. The complex landscape of manifestation of symptoms and the potential contribution of environmental factors makes this a massive undertaking.

Attempting to ensure that all relevant features of the phenomenon being modelled are included is a complicated process in any science. In neuroscience, there are further complications added by the multifaceted nature of neurological activity and its interaction with not only different levels of the brain and nervous system but also with other anatomical features such as the endocrine system. As well as causal effects from the environment, social landscapes, and epigenetic expression.

There are four components to a mechanism: the phenomena of interest, the parts that make up the mechanism, the causal relationship between these parts, and the organisation of these parts in space and time.[147] Mechanistic explanations reflect the search for causal relationships between parts; rather than simply describing the arrangement of the parts in time and space, they describe the causally relevant interactions between these parts.[148] I will now discuss these four components using Parkinson's disease.

3.3.1 Phenomena of interest

The first task of mechanistic explanation is to identify the phenomena of interest. In the example used in this section, the target is a neurological disease, Parkinson's disease. Parkinson's disease is a late onset, chronic, degenerative, neurological disorder that usually emerges in middle to late life.[149] It affects approximately 1.5% of the population and its symptoms are palsy, problems with memory and attention, and disordered movement.[150] It is associated with reduced quality of life, and a reduction in life expectancy.[151]

Parkinson's disease has a set of symptoms that provide clues to researchers; clues about which parts of the brain are malfunctioning. Mechanistic explanation in this area of research

[147] SEP

[148] Craver.

[149] Andrew J. Lees, John Hardy, and Tamas Revesz, "Parkinson's Disease," *The Lancet* 373, no. 9680 (2009); Roeland Vanhauwaert and Patrik Verstreken, "Flies with Parkinson's Disease," *Experimental neurology* 274, no. Pt A (2015).

[150] Lees, Hardy, and Revesz.

[151] Ibid.

is predicated on the relationship between neural features and whole-organism level behaviour and symptoms. The presence of anatomical and neurochemical features and how they interact with each other regulates behaviour in an organism. A mechanistic breakdown affects these systems and causes the disease, explaining the symptoms. These explanations rely on relating the presence of a mental health disorder to a malfunction in a specific neurological mechanism.

Identifying a phenomenon of interest that can be explored mechanistically can be an iterative process. Understanding something as seemingly well defined as movement control reveals relationships between many different systems, organs, neuroanatomy, and neurochemistry. Further research and investigation fixes the boundaries between parts, and describes the components that are of interest in the mechanism. As more is uncovered, knowledge is tested and revised, and theories are sharpened. Alongside this epistemic progress, tools and materials also advance, driving more fine-grained instruments and increased accuracy. In the case of Parkinson's disease the more that was understood about movement and its relationship to the brain, and to dopamine, the clearer the parts affected by the disease became. This leads to a discussion of the parts; the physical and chemical features of the mechanism under investigation.

3.3.2 Parts

Parkinson's disease affects motor control, which usually begins with the deterioration of dexterity, and, less commonly a slight dragging of one foot, and progresses to other difficulties with simple motor tasks such as walking, and fine movements (winding a watch, writing etc.).[152] The lag of two to three years between onset and diagnosis means that many early symptom profiles are based on recollection and not direct observation.[153] Later symptoms include loss of motor coordination, changes to gait, sleep disorders, and tremors

[152] Ibid.
[153] Ibid.

(palsy) of the hands.[154] Bradykinesia - slowness of movements - is present in later stages of the disease and is frequently the symptom that leads to diagnosis.[155]

While there are some factors that affect the likelihood of developing the disease: head injury, smoking, obesity, and other environmental factors, the disease is strongly correlated with seven genes.[156] Individuals with these genes will almost certainly begin to develop the disease past the age of sixty, with the timing and severity of the disease affected by some lifestyle and environmental factors.[157]

There are several sub-categories of Parkinson's where symptoms manifest slightly differently, these include 'lower-half' Parkinson's disease where a disrupted sense of smell, shaking gait and other symptoms are exhibited.[158] Different sub-types are distinguished through responsiveness to L-dopa treatment, observation of the brain using Magnetic Resonance Imaging (MRI), and the elimination of the possibility of other diseases.[159]

The symptoms of disordered movement, and the responsiveness to L-dopa treatment point to a problem in dopaminergic systems.[160] The brains of Parkinson's sufferers show decreased activity in key areas, and the loss of neurons.[161] These symptoms allow researchers to identify the parts of the mechanism of interest; the seven genes, dopaminergic receptors, neurotransmitters, proteins, and neurons.[162] Having narrowed down the parts of interest, researchers need to understand their arrangement, and their physical relationship to each other, both in space and in time.

Neuroscientific work has shown that movement, smell and many of the other anatomical and functional parts of the brain affected by Parkinson's are regulated by the dopaminergic

[154] Ibid.
[155] Ibid.
[156] Ibid.
[157] Ibid.
[158] Ibid.
[159] Ibid.
[160] Ibid.
[161] Ibid.
[162] Ibid.

systems.[163] Our understanding of these systems is in part possible because of the high homology between the Drosophila and human dopaminergic systems.[164]

Demarcating the relevant parts of a mechanism can be an extremely challenging task in any field of biology; neuroscience has made great strides in detangling and understanding the brain and its parts. Much of this work has been done with model organisms. In section 3.5, I will discuss some of the more innovative ways that behavioural assays of Drosophila have been undertaken, with early research utilising dopamine agonists, and antagonists allowing researchers to better understand the mechanisms that control movement. Mechanisms that are responsible for movement, and the successful treatment of symptoms with L-Dopa, bound the search for the mechanistic cause of Parkinson's Disease. The parts of the mechanism under investigation are demarcated by the symptoms, and by the pathology present in the brains of deceased sufferers, and the activity of those sufferers still alive. The loss of neurons, the movement problems, and dementia are clues, as are the specific chemical profiles found in autopsy.

3.3.3 Causal relationship between parts

Parkinson's is correlated with the presence of Lewy bodies in the brain.[165] Lewy bodies are proteins present in the brains of sufferers of Parkinson's Disease and other diseases with dementia as a symptom.[166] While there is controversy over whether they are the cause of the disease, or a symptom, they indicate that proteins are a part of the mechanism that causes Parkinson's disease.[167] To fully sketch the mechanistic explanation of the disease, the presence of the Lewy bodies needs to be explained. Parkinson's disease has a strong genetic component, making genes a candidate for a more complete picture of the disease. In the late 1990s, the first breakthroughs linking Parkinson's to a specific gene occurred.[168] From

[163] Erwan Bezard and Serge Przedborski, "A Tale on Animal Models of Parkinson's Disease," *Movement Disorders* 26, no. 6 (2011).
[164] Botella et al.
[165] Lees, Hardy, and Revesz.
[166] Zuzana Walker et al., "Lewy Body Dementias," *Lancet (London, England)* 386, no. 10004 (2015).
[167] Ibid.
[168] Dena G. Hernandez, Xylena Reed, and Andrew B. Singleton, "Genetics in Parkinson Disease: Mendelian Versus Non-Mendelian Inheritance," *Journal of Neurochemistry* 139, no. S1 (2016).

there researchers were able to use Drosophila to study the relationship between the gene and the development of Lewy bodies.[169] By engineering the Drosophila to carry the gene now implicated in Parkinson's disease, scientists now had a vessel to observe the actions of the gene on the brain and explain the formation of Lewy bodies.[170] This explanation relies on the mechanistic relationship between molecules in the brain.

The successful Drosophila model of Parkinson's disease has shown that proteins build up in the brain and cause the deterioration of neurons.[171] This is sometimes seen as neuropathological lesions in the pars compacta of the *substantia nigra*, and occasionally other parts of the brain.[172] The presence of these proteins causes deterioration of dopaminergic neurons, loss of dopamine production, and damage to the physical structures of the brain.[173] This damage leads to impairment of motor skills, loss of sense of smell, and other symptoms as outlined above.[174]

It is not enough for temporal sequences alone to explain a phenomenon.[175] The classic example of this comes from Aristotle and the example of the cock crowing for dawn.[176] That the cock crows in relationship to the sun rising does not explain the fact of the sun rising. In the example of Parkinson's Disease, it is not enough that Lewy bodies precede neurological degeneration, there needs to be a causal explanation too. The effects of protein build-up (the cause), such as palsy and behavioural changes etc. (effects) do not themselves explain the presence of the proteins, the proteins, explain the presence of the effects. The palsy, memory-loss and other symptoms of Parkinson's disease do not explain each other, instead, they have a common explanation. There needs to be an 'account of explanatory relevance'

[169] Bezard and Przedborski.
[170] Ibid.
[171] Ted M. Dawson, Valina L. Dawson, and Han Seok Ko, "Genetic Animal Models of Parkinson's Disease," *Neuron* 66, no. 5 (2010).
[172] Ryan J. H. West et al., "Neurophysiology of Drosophila Models of Parkinson's Disease," *Parkinson's disease* 2015 (2015).
[173] Lees, Hardy, and Revesz.
[174] Ibid.
[175] Craver.
[176] Ibid.

beyond the identification of a mechanism.[177] The inclusion of irrelevant information, such as the colour of the stain used to identify the Lewy bodies, does not explain the impairment of Parkinson's sufferers.

The presence of the biomarkers – protein build-up and Lewy's bodies – allows researchers to have a comparison between the Drosophila with Parkinson's disease characteristics and those of human sufferers. Without a biomarker, it is a harder task to accurately confirm the mechanism under investigation is the correct one.

3.3.4 Arrangement of parts

How parts are arranged relative to each other across space and time is a component of mechanistic explanation. Having identified the necessary components of Parkinson's disease, the causal relationships between the components, the arrangement of the parts will now be discussed.

The arrangement of parts in the mechanistic explanation of Parkinson's disease is straightforward.[178] The parts involved are neural structures and chemicals that are affected by the inability of mitDNA to clean up proteins.[179] The presence of proteins over time, damages neurons.[180] This is a mechanistic failure. The mitochondrial DNA does not properly recycle *Parkin* in the brain, and the build-up causes plaque that stops neurons from receiving dopamine, interfering with their signalling, and ultimately causing them to die.[181] Whether Lewy bodies have a causal relationship to the damage done to brains of sufferers, or if they are symptom of the damage will be settled through further research and the use of other species of model organism completing the mechanistic explanation.[182]

These successes of the explanation without the fine-grained explanation of the role of every part, are one of the reasons why some philosophers claim we should prefer mechanistic

[177] Ibid., 32.
[178] Ibid.
[179] Rafique Islam et al., "A Neuroprotective Role of the Human Uncoupling Protein 2 (Hucp2) in a Drosophila Parkinson's Disease Model," *Neurobiology of Disease* 46, no. 1 (2012).
[180] Lees, Hardy, and Revesz.
[181] Dawson, Dawson, and Ko.
[182] Bezard and Przedborski.

explanations to other explanations.[183] I will now explore this, and other arguments for preferring mechanistic explanations in biology. Regardless of whether Lewy bodies are mere symptoms or causes, the mechanistic explanation succeeds at identifying the parts of interest, the uncovering of the exact causal relationships is an iterative process.[184]

Mechanistic sketches can have partial predictive success without an exact and precise picture of the parts and arrangements, but how is it possible to have a mechanistic explanation without a full picture of all of the components? As illustrated above, it is possible to uncover the mechanism, and fill in minutiae as more knowledge is created, to begin with a mechanistic sketch and work towards filling in the details until a full explanation of the phenomenon is created.[185] The example of Lewy bodies illustrates how components are identified, and the causal relationships provide the explanatory power, research in this area moves quickly towards uncovering the causes between parts. The final mechanistic explanation will settle questions of the exact nature of the causal relationships between parts.[186] Indeed, it is arguable that requiring all parts to be identified, understood, and exactly explained is the goal of science.[187] Requiring this level of understanding before positing an explanation would render science impossible. Identifying the phenomena, its components, their causal relationship, and arrangement, sketches the mechanism without committing to having to already know what the exact structure and composition of the parts and their causal relationships is the first step to providing a mechanistic explanation.[188] For systems level, or computational models or explanations, the causal roles need to be understood prior to an attempt to model the phenomenon.[189] Once there is enough knowledge to show the broadly true causal relationships, more work can be done to

[183] Craver.
[184] Ibid.
[185] Ibid.
[186] Ibid.
[187] Ibid.
[188] Ibid.
[189] Ibid.

fine-tune that understanding and give a mechanistic explanation that satisfactorily explains the causal relationships as well as predicting the effects of changes.[190]

It is also possible to successfully predict the development of Parkinson's disease by screening for the mutations that give rise to the disease. This is an important component of mechanistic explanations.

3.4 Parkinson's Disease and Drosophila

The ability of scientists to manipulate the genetic profile of Drosophila, along with the ease of use of the fly – as discussed above – has led to the development of Drosophila models of Parkinson's disease.[191] The same target – the mechanism – is present in all animal models of the disease, and it is the behaviour that arises because of the mechanistic malfunction that is explored in different species. The target is contained within the model organism. A phenomenon is correlated with specific physical and chemical parts, and their causal relationships can be modelled in the Drosophila by engineering strains of Drosophila who carry the same mechanisms. These findings can be extrapolated to humans because the mechanism remains the same in model and target.

Drosophila share important features of humans – neurotransmitters such as glutamate, dopamine, serotonin, acetylcholine, and GABA, and they also exhibit complex behaviours and share conserved genes, as discussed above.[192] Thanks to the extensive history of Drosophila in the laboratory, the knowledge and technology exists to allow genetic manipulation to investigate the action of particular gene sequences in the organisms.[193] This reverse screening involves researchers inserting human genes into flies and observing the changes to the areas of interest – behaviour, brain anatomy, disruption to neurotransmission and the build-up of proteins, and the presence of Lewy bodies.[194]

Drosophila has also furthered the understanding of the protein, *Parkin* in mitochondrial

[190] Ibid.
[191] Vanhauwaert and Verstreken; Botella et al.
[192] Vanhauwaert and Verstreken.
[193] Ibid.
[194] Ibid.

function, and its relationship to dopamine.[195] *Parkin* was previously known to be important in dopaminergic systems, and also to play a role in Parkinson's disease.[196] Scientists can manipulate Drosophila genetically to produce strains that express no *Parkin*, or an abundance of *Parkin,* and the effects may be observed, leading to a better understanding of its role in Drosophila as well as human neurotransmission.[197]

Presently there is no treatment option for Parkinson's disease. Symptoms can be managed through a range of therapeutic treatments, most often medicating with dopamine and dopamine agonists.[198] But prevention and elimination of the disease is not presently possible. The desire to effectively, treat, diagnose, and prevent Parkinson's disease drives the need for a Drosophila model of the disease. This allows scientists to test treatment plans and to unravel the complexities of the disease ethically and efficiently.

As is discussed throughout this paper, Drosophila alone, do not do all the work to further research and create a complete model of the disease. Yeast, mice and other organisms are used to uncover and understand Parkinson's disease.[199] The knowledge that is created is the work of cross-disciplinary researchers, from the physicians who diagnose, to the experts in Drosophila, to neuroscientists and more, who together build the knowledge of the disease that can then be modelled in fruit flies.[200] The standards of nomenclature, tool use, and other forms of knowledge construction all build a working model and explanation of the disease.[201]

All of this is best illustrated in a quote from Botella et.al:

> *"The use of Drosophila models, albeit some of them require further characterization, has opened a tremendous opportunity to explore the role of the genetic and environmental factors in [Parkinson's Disease] PD and the*

[195] Botella et al.

[196] Ibid.

[197] Ibid.

[198] Jennifer Rose V. Molano, "Dementia with Lewy Bodies," *Seminars in neurology U6* 33, no. 4 (2013).

[199] Dawson, Dawson, and Ko.

[200] Botella et al.

[201] Sara Green, "When One Model Is Not Enough: Combining Epistemic Tools in Systems Biology," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 44, no. 2 (2013).

> *pathways in which they might be involved. We hope that the efforts from different labs worldwide using this and other animal models will assist in getting new and exciting insights into the aetiological and pathological aspects of this disease providing the bases for new therapeutic strategies for PD."*[202]

As Parkinson's Disease has been successfully modelled in Drosophila, the mechanisms can now be examined in other model organisms, to further understand how it gives rise to symptoms.[203] By using other model organisms, to study the disease and its pathology in mammalian species, a clearer understanding of the aetiology of the disease in humans is offered.[204] Different stresses and genetic factors can be modelled to create an even more robust understanding of the mechanism and its effect on different organisms.[205] Drug treatments and stresses that are complicated by the many differences between insects and mammals, and broadening the model of the disease into more homologous species overcomes some of these barriers.[206]

3.5 Searching for mechanisms

Robust explanation in neuroscience is only possible by negotiating the different levels of functions and drawing boundaries around the explanatorily relevant. In the example of Parkinson's disease, there are relevant facts about the disease that will shape the search for a model.

The late onset of Parkinson's disease – middle to early late age – and the discovery of Lewy bodies provide an important boundary around study of how the disease progresses, and of the build-up of proteins, and the development of Lewy bodies over time.[207] The molecular and cellular relationship to symptoms were furthered through the understanding of the role of dopamine in regulating memory and movement.[208] Memory and movement disorders are two of the symptoms of advanced Parkinson's disease.[209] The symptoms arise from a

[202] Botella et al.
[203] Ibid.
[204] Ibid.
[205] Ibid.
[206] Ibid.
[207] Lees, Hardy, and Revesz.
[208] Ibid.
[209] Ibid.

disorder in the transmission of dopamine, proteins are not recycled by mitDNA and their presence interferes with and damages neurons and dopamine transmitters.[210] This explains the symptoms, and gives a partial explanation of how the symptoms relate to the molecular activity in the brain.

The ways that symptoms manifest; the timing, early warning signs and other symptoms, understood from the perspective of psychology and psychiatry may shape some of the relevant properties for further study at an anatomical or neurochemical level. These symptoms can then be reduced to the actions of neurotransmitters in the brain. This unification of terminology, expertise and tools guides the search for mechanistic explanation.

3.6 Predictive power of mechanistic explanations

A mechanistic account can handle the different neurochemicals, architecture, and other features that differ between human and Drosophila, as it is concerned about functions and relationships between parts not just about accurate description of components and predictions about them.[211]

Mechanistic explanation can also provide description and prediction but its grounding is in answering the "why" questions. This allows it the flexibility to describe how the Drosophila can model for human mental health disorders.[212] The identification of these kinds of forms of mechanistic explanation is predicated on a similarity between Drosophila and humans, as discussed in sections 1.2.3/4, and this similarity can lead to reliable models of other human diseases.

There are many ways to describe the activity of the brain, but mere descriptions lack explanatory power, they state what is happening but not why. Complicated and overlapping mechanisms are responsible for neurological activity and mental output. Just how genes, proteins, hormones and neurotransmitters interact to regulate brain activity is being

[210] Ibid.
[211] Atanasova.
[212] Ibid.

investigated through many different experiments, models and research by neuroscientists.[213] By understanding how these mechanisms are governed and kept in homeostasis can reveal how dysfunction causes mental health disorders and disrupt higher order, meta-functions such as behaviour.[214] These relationships are so complex and intertwined that finding simple models, or mechanistic explanations allows scientists to simplify some aspects and manipulate them to better understand the molecular actions and interactions that have potential for treatment, or intervention to correct problems.[215]

It has been argued that we should prefer these kinds of mechanistic explanations as they explain the phenomena of interest and they are able to predict what changes to the part will mean for the whole.[216] A mere description of the parts will not have predictive power; knowing the arrangement of the muscles in an arm does not predict what will arise if one of the parts is damaged. Including a causal explanation of the relationship between the parts means that we can predict what damage of one part will mean for the movement of the arm.

4 Chapter Three: Schizophrenia and the search for mechanistic explanations

In this chapter I will begin by exploring the role of idealisation in the development of Drosophila models in neurological research. The simpler brains of Drosophila give scientists a well understood medium for testing the molecular actions of mechanisms on neural structures and neurotransmission.[217]

There are complications in the search for a Drosophila model of schizophrenia that are not present in the Parkinson's disease case. The diagnosis of schizophrenia, and the difficulty in

[213] Bechtel, "Mechanism and Biological Explanation."
[214] Bickle.
[215] CRAVER
[216] SEP
[217] Swinderen and Andretic.

finding suitable behavioural models of a complex mental health disorder in an insect, are considerable. Drosophila represents an opportunity to better describe and understand the causal mechanisms that drive schizophrenia, but this work is restricted by the inability of Drosophila to display the symptoms of schizophrenia. There are some correlates between circadian rhythms, disordered sleep, and the startle reflex that will be discussed as potential candidates for accurate diagnosis.[218] There appears to be a correlation between circadian rhythms and schizophrenia and this is a good place to being to look for possible causal links between the disease and neurological mechanisms.[219] The fact that the majority of sufferers are male may not be relevant to the mechanical explanation. While it is unlikely that being one's gender is entirely irrelevant to the mechanistic explanation of schizophrenia; this could be explained by social factors alone, although this is doubtful. However, such a factor cannot be ruled out without further research. The demarcation of the relevant parts of the disease is bounded by the work that has come before it. It becomes a resonant project, that may shape understanding at a psychiatric level by exposing different diagnosable types of schizophrenic diseases or reveal a spectrum rather than a disease and sub-types.[220]

I will revisit some of the claims in the previous chapters, to draw my conclusion that we should see the Drosophila's role in mechanistic explanations of schizophrenia as one of a tool or vessel for *in vivo* experiments on mechanisms. I will conclude by considering the role of Drosophila in a network of model organisms, with scientists working together to better understand the action of mechanisms.[221] Drosophila are the natural start for the development of mechanistic explanations of disease. The work to confirm theories and

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[218] Gardner et al; Veena Kumari et al., "Reduced Prepulse Inhibition in Unaffected Siblings of Schizophrenia Patients," *Psychophysiology* 42, no. 5 (2005).

[219] Sofia Axelrod, Lino Saez, and Michael W. Young, "Chapter One - Studying Circadian Rhythm and Sleep Using Genetic Screens in Drosophila," in *Methods in Enzymology*, ed. Sehgal Amita (Academic Press, 2015); Zordan and Sandrelli; William Bechtel, "Circadian Rhythms and Mood Disorders: Are the Phenomena and Mechanisms Causally Related?," *Frontiers in psychiatry* 6 (2015); Siddharth Sukumaran et al., "Circadian Rhythms in Gene Expression: Relationship to Physiology, Disease, Drug Disposition and Drug Action," *Advanced Drug Delivery Reviews* 62, no. 9–10 (2010); Pritchett et al; Aoife Larkin et al., "Neurexin-1 Regulates Sleep and Synaptic Plasticity In drosophila Melanogaster," *European Journal of Neuroscience* 42, no. 7 (2015); Ozgur Tataroglu and Patrick Emery, "Studying Circadian Rhythms in Drosophila Melanogaster," *Methods* 68, no. 1 (2014); Hendricks and Sehgal.

[220] Green.

[221] L. Huber and L. K. Keuck, "Mutant Mice: Experimental Organisms as Materialised Models in Biomedicine," *Studies in History and Philosophy of Science Part C :Studies in History and Philosophy of Biological and Biomedical Sciences* 44, no. 3 (2013).

further the knowledge should then be continued through an iterative, resonant process incorporating multiple models, and disciplines.

4.1 Schizophrenia

Schizophrenia is a complex and debilitating disease of the mind. Approximately 1% of the population suffer from schizophrenia.[222] It has a high co-morbidity with other mental health disorders such as depression, anxiety, and autism.[223] It is correlated with a decreased life expectancy for sufferers – 15 years lower than the general population – as well as a nine-fold increase in the number of suicides in schizophrenics compared to the general population.[224] Schizophrenia is thought to result from multiple genetic and environmental factors, which further complicates attempts to treat sufferers, or prevent the disease.[225]

The most widely used tool for mental health professionals to diagnose mental health disorder is the Diagnostic and Statistical Manual of Mental Health Disorders (DSM), which provides this diagnostic criterion of schizophrenia is from the most recent edition (V):

> *"Two (or more) of the following each present for a significant portion of time during a 1 month period (or less if successfully treated). At least on these must be (1), (2), or (3):*
>
> 1. *Delusions.*
> 2. *Hallucinations.*
> 3. *Disorganised speech (e.g., frequent derailment or incoherence).*
> 4. *Grossly disorganised or catatonic behaviour.*
> 5. *Negative symptoms (i.e., diminished emotional expression or avolition)."*[226]

The above describes the major positive and negative symptoms of schizophrenia. The presence of delusions, are beliefs in things that are not grounded in reality - believing one is

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[222] Jun-Ming Li et al., "Genetic Analysis of the Dlgap1 Gene as a Candidate Gene for Schizophrenia," *Psychiatry Research* 205, no. 1–2 (2013).
[223] E C Harris and B Barraclough, "Excess Mortality of Mental Disorder," *The British Journal of Psychiatry* 173, no. 1 (1998).
[224] Ibid.
[225] Joseph L McClay et al., "Genome-Wide Pharmacogenomic Analysis of Response to Treatment with Antipsychotics," *Molecular psychiatry* 16, no. 1 (2011).
[226] American Psychiatric Association and American Psychiatric.

Jesus Christ. Hallucinations are seeing or hearing something that is not there. Speech that is incoherent or hard to follow, and behaviour that is not suitable for the context. Negative symptoms describe the absence of behaviours and emotions found in people not suffering mental health disorders. A diagnosis of schizophrenia cannot be made without the presence of delusions, hallucinations, or disorganised speech.[227] The symptoms will be present for "a significant portion of time" over the period of one month, leaving some of the criteria vague and open to interpretation.[228] Successful treatment of the symptoms before the symptoms have persisted for a month, does not prevent diagnosis. Leaving aside some of the imprecision inherent in diagnosing schizophrenia in a human, in this section I will consider how we might recognise schizophrenia in an insect.

Schizophrenia and psychosis are distinguished from each other through the persistence of symptoms over time. It should be noted that the DSM exists for practitioners of psychiatry and psychology, as well having an important legal and social role.[229] The behaviours and symptoms are defined using language and terms from the field of psychiatry. This description draws boundaries between schizophrenia and other diseases and shapes the understanding for people working on the disease in other fields. The model is only robust if it relates to the above definition. The ways we understand the symptoms of the disease in humans will inform the ways we look for symptoms on animal models.

Treatment of schizophrenia is usually through psychotropic drugs, with a low rate of success when compared to drug treatments for non-psychiatric disorders.[230] The majority of patients will be prescribed different treatments over time, with a variety of side-effects and varying level of success.[231] There is a strong genetic component to schizophrenia, with family members of a schizophrenic patient at much higher risk of affliction than the general

[227] Ibid.

[228] Rajiv Tandon et al., "Definition and Description of Schizophrenia in the Dsm-5," *Schizophrenia Research* 150, no. 1 (2013).

[229] Ibid.

[230] McCammon and Sive.

[231] McClay et al.

population.[232] Research has shown that siblings of schizophrenic patients share some of the correlates of the disease without themselves being schizophrenic.[233]

4.2 Schizophrenia and Drosophila

As has been achieved with Drosophila and Parkinson's disease, scientists are hopeful of developing an animal model to further our understanding of schizophrenia, an organism that contains the mechanism that drives the disease.[234] Not only will increased understanding lead to better outcomes for sufferers through the development of treatment options, early diagnosis may be possible and the removal of potential environmental triggers controlled, for those at risk of developing the disease.

Schizophrenia has a broad manifestation of symptoms and sub-types. The difficulty in identifying the salient features of schizophrenia for diagnosis has led to some psychiatrists calling for new subdivisions, and possible separate diagnoses for the disease.

> *"After genotype clusters were matched to phenotype clusters, eight distinct classes of schizophrenia were differentiated, suggesting for the first time that schizophrenia may be eight different disorders instead of one…Researchers should exercise caution regarding the relationship between an endophenotype and a complex disorder, and con- firming genetic linkage for intermediate phenotypes may also be useful for revealing mechanistic information for pathology."*(175)[235]

McCammon and Sive are discussing the research to delineate schizophrenia into clearer subcategories. There are many who believe that schizophrenia is a spectrum of diseases, akin to autism, rather than a disease with many subtypes.[236] By linking genotype to phenotype – genes to behaviour – better categorisation of the disease can result, and for many researchers, the fruit fly is the perfect tool for the job. As is explicit in the statement above, the search is for the mechanisms that give rise to the disease is being conducted by testing candidate mechanisms in Drosophila. This can help not only to increase our

[232] McCammon and Sive.

[233] Kumari et al.

[234] van Alphen and van Swinderen; Narayanan and Rothenfluh; Furukubo-Tokunaga, "Chapter 12 - Modeling Schizophrenia in Flies."; Zordan and Sandrelli; van Alphen and van Swinderen.

[235] McCammon and Sive.

[236] Tandon et al.

understanding of the mechanisms, but also the disease itself. The quote above illustrates how Drosophila models could give insight into this question, as well as providing better treatment, diagnosis, and possibly prevention in the future.

How do we understand the representation of schizophrenia generated through a Drosophila model? We can see it as a simplified, mechanistic account of the causes of a particular pattern or disorder in neurotransmission. We cannot see such a model as a model of schizophrenia, but rather a vehicle for the mechanism suspected to cause disordered neurotransmission. To look instead for a behavioural change that correlates or corresponds to schizophrenia in humans is another way to explore whether the model is providing a simplified, model of schizophrenia.

> *"As outlined in Fig. 1, there are three strategies to initiate a fly-based approach to studying cognitive disorders. In the first strategy (forward genetic screens), random mutations are tested for behavioural phenotypes. The second strategy (reverse genetics) uses known disorder genes, derived from patient studies, and examines their roles in an animal model. The third strategy uses animal models to test more general theories about disorders, by for example manipulating environmental variables."*[237]

The work being performed to screen for genetic causes of schizophrenia, involves screening for mechanisms, not for miniature schizophrenics. The screening tests the relationship between genes and malfunctioning neurology, and between environmental influences on genes, and any subsequent changes to neurology. Genetic screening can either test mutations for their behavioural phenotypes, looking for mutations that are correlated with certain consistent behaviours – forward screening. Mechanisms of interest, genes known to be disordered, gleaned from studying patients, can be examined in model organisms – reverse screening, and their molecular action studied *in vivo*.

This will be discussed further in the following section. The conclusion I reach is that while behavioural analysis is not a reliable diagnostic tool in Drosophila, it is perhaps a guide to some important changes, but it is impossible to diagnose a fly with schizophrenia. The fruit fly cannot model a complex and debilitating disruption to the human mental landscape. That task can be furthered through mammalian models, in particular rodents.

[237] van Alphen and van Swinderen, 2.

4.3 Diagnosis

In this section I will examine some of the problems of diagnosing an insect with a mental health disorder. The role of Drosophila as a stand-in for human schizophrenics faces several challenges: the mammoth task of unravelling epigenetic factors, the existence of symptoms such as an inhibited startle reflex in siblings of schizophrenics (who do not suffer from schizophrenia), and the detection and classification of social behaviours in Drosophila. There have been many interesting experiments with flies and various drugs, to explore the neurochemical relationship between the drugs and behaviour.[238] These play an important role in understanding the biochemical and neurochemical effects of the drugs, but are not models of hallucination or of the symptoms of schizophrenia, as has been suggested.

I will argue that success will be achieved by understanding the target of this research to be an idealised mechanism. The target is correlated with schizophrenia and Drosophila is engineered to explore it. The role of the Drosophila is not to model the disease, but to model the mechanism responsible and study its molecular action, *in vivo*.

4.4 Salience, sleep, schizophrenia, and fruit flies

Mechanistic explanations define a phenomenon and seek to demarcate the relevant physiological component's functions.[239] The principle that drives mechanistic explanations is that all biological processes are governed by the same laws that govern physical and chemical interactions elsewhere.[240] There are several symptoms that can guide researchers to where mechanistic breakdown is causing disease. Researchers have found a few target neurotransmitters, that are thought to be involved in schizophrenia that are also either present in Drosophila, or have a homologue.[241] In schizophrenia, there is an association

[238] C. D. Nichols et al., "Hallucinogens and Drosophila: Linking Serotonin Receptor Activation to Behavior," *Neuroscience* 115, no. 3 (2002); Adrian Rothenfluh and Ulrike Heberlein, "Drugs, Flies, and Videotape: The Effects of Ethanol and Cocaine on Drosophila Locomotion," *Current Opinion in Neurobiology* 12, no. 6 (2002).
[239] Laurel Graves, Allan Pack, and Ted Abel, "Sleep and Memory: A Molecular Perspective," *Trends in neurosciences* 24, no. 4 (2001).; Leonie Kirszenblat and Bruno van Swinderen, "The Yin and Yang of Sleep and Attention," ibid.38, no. 12 (2015).
[240] Kaplan and Craver.
[241] Verónica T. Cheli et al., "Genetic Modifiers of Abnormal Organelle Biogenesis in a Drosophila Model of Bloc-1 Deficiency," *Human Molecular Genetics* 19, no. 5 (2010). Larkin et al. Charles D. Nichols, "5-Ht2

between disordered sleep, attention, memory, dreaming and salience attribution that point towards the dopaminergic system as a starting point to look for causes of schizophrenia.[242]

4.4.1 Salience misattribution

The misattribution of salience is a positive symptom of schizophrenia. A misattribution of salience leads seeing patterns where none exist, finding meaning in unconnected events, and believing there are forces and things that you perceive that no one else does.[243] It also describes hallucination, where internally generated stimuli are mistaken for externally produced phenomena.

> *"The positive symptoms within schizophrenia can be considered as a disorder involving the misattribution of salience, where patients tend to respond in a maladaptive way to both external and internally generated stimuli. Salience is largely regulated by dopaminergic systems, and several cognitive disorders involve impaired dopamine signaling. The mechanism/s by which an early alteration in dopamine systems might influence aberrant salience allocation in adulthood remains unknown… Genetic models such as the fruit fly Drosophila melanogaster offer the potential to test the dopamine ontogeny hypothesis in a precisely controlled context. Drosophila provides several advantages for modeling psychiatric disorders potentially linked to dopaminergic dysregulation. As with humans, dopamine also modulates arousal and attention in Drosophila, suggesting that similar mechanisms might be involved in allocating salience to stimuli. Since a key aspect of the dopamine ontogeny hypothesis posits a transient effect on dopaminergic signaling during development, it is necessary to develop models that might accurately mimic such temporary changes in dopamine activity or receptor function."*[244]

In this quote, we can see an example of the many papers calling for a mechanistic explanation of schizophrenia – the symptom, salience misattribution, is posited to be a result of a an impairment in dopamine signalling, which is further discussed in relationship to the disruption of sleep wake cycles. Here we can see an example of a search for mechanistic explanations of schizophrenia. Changes to the expression of dopamine in

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Receptors in Drosophila Are Expressed in the Brain and Modulate Aspects of Circadian Behaviors," *Developmental neurobiology* 67, no. 6 (2007). Jamain et al.

[242] D. Eyles, J. Feldon, and U. Meyer, "Schizophrenia: Do All Roads Lead to Dopamine or Is This Where They Start? Evidence from Two Epidemiologically Informed Developmental Rodent Models," *Translational psychiatry* 2, no. 2 (2012).

[243] Kirszenblat and van Swinderen.

[244] Lachlan Ferguson et al., "Transient Dysregulation of Dopamine Signaling in a Developing Drosophila Arousal Circuit Permanently Impairs Behavioral Responsiveness in Adults," *Frontiers in Psychiatry* 8 (2017): 1-2.

development are posited as a key to understanding the mechanisms that cause the disease. Disordered dopamine signalling in development is thought to make the changes that lead to salience misattribution in later life. This explanation looks to neurochemistry, dopamine, to explain the symptoms of schizophrenia and proposes the use of Drosophila to model the changes in the dopaminergic system in utero that lead to the development of schizophrenia in later life.

The problem this runs into is again how to describe the behavioural changes that arise in engineered Drosophila. The call for a model that mimics such temporary changes is achievable but those changes will not be recognisable in a fly. Drosophila cannot exhibit behaviour associated with salience misattribution. Scientists can induce the dopaminergic mechanisms that are thought to give rise to salience misattribution in humans but they have no way of testing the salience attribution of a fruit fly. They can dissect flies at various stages of development and examine the changes to neurotransmission and neuro-circuitry. Disordered dopamine signalling and processing will provide evidence of a mechanistic failure in those systems. It will be changes to the molecular profile or relevant parts of the brain that confirm the experiment.

Dopamine also regulates circadian rhythm, which is another possible mechanism where malfunction could give rise to schizophrenia.[245] Circadian rhythms regulate sleep, wakefulness and attention, all things affected by schizophrenia.

4.4.2 Circadian Rhythms

Disruptions to the functions of the circadian rhythms have been observed in schizophrenic patients; sleep disorders are common across patients despite the large variation in the presentation of symptoms from catatonic to hallucinatory manifestations.[246] Drosophila, as many organisms do, have circadian rhythms, “clock genes” that are responsible for the regulation of body temperature, melatonin production, cortisol, and sleeping and waking

[245] Pritchett et al; Zordan and Sandrelli.

[246]; Eyles, Feldon, and Meyer.; Narayanan and Rothenfluh.; Llewellyn; Pritchett et al; Zordan and Sandrelli.

cycles.[247] Sleep also plays a role in the formation of long and short term memory, and in attention.[248] Disruptions to attention and to memory are also present in schizophrenia.[249] These correlates are not symptoms of the disease, nor are they biomarkers; there are many people who suffer disruptions to their circadian rhythms and are not schizophrenic.[250] Circadian rhythm disruption can also *cause* a number of different symptoms in shift workers and jet-leg sufferers for example.[251]

The underlying mechanism that controls an organism's periods of rest and arousal are the circadian rhythms.[252] To provide a mechanistic explanation of sleep, the relationship between circadian rhythms, brain activity, alertness and other factors is detailed.[253] If we can uncover the physical and chemical components of a phenomena of interest then we can apply knowledge of biology, chemistry, and physics to explain how they interact.[254] In the case of sleep this means understanding how the circadian clock drives cycles in the human body that cause us to have different levels of arousal throughout the day.[255] This explanation focuses on the underlying causal mechanisms of sleep and provides an account of how these mechanisms interact both in space and time, to produce the phenomena of interest.[256]

It has been proposed that a disorder in circadian rhythms may be responsible for the manifestation of schizophrenia.[257] Circadian rhythms have a relationship with the

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[247] Paul E. Hardin, "The Circadian Timekeeping System of Drosophila," *Current Biology* 15, no. 17 (2005).; Zordan and Sandrelli.

[248] Michel and Lyons.; Hendricks and Sehgal.

[249] Stickgold and Walker.

[250] Sukumaran et al.

[251] Pritchett et al.

[252] Michel and Lyons.; Hardin.

[253] Graves, Pack, and Abel.; William J Joiner, "Unraveling the Evolutionary Determinants of Sleep," *Current Biology* 26, no. 20 (2016).

[254] Atanasova.; Craver.

[255] Graves, Pack, and Abel.

[256] Chiara Cirelli and Giulio Tononi, "The Search for the Molecular Correlates of Sleep and Wakefulness," *Sleep Medicine Reviews* 5, no. 5 (2001).

[257] Pritchett et al; Sukumaran et al; Zordan and Sandrelli; Gottesmann and Gottesman; Peter H Kelly, "Defective Inhibition of Dream Event Memory Formation: A Hypothesized Mechanism in the Onset and Progression of Symptoms of Schizophrenia," *Brain research bulletin* 46, no. 3 (1998); Ming Li, William D.

production of many physiological processes and functions.[258] Circadian rhythms have complex feedback loops that are correlated with cycles of sleep and wakefulness as well attention, memory capacity and other features.[259] There are changes to the circadian rhythms in people diagnosed with schizophrenia, and disruptions and changes to stable circadian rhythms can occur during key development windows when at risk individuals start exhibiting symptoms.[260] By using circadian rhythms as a diagnostic tool, and as a guide to the mechanism that gives rise to schizophrenic symptoms, we might arrive at a closer point to the kind of sophisticated mechanistic explanation of the disease.

4.4.3 Circadian rhythms not the answer?

Bechtel has proposed that the relationship between circadian rhythm disruption and mood disorders – seasonally affected disorder, and major depressive mood disorder may not actually be causally related to each other but instead by the result of pleiotropy.[261] Pleiotropy describes the action of a gene in two or more unrelated phenotypic traits. The genes that drive circadian rhythms could also control the expression of another unrelated feature that is actually the causal mechanism behind mood disorders, and potentially schizophrenia.[262] This is a further complication, but one that scientists are confident of overcoming through the continued widening of the knowledge about the brain, mechanisms, and interactions between parts.[263] Unravelling the relationships between genes, serotonin, dopamine, and circadian rhythms with disease is exactly the kind of search for mechanistic explanation that can utilise Drosophila.[264]

Spaulding, and SpringerLink, *The Neuropsychopathology of Schizophrenia: Molecules, Brain Systems, Motivation, and Cognition*, vol. 63 (Cham: Springer International Publishing, 2016); Nichols.

[258] Axelrod, Saez, and Young; Cirelli and Bushey; Hardin; Michel and Lyons; Sukumaran et al; Tataroglu and Emery.

[259] Cirelli and Bushey; Michel and Lyons; Tataroglu and Emery.

[260] Cirelli and Bushey; Hendricks and Sehgal; Larkin et al; Pritchett et al; Sukumaran et al; Zordan and Sandrelli.

[261] Bechtel, "Circadian Rhythms and Mood Disorders: Are the Phenomena and Mechanisms Causally Related?."

[262] Ibid.

[263] Bechtel, "Circadian Rhythms and Mood Disorders: Are the Phenomena and Mechanisms Causally Related?."

[264] van Alphen and van Swinderen.

There are some areas to be clarified in this; there is the problem of pleiotropy and a lack of clarity about the hierarchy and interrelatedness of aspects of the clock genes, circadian rhythms and some of the neurological processes they are involved in.[265] Some of the important functions of clock genes, that regulate our circadian rhythms, are: memory formation, arousal thresholds and sleep/ wake cycles (and many more aspects that are not relevant to this discussion of research using Drosophila). How memory is related to sleep, how our ability to pay attention is regulated by our circadian rhythms and other aspects of neurology are still being explored and defined, and the literature can be overlapping and confusing.

4.4.4 Sleep cycles and dreaming

This section examines some of the potential challenges of using Drosophila as a model for human sleep cycles. Much of the work on sleep and circadian rhythms in Drosophila is focussed on molecular relationships, providing mechanistic accounts of the functions, processes and feedbacks of the genes, neurotransmitters and anatomical features involved in regulating sleep.[266] These mechanistic accounts run into the same challenges outlined in the section above, but in this section I will delve further into the question of how other neurological processes such as dreaming, are handled in the Drosophila model of schizophrenia.

A complication in using Drosophila to model sleep is the lack of a bi-phasic sleep pattern in insects.[267] Bi-phasic sleep has been observed in birds and mammals but not in insects.[268] There are some researchers challenging this position, proposing that insects may have something like bi-phasic sleep but this is unverified at this stage.[269] This is important

[265] Cirelli and Tononi.

[266] Axelrod, Saez, and Young; Hardin; Hendricks and Sehgal; Michel and Lyons; Sukumaran et al; Tataroglu and Emery; Zordan and Sandrelli.

[267] Mary A Carskadon and William C Dement, "Normal Human Sleep: An Overview," *Principles and practice of sleep medicine* 4 (2005).

[268] Jerome M. Siegel, "Do All Animals Sleep?," *Trends in Neurosciences* 31, no. 4 (2008).; Albrecht P. Vorster and Jan Born, "Sleep and Memory in Mammals, Birds and Invertebrates," *Neuroscience & Biobehavioral Reviews* 50 (2015).

[269] Bart van Alphen et al., "A Dynamic Deep Sleep Stage in Drosophila," *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33, no. 16 (2013).

because disruptions to circadian rhythms, and in particular to the Rapid Eye Movement (REM) stage of sleep, are one of the more consistent correlates of schizophrenia.[270] Drosophila, as far as we know now, do not have an REM sleep stage. Some scientists have suggested that it is a malfunctioning of the mechanisms that control REM sleep that leads to the symptoms of schizophrenia.[271] There is also a suggestion that schizophrenia is caused by a kind of waking sleep, where the brain is in fact engaged in dreaming activity despite the sufferer being awake.[272] Do Drosophila dream? If they lack bi-phasic sleep then the answer is probably not. A lack of a REM sleep could mean that Drosophila lack the very mechanism that is affected in schizophrenia.

Anecdotal reports from patients with schizophrenia report feeling like being in a dream to describe their experiences of hallucinations.[273] There has also been research suggesting that the brain of a schizophrenic who is hallucinating more closely resembles the brain of someone who is in the REM stage of sleep than someone who is awake.[274] The disruptions to sleep most commonly seen in schizophrenic patients is to delta wave cycles, sleep cycles that are not present in Drosophila sleep, as far as we know.[275] Dreaming is a relatively poorly understood phenomenon in science; there is a lack of understanding about the role dreams play, or if indeed they are an essential process, or merely a result of the random electrical firing of the brain.[276] If schizophrenia is a molecular brain that causes the waking brain to mimic a brain in REM, then Drosophila simply cannot model these affects, as they do not have the homology.[277]

4.4.5 Startle reflex

There are other correlates of schizophrenia that could potentially assist researchers to create a Drosophila model of schizophrenia. One such candidate is an inhibited startle

[270] Gottesmann; Gardner et al.
[271] .; Gottesmann.
[272] Llewellyn.
[273] Gottesmann; Llewellyn.
[274] Gottesmann.
[275] Kirszenblat and van Swinderen.
[276] Carskadon and Dement.
[277] Llewellyn.

reflex.[278] The startle reflex causes an involuntary reaction to unexpected stimuli.[279] This reflex is dampened in schizophrenic patients, they react later than control groups, and display less reaction.[280] However, the same is true of the siblings of schizophrenics, who do not have the disease. The startle reflex is not a reliable guide for whether an organism has schizophrenia.[281] This correlate should also serve as a cautionary note for researchers; the ethical implications of incorrectly identifying a correlate as a consistent symptom are enormous.

4.4.6 Epigenetics

In addition to the problems of cogently defining the similarity between model and target in sleep and circadian rhythms there is the large problem of epigenetic factors that affect gene expression in individuals.[282] Schizophrenia is a complicated disease with many comorbid symptoms and over 1000 genes are currently implicated in the development of the disease.[283]

There is almost unanimous agreement that at least some external factors cause individuals to develop schizophrenia where siblings with the same implicated genes may not.[284] Stress, and other external factors change the way genes are expressed in an individual.[285] Factors such as environment, temperament, epigenetics, diet, stress, and other potential influences are thought to play a role in the aetiology – history of the disease in a patient.[286] The development of schizophrenia is dependent on external conditions means that these conditions are a component of the disease.[287] When symptoms described above arise, is heavily dependent on conditions present throughout someone's life. Someone with genes

[278] Kumari et al.
[279] Ibid.
[280] Ibid.
[281] Ibid.
[282] van Alphen and van Swinderen.
[283] Ibid.
[284] Tandon et al.
[285] Aaron D. Goldberg, C. David Allis, and Emily Bernstein, "Epigenetics: A Landscape Takes Shape," *Cell* 128, no. 4 (2007).
[286] Tandon et al.
[287] Eyles, Feldon, and Meyer.

that increase their risk of schizophrenia may only develop the disease when their external environment, or their environment in utero, exposes them to these factors.[288] Schizophrenia is a disease that is intrinsically and extrinsically constituted; the presence of multiple factors may be the reason for a person developing the disease. Genetic screening in a Drosophila must therefore also screen for changes in gene expression through external stressors when searching for the genes responsible for schizophrenia.[289] Looking to factors outside of the genetic sphere is an immense task. It also involves looking beyond cellular processes and how they relate to each other, and to how these processes may be affected by the environment; social, physical, and other influences on development.[290] These factors can be manipulated by scientists and changes observed. While a huge task this is straightforward experimentation.

The emergence of schizophrenia at a key time in brain maturation suggests that something goes awry in a key stage of brain development.[291] The search for physical changes to the anatomical structures of the brain also leads to the same conclusion.[292] The search for malfunctioning neural transmitter is searching for the same kind of explanation of the disease, a mechanical explanation – this structure or chemical doesn't perform its task, is not present, is too high etc. and this leads to this behaviour or symptom. There are people diagnosed with schizophrenia after this key window of adolescence and there needs to be an aetiological explanation that accounts for the same disease being present despite different ages of onset. This is but one of the many arguments for considering schizophrenia to be a spectrum or cluster of diseases rather than a single disorder.[293] The fact that the disease is now broken into six different forms of the disease shows that it is a range, or a variety of different diseases, rather than a single disease.[294]

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[288] J. J. McGrath, A. J. Hannan, and G. Gibson, "Decanalization, Brain Development and Risk of Schizophrenia," *Translational psychiatry* 1 (2011).

[289] van Alphen and van Swinderen.

[290] Narayanan and Rothenfluh. van Alphen and van Swinderen; Zordan and Sandrelli.

[291] Dion K. Dickman and Graeme W. Davis, "The Schizophrenia Susceptibility Gene Dysbindin Controls Synaptic Homeostasis," *Science* 326, no. 5956 (2009).

[292] McGrath, Hannan, and Gibson.

[293] Sean A. Valles, "Validity and Utility in Biological Traits," *Biological Theory* 8, no. 1 (2013).

[294] Tandon et al.

4.5 Behavioural assays

It is not possible to have a Drosophila that suffers from schizophrenia, their mental landscapes are not complex enough to suffer from a debilitating mental health disorder.[295] The opposite has been explicitly suggested in several papers; there may in fact be some exhibition of symptoms in the fly of schizophrenic behaviour beyond disruptions to sleep, learning, and attention.[296] The problem of ascribing these symptoms to individual flies, and the difficulty in developing a model of even one symptom, hallucinations, will be discussed. I will also briefly discuss some of the technological breakthroughs in this area of research and how they may interact with the experimental/model system.[297]

Aggression, mating rituals, feeding, and other behaviours exhibited by Drosophila are well documented and understood.[298] They are social creatures, living in large groups with no hierarchical structure.[299] As they are insects, they emerge from their eggs as larvae which then pupate, finally emerging in their adult form.[300] Drosophila take eleven days from egg to maturity.[301] Males compete for females, and court potential mates with sounds and movements.[302] This social behaviour is complex; manipulating genes can give rise to mechanism that affect social behaviour, changing the ways flies interact with each other.[303]

Drosophila have been bred to display aggression, and other forms of anti-social traits.[304] This behaviour should not be classified as one analogous to human behaviour. The recognisable symptoms of an aggressive organism may lead us to the temptation to claim something about the personality of the fruit fly, but that is an unjustifiable slippery slope.

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[295] van Alphen and van Swinderen.

[296] Ibid.; Zordan and Sandrelli; Axelrod, Saez, and Young; Hendricks and Sehgal; Narayanan and Rothenfluh; Nichols et al.

[297] Zordan and Sandrelli.

[298] M. Sgrò and Linda Partridge.

[299] Kohler.

[300] Ibid.

[301] Ibid.

[302] Kohler.

[303] Oralee Johnson, Jaime Becnel, and Charles D Nichols, "Serotonin 5-Ht 2 and 5-Ht 1a-Like Receptors Differentially Modulate Aggressive Behaviors in Drosophila Melanogaster," *Neuroscience* 158, no. 4 (2009).

[304] Ibid.

We have no way of knowing why the flies are aggressive, we cannot ask them what triggers their behaviour. Nor can we presently understand the role of parents and environment in potentially overcoming a propensity towards violence. A molecular understanding of the relationship between this mutation, and aggression is extremely useful, and could certainly advance the understanding of behaviour and molecular causes in other organisms, but it cannot be understood as aggressive in a human way.

Displaying behaviour that seems to be the same as human behaviour does not lead to the conclusion that Drosophila have personalities. They have complex behaviours that are affected by their environment, genetic profiles, food availability, sex, social structures and much more. This complexity should not be interpreted as enough to attribute a theory of mind or consciousness to an insect. There are many steps to be taken before, and indeed if, that conclusion could be reached.

The same difficulty applies when describing the behaviour of a Drosophila used in an experiment to investigate molecular explanations of schizophrenia. Any changes that can be detected may be useful auxiliary evidence to changes in neurochemistry or neuroanatomy that point to the kinds of changes associated with sufferers of schizophrenia. Behavioural changes alone are not a good guide to the effect of the mechanism of interest on humans.

4.5.1 Drosophila models of hallucination?

There have been multiple studies to look at the effects of various psychotropic drugs on fruit flies, both the behavioural effects, and the physical changes to neurobiology.[305] One study administered lysergic acid diethylamide (LSD) to Drosophila and expressly claimed this may give us a model of a fly experiencing hallucinations.[306] In the study, the flies were administered a dose of LSD, and then performed a task, and the results compared to a control group, that performed the same task but without receiving the drug. Locomotor testing was undertaken; de-winged flies were exposed to the drug and their behaviour observed after ingestion or as a drug-free control group. Disruption to locomotion, was

[305] Rothenfluh and Heberlein; Yamamoto and Seto; Nichols et al.
[306] .

observed through the flies' ability to follow a moving line was recorded. The results supposedly show that there are similar disruptions to locomotion, brain chemistry, perception and more, in the fruit flies administered the drug, and humans who have ingested LSD. The complexity of human neuroanatomy and the ability of subjects in research to elucidate their experiences highlight the difficulty in extrapolating from drug to behaviours in a fruit fly.

Exactly how LSD works to alter perception and behaviour, and give rise to other symptoms is poorly understood. The changes to serotonin, behaviour, emotions, and visual perception are well documented, but the exact relationship between hallucination, drug and neurochemistry has not been satisfactorily explained.[307] While this experiment cleverly used antagonist, and agonist substances, combined with different strains of flies to show the changes in serotonin expression and metabolism in flies, it has not shown that the effects must be confined to serotonin.[308] This experimental work is very useful for many reasons, great care must be taken in the ways the results are interpreted and extrapolated to humans

There are many reasons why this a valuable experiment, however, it tells us nothing about the mental landscape of the flies. A human subject cannot be dissected to examine the molecular effects of a drug, but they can be questioned about their thoughts, motivations, and feelings both while under the influence of LSD and after the drug has worn off. This is obviously not possible with a fruit fly. It is questionable whether a fly would experience what we understand to be hallucinations at all. Does a fruit fly have the ability to experience the kinds of sensory, auditor, and visual disruption a hallucinating human can perceive? These questions cannot be answered by this experiment, or indeed possibly ever.

The experiment does, however, demonstrate that dopamine and serotonin secretion and signalling appears to utilise a conserved set of genes present in both Drosophila and humans.[309] The recycling system of serotonin, controlling uptake, reuptake, and removal, is

[307] Ibid.
[308] Ibid.
[309] Ibid.

homologous between humans and Drosophila.[310] The relationship between pigmentation and dopamine, briefly mentioned, is fascinating but we do not have space to go into it here except to say it furthers my argument that model organisms are used for interest in specific mechanisms and their molecular actions in certain systems, not the whole organism.

4.6 Diagnosis through multiple models and organisms

Models of particular features need to make claims that hold across species. I have previously discussed why it is possible to use insects to model biological features. These models can only be considered to hold across species when they are confirmed in other organisms. Knowledge is confirmed and refined through multiple models, increasing the homology to humans, and testing theories in new experimental apparatus.[311] The creation of an animal model of schizophrenia, begins with the fruit fly, a powerhouse that quickly and efficiently allows for the screening of genes for potential candidates. Introducing stressors allows scientists to study the effect of environment on gene expression and mechanisms. Dissection can reveal specific molecular actions of mechanisms, and the mechanistic causes of schizophrenia uncovered.

As discussed above, there are complications in diagnosing schizophrenia in human sufferers, so how can expect to diagnose the disease in a fly that cannot answer questions about their mental landscape? Behavioural assays can be useful in showing that flies have altered behaviour after being engineered to carry the mechanisms that are associated with schizophrenia. We can start to see where locomotion and functions have been impaired and follow up to see physical, and genetic change in the brains to the flies. The role of the Drosophila is to serve as a tool for *in vivo* experiment on the target of interest. Identifying the changes that may arise from altering genes, creating environmental stressors, and other avenues of investigation, is possible thanks to the large body of knowledge about the Drosophila, and its history of use in science. It is an ideal place to begin exploring the mechanism, but cannot display the kinds of behaviour exhibited by a schizophrenic.

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[310] Ibid.; Qili Liu et al., "Two Dopaminergic Neurons Signal to the Dorsal Fan-Shaped Body to Promote Wakefulness in Drosophila," *Current Biology* 22, no. 22 (2012).

[311]

Multiple animal models will be needed in the case of schizophrenia. No matter how sophisticated tools to observe fruit flies become, they still cannot display the kinds of behaviours of a human schizophrenic would. Perhaps rodent models can bridge some of the gap between insect and human.[312] The longer lives of rats and mice, and their complex social structures are better suited to modelling changes to neurochemical and neuroanatomical features explored affected by schizophrenia.[313] Rodents can also be genetically manipulated to give rise to the changes and malfunctions correlated with schizophrenia, and environmental factors can be more slowly, but also more accurately explored.

Drosophila is an *in vivo* experiment, where the model is the mechanism and its effect on neural circuitry, neurotransmitters, and the molecular changes that it causes. This *in vivo* experiment is the result of shared knowledge across many disciplines, and multiple animal models that provide mechanistic explanations for disease. The mechanisms can then be studied in more complex organisms, and ones that more closely related to us; rodents.[314] Rodents may be able to develop something more akin to schizophrenia, there are still considerable difficulties in diagnosing a rat or mouse with schizophrenia, but they are a step closer to the complexity and biology of the target organism; human sufferers of schizophrenia. The iterative processes of knowledge construction rely on the use of multiple organisms, and multiple species to refine the understanding of the mechanistic causes of disease.[315]

4.7 Success

By starting with the Golden Bug, Drosophila, researchers have a tool to quickly and cheaply perform vital genetic screenings of potential mechanisms that give rise to schizophrenia.[316] Their short life span, and the ease with which they can be genetically engineered, make

[312] Sawa, "Genetic Animal Models for Schizophrenia: Advantages and Limitations of Genetic Manipulation in Drosophila, Zebrafish, Rodents, and Primates."; van Alphen and van Swinderen.
[313] Sawa, "Genetic Animal Models for Schizophrenia: Advantages and Limitations of Genetic Manipulation in Drosophila, Zebrafish, Rodents, and Primates."
[314] Waters.
[315] Green.
[316] van Alphen and van Swinderen.

them the ideal organism for exploring the molecular actions of mechanisms. Drosophila carry the mechanisms of interest, allowing researchers to explore their effects *in vivo*.

Scientists can explore mechanisms that are candidates for disease, in rodent and other models and their actions observed. With more complex creatures that have a higher-fidelity to humans, the action of the mechanism will presumably give rise to changes that cannot be observed in fruit flies, such as complex behavioural changes. By investigating the idealised target – mechanisms – in many different models, the knowledge created expands to encompass the complexity of interactions between mechanism and whole organisms. By using a rodent model to explore a possible explanation of schizophrenia uncovered in a fruit fly, the knowledge of the mechanism expands to include its effects in rodents.

This expansion and layering of knowledge about an idealised mechanism creates robust knowledge and gives confidence to researchers wishing to apply their discoveries to the development of treatment options. Drug testing must take place in many organisms and go through many stages before it can be tested in human populations, precisely to overcome the risk of extrapolating from model organism to human without testing for possible variance between species.[317] Knowledge is shaped in multiple laboratories using multiple tools, organisms, and techniques. There are checks and balances in place to test, retest, and verify results.

This argument also fits with Green's approach to the problem of iterative knowledge construction posed by Rheinberger.[318] In her discussion, she claims that the interdisciplinary and many model approach in biological systems is overcome through the resonance of knowledge through models, and across fields. Knowledge that only holds for one organism, system or field will lose out in favour of explanations that remain robust in many contexts. This partially overcomes the problem of isolation and embedded knowledge that might arise in a field of study.

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[317] Charles D Nichols, "Drosophila Melanogaster Neurobiology, Neuropharmacology, and How the Fly Can Inform Central Nervous System Drug Discovery," *Pharmacology & therapeutics* 112, no. 3 (2006).
[318] Green.

5 Chapter Four: Conclusion

Drosophila represent humans in two ways in science, as a model for a class of organisms, and as a vehicle for investigating the mechanistic causes of disease.[319] I have argued that we should understand the role of the Drosophila, in this second category of use, as a vehicle for investigating the mechanisms behind disease not as models of disease. Drosophila are used in neuroscientific investigation of disease to study the molecular actions of mechanisms.[320] We should prefer mechanistic explanations as they are able to make predictions about how changes to components of the mechanism will affect their actions.[321]

Tales of success like the Parkinson's disease case, drive the development of models of increasingly complex mental health disorders such as autism and schizophrenia.[322] By examining the limitations of modelling a debilitating and complicated mental health disorder, schizophrenia, I have claimed that Drosophila cannot be a model of schizophrenia, it can only be used to investigate the mechanism thought to cause it. It is possible to investigate the mechanisms, but it is not possible to have a Drosophila model that has recognisable and classifiable symptoms of schizophrenia. The lack of a biomarker, such as Lewy bodies, or clear symptoms such as movement disorder, problematizes the search for mechanisms for schizophrenia in Drosophila compared to Parkinson's disease.

5.1 Drosophila as a vessel for *in vivo* experimentation

To understand how Drosophila is used to model neurological disease, it is necessary to draw on some of the claims made in the previous chapters. There I argued that model organisms can model diseases thanks to a shared genetic phylogeny and the conservation of features. This does not lead to the conclusion that we should think of the fruit flies as idealised humans. Their role is to be a vessel for the idealised components that researchers are

[319] Levy and Currie; Germain.

[320] Weber, *Philosophy of Experimental Biology*; Kaplan and Craver; Bickle.

[321] Craver.

[322] Furukubo-Tokunaga, "Modeling Schizophrenia in Flies."; Narayanan and Rothenfluh; Sawa, "Genetic Animal Models for Schizophrenia: Advantages and Limitations of Genetic Manipulation in Drosophila, Zebrafish, Rodents, and Primates."; Tataroglu and Emery; van Alphen and van Swinderen; West et al; Zordan and Sandrelli.

studying. This statement holds whether we are looking at the original research undertaken by Morgan or many of the modern day uses.

Model organisms are vehicles for features correlated with behaviours or symptoms. Genetic research focusses on engineering the model to carry certain genetic features thought to play a part in the development of certain phenotypes. When these features are tested in an *in vivo* experiment, the model organism is the vessel for testing theories about the part and its relationship to the whole organism, and phenotypes or phenomena of interest. This requires idealising the parts and isolating the mechanism to test theories about their role in producing a phenomenon. The use of these parts requires an understanding of the homology between the target, (humans), and the model organism.

When using a model organism the relevant parts thought to be causally related to the phenomena of interest are demarcated. In the case of Parkinson's disease, the discovery of Lewy bodies was the first step towards understanding the biomarkers and physical causes of the symptoms of dementia.[323] In later years, as our understanding of the brain progressed, more sophisticated explanations were advanced. Palsy, memory problems, symptoms of the disease, have been correlated to neurotransmitters and neurons that were known to play a part in movement.[324] Disordered movement is one of the main symptoms of Parkinson's disease.[325]

This reduction of the phenomena, dementia, to a particular process in the brain, is the basis of explorations of disease using model organisms. The nature of the disease is explored by attempting to understand, and hopefully treat, the causes of symptoms. By reducing the disease to a mechanistic model, we can find ways to prevent or treat it.

5.1.1 Drosophila as a tool

Should we consider Drosophila a tool, an instrument of science? This argument was put forward by Kohler to capture the extraordinary role that Drosophila has played in biological

[323] Botella et al.
[324] Lees, Hardy, and Revesz.
[325] Ibid.

sciences and the physical manipulation it has undergone. Kohler is a sociologist of science, and I will briefly consider this from a philosophical perspective.

Weber claims:

> *"The instrument- or tool-like character of experimental organisms also arises because scientists spend a lot of work modifying, developing, and standardizing them. Laboratory flies are highly inbred creatures, some of which were deliberately bred to contain certain combinations of genes. In molecular biology, scientists even introduce deliberate changes in specific genes, or they introduce genes from a different, sometimes unrelated organism. Most of the experimental work would be impossible without these modifications of the experimental organisms. However, these modifications do not make these organisms instruments or tools. They are simply interventions in a natural object, which are the hallmark of experimentation."*[326]

Weber claims we cannot think of the Drosophila as a tool just because it has been modified and standardized. The incredible manipulation of the Drosophila by researchers is not enough to classify them as a tool or instrument no matter how sophisticated. Central to his argument is the claim that modification of natural objects is the "hallmark of experimentation." Experiments involve intervening in an object from nature to test a hypothesis or observe the changes that may arise through alteration. Much of the work in biology and its sub-disciplines would not be possible without experimental and model organisms. I argue that by becoming the medium for understanding the mechanisms by disease, the Drosophila is a piece of equipment, a tool for observing the molecular actions of mechanisms, *in vivo*.

In the experiments described by Weber it does seem that the whole organism is the object of interest, but as our methods and knowledge has advanced, we can now investigate parts of the organism. Our interest is no longer with the whole organism, but with idealised mechanisms or modifications that allow us to observe the actions of these *in vivo*.[327] I argue that experiments using Drosophila are neuroscientific experiments, which are not concerned with the whole organism, but with the action of the modification to a component or feature of the organism. The outcome of the experiment is not the whole organism, but

[326] Weber, *Philosophy of Experimental Biology*, 170.

[327] Germain.

the changes to specific components of the organism causally linked to the modification or introduction of a mechanism. Researchers are not simply observing the whole organism; instead they are interested in the changes specific to the highly-sophisticated modifications made to particular groups of Drosophila. The function of wild types is to provide an idealised, controlled, and stable organism against which specific changes can be measured. The changes of interest relate to the mechanism under investigation and its action within the organism.

In many experiments into the effects of different psychedelic drugs on Drosophila the insects were administered the drug, subjected to behavioural assays, and then dissected so that changes to dopamine and other neurotransmitters could be observed.[328] The organism as a whole was not the object of interest, rather the effects of stimulants on specific parts of the organisms, such as attention, memory, and dopaminergic systems, were.[329] Researchers were not interested in other effects of the drugs that are not analogous to humans. If the drugs had caused physical changes with no analogue in human users, the changes would not be of interest.

Returning to the example of Parkinson's disease, where the object of interest, genetic mutations linked to the development of the disease, were introduced to a strand of flies.[330] These flies were genetically altered to carry the same mutations as human sufferers. The action of these genes within the organism was then studied. This involved dissection at various stages and many hours of rigorous checking, testing and observing.[331] The control for this experiment was a strain of wild type flies. This shows that in their observation and experimentation, scientists were not interested in the whole organisms. Rather their focus was on specific neuroanatomical, and neurochemical features that are the result of the action of the mechanism of interest. Molecular changes can be measured against the control to confirm the actions of the mechanism of interest.

[328] Rothenfluh and Heberlein. Yamamoto and Seto.
[329] Nichols et al.
[330] Botella et al.
[331] Vanhauwaert and Verstreken.

The homology of the two organisms, fruit fly and human, and the ability of researchers to both identify and isolate the mechanisms correlated with disease and engineer Drosophila to examine the action of that mechanism creates robust mechanistic explanations. These explanations succeed in part because of the clear symptoms of Parkinson's disease, symptoms visible in fruit files and humans.

5.1.2 Drosophila are a tool for understanding mechanisms

The Drosophila is a stable, controlled organism used in neuroscience to investigate the actions of mechanisms of interest. Thanks, in part, to a long role in science as a model for different biological phenomenon, Drosophila are a sophisticated tool that can be manipulated and engineered to investigate mechanisms.[332] Drosophila are genetically engineered into strains that carry mechanisms thought to give rise to disease. The fruit flies are not the objects under investigation, they are tools that allow us to see the interactions of the mechanism within an organism. This allows scientists to better understand a phenomenon and extrapolate this knowledge to other creatures.

The search for mechanistic causes of disease involves the isolation of mechanisms based on symptoms. Strains of Drosophila are created; engineered to carry a new homology; the mechanism of interest. The actions of the mechanism can then be investigated *in vivo,* giving insight into the molecular action of the mechanism in an organism. Scientists then introduce the mechanism into other model organisms to study the molecular action of the mechanism in a new medium.

Drosophila are the ideal organism to begin investigations of the mechanisms behind disease as they have a robust material practise, refined and advanced through over one hundred years of use in laboratories.[333] Their quick life-cycle, fecundity, cheap and easy housing make them an efficient place to test theories about mechanisms.[334] Over one hundred years in the laboratory have shaped the Drosophila into a sophisticated piece of scientific

[332] Germain.
[333] Leonelli and Ankeny, "What Makes a Model Organism?."
[334] Kohler.

equipment, perfect for the efficient and fast testing of candidate mechanisms in an organism.

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