Review

# Modeling neurodegenerative and neurodevelopmental disorders in the *Drosophila* mushroom body

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**The common fruit fly *Drosophila melanogaster* provides a powerful platform to investigate the genetic, molecular, cellular, and neural circuit mechanisms of behavior. Research in this model system has shed light on multiple aspects of brain physiology and behavior, from fundamental neuronal function to complex behaviors. A major anatomical region that modulates complex behaviors is the mushroom body (MB). The MB integrates multimodal sensory information and is involved in behaviors ranging from sensory processing/responses to learning and memory. Many genes that underlie brain disorders are conserved, from flies to humans, and studies in *Drosophila* have contributed significantly to our understanding of the mechanisms of brain disorders. Genetic mutations that mimic human diseases—such as Fragile X syndrome, neurofibromatosis type I, Parkinson's disease, and Alzheimer's disease—affect MB structure and function, altering behavior. Studies dissecting the effects of disease-causing mutations in the MB have identified key pathological mechanisms, and the development of a complete connectome promises to add a comprehensive anatomical framework for disease modeling. Here, we review *Drosophila* models of human neurodevelopmental and neurodegenerative disorders via the effects of their underlying mutations on MB structure, function, and the resulting behavioral alterations.**

Brain disorders affect a large percentage of the human population —current estimates suggest that ~15% of people suffer from neurological disorders (Feigin et al. 2020) and 49.5% are affected by at least one class of mental health disorder (Merikangas et al. 2010). Two major classes of brain disorders are neurodevelopmental disorders and neurodegenerative disorders. Neurodevelopmental disorders alter biological processes during development, often impacting cognitive function and behavior. Such disorders affect 1%–3% of the world population (Kochinke et al. 2016). In addition, neurodegenerative disorders, characterized by progressive loss of neurons, affect 12%–14% of the population (Feigin et al. 2020). In some cases, genetic mutations are the root cause of the disorder. Such mutations exert complex effects on cellular signaling pathways, circuit function, and systemic physiology. Given this complexity, powerful genetic models such as *Drosophila* facilitate mechanistic dissection of disease pathophysiology. There is significant conservation of genes and cellular functions between flies and humans (Adams et al. 2000; Mohr and Perrimon 2019); ~75% of known human disease-causing genes have orthologs in *Drosophila* (Rubin et al. 2000). To facilitate investigation of these conserved genes and signaling pathways, databases of human diseases have been generated for *Drosophila* (Millburn et al. 2016). Genetic screens and high-throughput phenotypic analyses in *Drosophila* have advanced the understanding of human diseases that result from a variety of genetic mutations.

The *Drosophila* mushroom body (MB) provides a robust anatomical platform to dissect the mechanisms underlying sensory integration/processing, complex behaviors such as learning and memory, and the effects of human disease-causing mutations on these processes. The MB consists of approximately 2000 intrinsic neurons in each hemisphere, which are called Kenyon cells (KCs). KC somata and dendrites are in the posterior brain and project fasciculated axon bundles anteriorly. As these axon bundles approach the front of the brain, they diverge, sending collaterals dorsally and medially into five lobes: the α, α′, β, β′, and γ lobes (Fig. 1A,B; Crittenden et al. 1998; Aso et al. 2014a). Along the longitudinal length of each lobe, there are multiple anatomically and functionally distinct compartments (Fig. 1B; Tanaka et al. 2008; Mao and Davis 2009). Each compartment receives input from discrete sets of modulatory afferent neurons (such as dopaminergic neurons) and sends their cholinergic output to discrete downstream output neurons (MBONs) that have different behavioral roles (Aso et al. 2014b; Barnstedt et al. 2016). This allows sensory information to drive different behavioral responses in a context-dependent manner (Aso et al. 2014b). Multimodal sensory signals are processed in the MB including visual, olfactory, gustatory, tactile, and auditory stimuli (Wolf et al. 1998; Liu et al. 1999; Popov et al. 2003; Kirkhart and Scott 2015; Vogt et al. 2016). Information is processed and modified by experience to alter learned behaviors via plasticity in the MB (Yu et al. 2005, 2006; Séjourné et al. 2011; Perisse et al. 2013; Tomchik and Davis 2013; Boto et al. 2014, 2019; Cohn et al. 2015; Hige et al. 2015; Yamagata et al. 2015; Berry et al. 2018; Louis et al. 2018; Handler et al. 2019; Phan et al. 2019; Zhang et al. 2019; Bilz et al. 2020; Baltruschat et al. 2021; Stahl et al. 2022). Along with associative learning, the MB modulates state-dependent behaviors such as sleep and hunger (Pitman et al. 2006; Sitaraman et al. 2015; Tsao et al. 2018).

In this review, we will highlight major findings in two broad categories of neurological diseases that are modeled in the *Drosophila* MB: neurodegenerative and neurodevelopmental disorders. Multiple genetic mutations that drive brain disorders in

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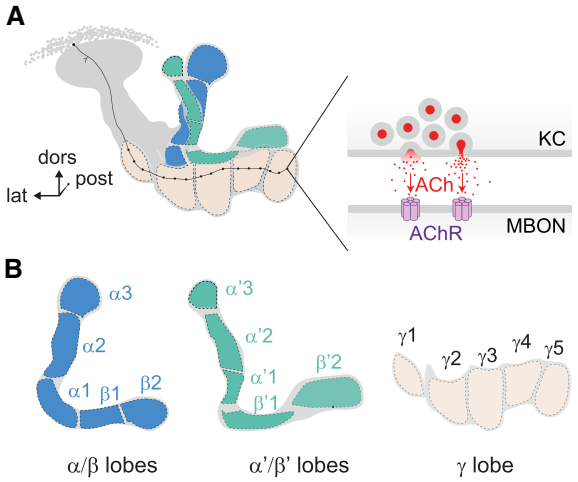


**Figure 1.** Diagram of mushroom body (MB) anatomy. (*A*) Frontal view of the MB lobes and their compartments. A single KC innervating the γ lobe is shown in black. The KC axon travels through multiple compartments, making *en passant* synapses with monoaminergic (e.g., dopaminergic) neurons (not shown) and downstream mushroom body output neurons (MBONs). (*Inset*) Expanded synaptic-scale view showing the presynaptic release of acetylcholine (ACh) onto a downstream MBON, activating ACh receptors (AChRs). (dors) Dorsal, (post) posterior, (lat) lateral. (*B*) Separate views of the α, β, α′, β′, and γ lobes. Each KC innervates either the α/β lobe, the α′/β′ lobe, or the γ lobe, passing through multiple synaptic compartments. Each numbered compartment is labeled.

humans affect MB structure and function. The thoroughly characterized anatomy of the MB, along with its role in mediating complex behaviors, makes it an outstanding platform to dissect the mechanisms of these disorders. Complete coverage of the literature in this area would be too vast for a single review, and readers are directed to additional reviews for more information (Jaiswal et al. 2012; Şentürk and Bellen 2018; Mariano et al. 2020). *Drosophila* have been used in genetic research for more than 100 y, and a vast genetic toolkit has been developed over this time. For further information, readers are directed to technical reviews describing the Gal4/UAS system (and numerous derivatives/alternatives) (Luan et al. 2020), the types of genetic screens used (Yoon 2023), and current catalogs of RNAi and CRISPR mutations (Adams et al. 2000; Port et al. 2020; Hu et al. 2021; Zirin et al. 2022). The first sections of this review focus on major findings from studies on neurodegenerative disorders, defined by a progressive loss of susceptible neuronal populations (Dugger and Dickson 2017). In the neurodegenerative realm, we will focus on modeling Alzheimer's disease (AD) and Parkinson's disease (PD). Next, we will cover neurodevelopmental disorders, which are defined by their onset during a developmental period (Morris-Rosendahl and Crocq 2020). In this realm, we will highlight research into Fragile X syndrome (FXS) and neurofibromatosis type 1 (NF1). Finally, we briefly discuss several other disorders modeled in *Drosophila*. Throughout the review, we emphasize research that involves the MB.

## Alzheimer's disease

AD is a neurodegenerative disease that typically appears late in adulthood. The disease results in neurodegeneration, with severe cases causing cortical shrinkage and ventricle enlargement (Fig. 2A,B). The first clue into the molecular nature of AD came from the discovery that the amyloid beta (Aβ) peptide accumulates in the brains of AD patients (Yoshikai et al. 1990). Aβ is generated via cleavage of the amyloid precursor protein (APP) (*Drosophila* express an APP-like protein, APPL). Under nonpathological conditions, this cleavage is catalyzed by α-secretase; however, under disease-state conditions, γ-secretase/β-site APP cleaving enzyme-1 (BACE1) produces a less soluble, neurotoxic Aβ peptide: Aβ42 peptide (De Strooper and Annaert 2000; O'Brien and Wong 2011; Liu et al. 2019). Pathophysiology of AD may involve altered neuronal excitability; accumulation of Aβ42 increases the excitability of neuronal circuits associated with neuronal degeneration (Ping et al. 2015; Tabuchi et al. 2015; Kaldun et al. 2021). Loss of synaptic inhibition leads to the neuronal excitation of cells localized near plaque formations (Busche et al. 2008). This potential pathophysiological mechanism has been modeled extensively in the MB; excess Aβ42 in the MB impairs courtship memory (Feng et al. 2018a), aversive short-/middle-term memory (Martin-Peña et al. 2017; Kaldun et al. 2021), forgetting (Kaldun et al. 2021), and middle-term appetitive memory (Kaldun et al. 2021). Mouse models have shown both increases in neuronal activity in some brain regions (e.g., the hippocampus) and decreases in activity of others (e.g., the amygdala, which exhibits increased inhibitory transmission) (Busche et al. 2008; Klein et al. 2014; Šišková et al. 2014). Notably, accumulation of Aβ42 in the MB α, β, and γ lobes decreases neuronal activity due to age-dependent loss of the A-type $K^+$ channel $K_v4$ (Aso et al. 2009; Feng et al. 2018a). Behavioral alterations, such as impaired courtship memory, could result from a decrease in the odor-evoked activity of the MB (Feng et al. 2018a), where Aβ42 has aggregated (Higham et al. 2019). The loss of $K_v4$ activity also affects circuits outside of the MB, including those mediating circadian rhythms and flight maintenance (Ryglewski and Duch 2009; Feng et al. 2018b; Smith et al. 2019).

Aggregation of Aβ42 is highly dependent on the specific mutation(s) in the precursor peptide. Sequencing of patient-derived mutations has pinpointed mutations responsible for early onset

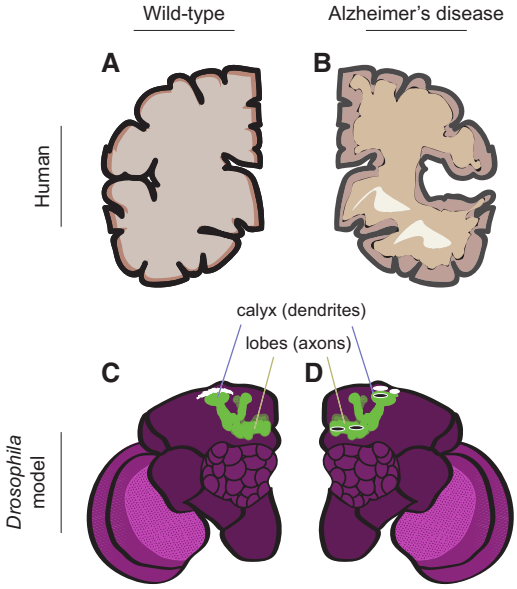


**Figure 2.** Alzheimer's disease (AD) pathology in humans and in the *Drosophila* AD model. (*A*) Diagram of a transverse section of healthy human brain. (*B*) AD pathology in the human brain (contralateral view relative to *A*), showing atrophied cerebral cortex and enlarged ventricles (white patches). (*C*) Diagram of a wild-type *Drosophila* brain, showing the MBs in green. (*D*) Pathology in the *Drosophila* R406W AD model (contralateral view relative to *C*). White ellipses represent vacuoles in the MB calyx (dendritic) regions, and black ellipses represent tau accumulation of R406W in the MB γ-lobe (axonal) and calyx (dendritic) regions.

AD (EOAD). EOAD is characterized by a severe amalgamation of misfolded amyloid structures identified in individuals before the age of 65 (Nilsberth et al. 2001). One model of EOAD involves expressing mutant Aβ containing the Arctic mutation (Aβ42Arc). This mutation (APP E693G) is one of several that produces an autosomal dominant form of AD. When Aβ42Arc is expressed in the MB, the flies exhibit neuronal cell loss, visible in the dendritic region of the MB (calyx) as well as its axonal lobes (Fig. 2C,D; Iijima et al. 2008). Further, *Drosophila* models of EOAD cause progressive aggregation of Aβ42, and learning and memory deficits appear 7–9 d posteclosion. Other pathologies, such as mitochondrial perturbations, are observed even earlier (Kaldun et al. 2021; Wang and Davis 2021).

A second hallmark of human AD is the presence of neurofibrillary tangles composed of aggregated tau, a microtubule-binding protein. This aggregation occurs due to tau hyperphosphorylation and subsequent dissociation of the protein from microtubules (Hutton and Hardy 1997). Tau is critical for microtubule stability and for proper axonal trafficking (Cowan et al. 2010). Overexpression of wild-type tau in the *Drosophila* MB does not produce a degenerative phenotype (and *Drosophila* do not exhibit neurofibrillary tangles). Nonetheless, tau hyperphosphorylation recapitulates some features of human AD, including neuronal degradation (Wittmann et al. 2001). Modeling a form of EOAD, expression of the R406W mutation in *Drosophila* drives axonal decay and vacuole formation through the accumulation of hyperphosphorylated tau in cholinergic neurons (Fig. 2; Wittmann et al. 2001; Mershin et al. 2004). Comparing the pathology of human AD and the R406W model, *Drosophila* exhibit brain vacuoles but not neurofibrillary tangles, and AD patients exhibit neurofibrillary tangles, but not vacuoles. Despite these differences, a common feature is neurodegeneration, and neurodegeneration in the R406W model is progressive with age (Wittmann et al. 2001; Ali et al. 2012; Passarella and Goedert 2018). Further, there is impairment of learning and memory in *Drosophila*—accumulation of tau in the MB reduces short-term olfactory aversive memory (Mershin et al. 2004). Although overexpression assays identified tau as a target for neurodegenerative alterations, the molecular mechanisms were initially unclear. Genetic modifier screens targeting tauopathies subsequently identified a group of proteins that alter tau phosphorylation (Shulman and Feany 2003). The PAR-1 kinase kicks off a cascade of downstream phosphorylation events following the initial phosphorylation of *Drosophila* tau (Nishimura et al. 2004). Further, the key neurotoxic effects are localized to the phosphorylation sites at $Ser^{238}$ and $Thr^{245}$ (Kosmidis et al. 2010).

A common feature of many neurodegenerative diseases is misfolding and accumulation of proteins (Colla 2019). The unfolded protein response (UPR) is activated to restore proper endoplasmic reticulum (ER) homeostasis by increasing folding capacity (Walter and Ron 2011). This response is primarily due to a loss of $Ca^{2+}$ homeostasis within the cell (Torres et al. 2010). There are three downstream components of the UPR pathway, inositol-requiring enzyme 1 (IRE1), PPKR-like endoplasmic reticulum kinase (PERK), and activating transcription factor (ATF6) (Mou et al. 2020) The UPR stress response of both IRE1 and PERK increase autophagy by increasing expression of autophagy receptors SQSTM1/p62, NBR1, and BNIP3L/NIX levels (Adolph et al. 2013; Deegan et al. 2015). Because of ER stress, PERK increases apoptotic response and translational arrest by activating eLF2α (Lin et al. 2007; Urra et al. 2013).

As understanding of AD pathology has increased, the range of potential therapeutic targets has expanded. Genetic screens in *Drosophila* have uncovered a range of mechanisms underlying AD dysfunction, involving oxidative stress, JNK signaling, and apolipoprotein D (Bowers et al. 2011; Hopkins 2013; Briston and Hicks 2018). These findings point to oxidative stress as a major contributor to AD pathology. Relatedly, metabolic changes, including changes in glucose metabolism through the TCA cycle, are potential therapeutic targets for AD (Lin and Beal 2006; Mattson et al. 2008; Reddy 2009; Wang et al. 2009). In *Drosophila*, expression of human tau drives mitochondrial elongation (along with mitochondrial dysfunction and cell death), implicating altered mitochondrial fusion/fission dynamics (DuBoff et al. 2012). Further, aggregation of Aβ42 alters the localization of mitochondria, increasing soma localization and decreasing mitochondrial localization to dendritic and axonal regions. This process involves a cAMP/PKA-dependent mechanism (Iijima-Ando et al. 2009). Translocation of mitochondria away from the axons and dendrites depletes local ATP sources that are used to generate cAMP, limits the mobilization of synaptic vesicles to the cleft for neurotransmission, and reduces synaptic strength (Verstreken et al. 2005). This neuropathological response is already present on the first day after eclosion, when mitochondria exhibit an increased number and altered morphology (Wang and Davis 2021).

An array of potential therapeutic treatments to rescue physiological, morphological, and behavioral responses have been explored using the MB as a test bed. Initial studies focused on the inhibition of the cleavage pathway for Aβ42 through the utilization of γ-secretase inhibitors (Chakraborty et al. 2011). Recent studies have focused on decreasing neuronal excitability induced by AD. Aβ42Arc expression induces sleep fragmentation, implicating sleep disruption and alteration of excitability in sleep-regulating circuits as a potential AD mechanism (Tabuchi et al. 2015; Gerstner et al. 2017). To ameliorate the alteration in neuronal excitability, gaboxadol and levetiracetam have been tested. Application of these drugs in flies expressing Aβ42Arc rescues memory deficits through reduction of circuitry excitability (Kaldun et al. 2021). Most recently, clinical trials have been initiated within individuals that suffer from Down syndrome, a population with the greatest risk of EOAD. The triplicate copy of Chromosome 21 may increase AD risk due to an extra copy of the DYRK1A kinase, which hyperphosphorylates tau (Ryoo et al. 2007). Administration of a DYRK1A inhibitor decreases the amount of phosphorylated tau, while rescuing both sleep and memory deficits in *Drosophila* (Zhu et al. 2022). Although a number of pathological mechanisms have been identified in AD, the genetic architecture underlying the disease is complex (Andrews et al. 2023). Future research will likely include more genetic sequencing of patients, as well as mechanistic studies and screens in animal models.

## Parkinson's disease

PD is the most common movement disorder, characterized by the progressive loss of dopaminergic neurons in the nigrostriatal pathway (Fig. 3A,B) and concomitant motor dysfunction (Schrag et al. 2015). Locomotor deficits in PD include resting tremors, impaired movement initiation, and general instability (Whitworth 2011). The disease often drives accumulation of α-synuclein (α-syn) into globular structures referred to as Lewy bodies (Spillantini et al. 1997). Some cases of PD result from mutations in a single gene, though most result from a complex interaction of genetic and environmental factors (Selvaraj and Piramanayagam 2019). PD is modeled in *Drosophila* by depleting dopaminergic neurons via several approaches: inhibition of the mitochondrial respiratory transport chain (using the drug rotenone) (Betarbet et al. 2000), inducing oxidative stress (using paraquat) (Przedborski and Ischiropoulos 2005), or transgenically expressing α-syn (Feany and Bender 2000). Although *Drosophila* do not express an endogenous *α-syn* gene, transgenic expression of human *α-syn* recapitulates the central features of the disorder (progressive loss of dopaminergic neurons and locomotor dysfunction) (Feany and Bender 2000).

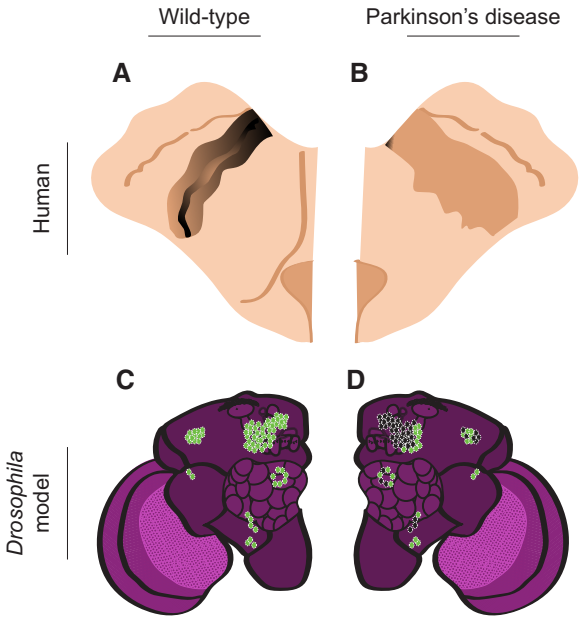


**Figure 3.** Parkinson's disease (PD) pathology in humans and in the *Drosophila* PD model. (*A*) Diagram of the human midbrain in transverse section, with the substantia nigra in black. (*B*) PD diminishes the substantia nigra (light brown) (contralateral view relative to *A*). (C) Diagram of dopaminergic neurons in wild-type *Drosophila*. Green circles represent dopaminergic neurons. (*D*) In the Pink1 *Drosophila* model of PD, dopaminergic neurons are lost in the PPL1, PPL2, and PPM1,2,3 clusters (contralateral view relative to C). Healthy neurons are shown in green and black circles represent neurons lost in the PD model.

Several subsets of dopaminergic neurons exhibit degeneration or morphological alterations in *Drosophila* PD models, including PPL1, PPL2, PAM, PPM1/2, PPM3, and PAL dopaminergic neurons (Fig. 3C,D). Among these, the PPL1, PPL2, and PAM neurons innervate the MB, modulating locomotion and learning (Claridge-Chang et al. 2009; Liu et al. 2012; Aso et al. 2014a; Galili et al. 2014; Cassari et al. 2015; Boto et al. 2019). To examine motor aberrations induced by α-syn aggregation and identify key dopaminergic clusters, a range of behavioral assays have been used, including startle-induced negative geotaxis (Riemensperger et al. 2013). This approach identified 15 protocerebral anterior medial (PAM) neurons, which directly innervate the β′ lobe, as crucial for locomotor alterations (Riemensperger et al. 2013). Pathophysiological changes to this circuitry involve neuronal hyperexcitability that progresses in an age-dependent manner; this diminishes connectivity between PAM neurons and KCs (Riemensperger et al. 2013). Correspondingly, α-syn aggregation causes the loss of neurons in the PPL1 and PPM1/2 clusters (Narwal et al. 2024).

The most common form of heritable PD results from mutations in the leucine-rich repeat kinase (LRRK2) (Paisán-Ruíz et al. 2004; Zimprich et al. 2004; Rajput et al. 2006; Ross et al. 2006). A hallmark of this form of PD is sleep deficiency (Berg et al. 2005). Expression of human *LRRK2 (hLLRK2)* in the MBs leads to a fragmentation in sleep that can be attenuated by melatonin (Sun et al. 2016). Furthermore, melatonin can also rescue long-term memory deficits induced by *hLRRk2* expression (Ran et al. 2018). The pathological changes that produce PD-like behavioral outcomes likely involve changes in multiple signaling cascades including AKT, PTEN, and JNK (Mehdi et al. 2016). Expression of *hLLRK2* leads to the degeneration of dopaminergic neurons localized to the PPL1 and PPM1/2 clusters (Islam et al. 2016).

The second most common form of inherited PD is due to a mutation in the PTEN-induced putative kinase (PINK1) (Kasten et al. 2018). In mammals, the hallmark of PD caused by PINK1 mutations is increased energetic demand within the dopaminergic neurons of the substantial nigra (Bolam and Pissadaki 2012). The increased energetic demand suggests that PINK1 mutations affect mitochondrial function (Pilsl and Winklhofer 2012). Neurons are lost in the PPL1, PPL2, PPM 1/2, and PPM3 clusters (Pirooznia et al. 2020; Zárate et al. 2022). In *Drosophila*, PINK1 binds directly to the mitochondrial protein PGAM5 to activate mitochondrial degradation followed by cell loss (Imai et al. 2010). PINK1 mutations can be exacerbated with the loss of PGAM5 (Ishida et al. 2012). PGAM5 increases mitochondrial turnover and fission events (Yu et al. 2020). Although there are additional *Drosophila* models of PD, we focus here on those that affect the MB. Mutations in *hLRRK2*, *PINK1*, *α-syn*, and *Parkin* also result in the loss of dopaminergic neurons that do not innervate the MB (MacLeod et al. 2013; Fellgett et al. 2021; Narwal et al. 2024). Examples of affected areas include dopaminergic neurons innervating the central complex (Dumitrescu et al. 2023) and subesophageal ganglion (Cording et al. 2017).

Emerging research has begun to unravel the roles of apoptosis and the UPR (Martinez et al. 2019). Accumulation of α-syn within the ER creates a stress-like response, activating the UPR (Walter and Ron 2011). In *Drosophila*, the response to the accumulation of α-syn involves hyperactivation of the IRE1 (Yan et al. 2019). Alternatively, the ATF6 pathway, which plays a role in the liberation of proteases, is inhibited through α-syn accumulation, causing dopaminergic neuronal death (Egawa et al. 2011). Unlike ATF6, the attenuation of PERK, which has been shown to cause apoptosis, can rescue the loss of PPL1 neurons in the Pink1 background (Popovic et al. 2023).

The primary treatment for PD, the administration of levodopa (L-DOPA)—a precursor to dopamine—has been used since the early 1970s (Tolosa et al. 1998). However, long-term exposure to high doses of L-DOPA can lead to a drug-induced dyskinesia (Parkinson Study Group 2000). Importantly, the effect of PD on monoaminergic pathways involves more than the loss of dopaminergic neurons. In *Drosophila*, L-DOPA decreases the innervation of the α/α′ lobes by serotonergic dorsal paired medial (DPM) neurons (Niens et al. 2017). Furthermore, the loss of PPL2 neurons that innervate the MB dendrites (among other brain regions) can be rescued by increasing serotonergic activity (Zárate et al. 2022). Overall, research in *Drosophila* has shed light on the molecular mechanisms that potentially drive the pathophysiology of PD (Shukla et al. 2014; Maitra et al. 2019; Ma et al. 2022; Zhang et al. 2023). Examining these molecular mechanisms within the well-defined anatomical context of the MB and its associated dopaminergic circuitry provides a platform to test novel therapeutic strategies for PD. Moving forward, these will likely include targeting α-syn receptors, autophagy-mediated pathways, and/or niacin targets (Rai et al. 2021).

## Fragile X syndrome

FXS is a monogenetic inherited disorder (affecting ∼1 in 6000 births) caused by an expansion in the CGG trinucleotide repeat in the 5′-untranslated region of the *FMR1* gene. Up to 55 repeats are present in normal individuals, and this expands to more than 200 in severely affected individuals (Willemsen et al. 2011). The number of CGG repeats affects *FMR1* transcription, with longer repeats decreasing the amount of FMR protein (FMRP) (Schwemmle et al. 1997). FMRP is a major regulator of mRNA, modulating mRNA transport, stabilization, and translation (Bagni and Greenough 2005; Bassell and Warren 2008). FXS causes a range

of symptoms, including developmental delays, learning disabilities, social and behavioral problems, impaired executive function, attention-deficit/hyperactivity disorder, sleep disturbances, intellectual disability, and anxiety (Crowe and Hay 1990; Fisch et al. 2002; Loesch et al. 2004; Scharf et al. 2015). Morphological alterations in the brain include aberrant dendritic spine morphology (Fig. 4A,B; Irwin et al. 2000).

The *Drosophila FMR1* gene (*dFMR1*) has high sequence homology with the human variant, including a conserved pair of KH domains (Wan et al. 2000). Loss-of-function mutations in *dFMR1* alter circadian rhythms, courtship behaviors, and synaptic branching (Dockendorff et al. 2002). These mutations also alter MB morphology. In *dFMR1* mutants, the KC axons that form the MB β-lobe aberrantly cross the midline of the brain (Fig. 4C,D), merging with the β lobe in the contralateral hemisphere (Michel et al. 2004). The dendritic branching pattern of the KCs is also altered by the addition of higher-order branches and supernumerary dendritic process formation (Pan et al. 2004). Long-term memory is dependent on *dFMR1* expression (Dockendorff et al. 2002; McBride et al. 2005; Kanellopoulos et al. 2012). These morphological aberrations likely contribute to the deficits in learning. *dFMR1* mutants also exhibit increases in synaptic boutons along the axons with increases in synaptic vesicle area. These phenotypes are likely due to either hyperactivity or inhibition of exocytotic events (Pan et al. 2004). Interestingly, *dFMR1* heterozygotes have normal MBs but still show impaired long-term memory (Kanellopoulos et al. 2012).

Some FXS phenotypes may result from alterations in cAMP/PKA signaling. Human blood cell samples from FXS patients provided an early indication that FMRP could regulate the cAMP/PKA pathway (Berry-Kravis and Huttenlocher 1992). cAMP/PKA signaling plays a role in both memory acquisition and consolidation (Zars et al. 2000; Blum et al. 2009), and FMRP decreases cAMP generation following stimulation of adenylyl cyclases (Kelley et al. 2007). To examine the role of cAMP/PKA in a developmental/anatomical context, several studies investigated the role of FMRP in PKA regulation in the MB. PKA dynamically regulates the actin cytoskeleton to ensure proper neuronal growth (Lin et al. 2005; Cingolani and Goda 2008; Zhu et al. 2015). Localization of PKA is an important factor in its developmental effects; A-kinase anchor proteins (AKAPs) localize and regulate PKA activity (Smith et al. 2017; Wild and Dell'Acqua 2018). The *Drosophila* AKAP homolog, *Rugose*, interacts with PKA in the MB γ lobe and modulates short-term memory (Zhao et al. 2013). In FXS models, loss of FMRP down-regulates the expression of *Rugose*. This decreases PKA activity and alters F-actin assembly in the MB γ lobe (Sears et al. 2019). Patient-derived mutations have revealed other previously undefined roles of the arginine–glycine–glycine (RGG) domain of FMRP. For instance, a negative self-regulatory feedback loop suppresses FMRP levels due to PKA activation (Sears and Broadie 2020).

The role of FMRP in the maturation and pruning of dendrites was first identified in a mouse model, where the loss of FMRP led to increases in spine lengths and decreases in pruning identified in pyramidal neurons (Comery et al. 1997). Similarly, in dendritic arborization (multidendritic) neurons of *Drosophila* larvae, loss of FMR1 increases higher-order dendritic arborizations (Lee et al. 2003). One factor associated with increases in spine density is the activation of metabotropic glutamate receptors (mGluRs), which leads to the increase of FMRP in postsynaptic dendrites. Loss of FMRP generates an excessive number of long and thin dendrites (Fig. 4; Weiler and Greenough 1999). Similar to the mouse model, the MB possesses mGluRs localized to the dendrites within the calyces (Devaud et al. 2008). *dFMR1* mutants exhibit increased mGluR expression, which leads to learning deficits that can be rescued through knockdown or pharmacological inhibition of mGluR (Kanellopoulos et al. 2012). Interestingly, increasing cAMP levels by inhibiting the phosphodiesterase also rescues mGluR-mediated learning deficits (Kanellopoulos et al. 2012; Choi et al. 2016).

Although therapeutic targeting of mGluR5 has shown promising results in rodents, clinical trials in humans have yet to produce an FDA-approved therapy. This is likely a consequence of the multitude of FXS symptoms (Scharf et al. 2015). Currently, symptoms are individually targeted, increasing the risk of side effects. Because the syndrome is monogenetic, much current research on potential therapeutics focuses on methods to increase endogenous FMR1 expression.

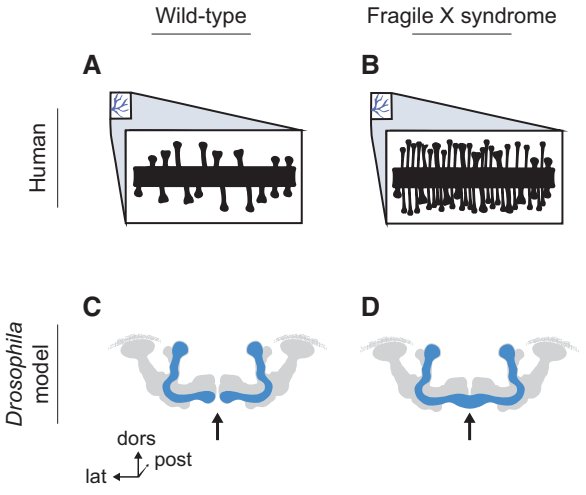


**Figure 4.** Fragile X syndrome (FXS) pathology in humans and in the *Drosophila* FXS model. (*A*) Diagram of dendritic spines in healthy humans. (*B*) Effects of FXS on dendritic spine morphology in humans. (*C*) Diagram of wild-type *Drosophila* MBs, showing the α/β lobes (in blue). The midline of the brain is marked with an arrow—note that the β lobes do not cross the midline. (dors) Dorsal, (post) posterior, (lat) lateral. (*D*) Pathology in the *Drosophila* FXS model. The β lobes overgrow, crossing the midline and infiltrating the contralateral lobe (arrow).

## Neurofibromatosis type 1

NF1 results from loss-of-function mutations in the *NF1* gene in humans, which encodes a protein called neurofibromin (Nf1). This disorder affects ∼1 in 3500 individuals (Evans et al. 2010; Hirbe and Gutmann 2014; Uusitalo et al. 2015). Although it is monogenetic in origin, genetic modifiers influence NF1 symptoms (Easton et al. 1993). Symptoms include the formation of tumors/cancers as well as an increased incidence of brain disorders. These include attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), learning disabilities, sleep disturbances, and others (North et al. 1994, 1995; Ferner et al. 1996; Wang et al. 2021). The Nf1 protein contains a central Ras-GTPase-activating protein-related domain (GRD), which negatively regulates Ras activity (Martin et al. 1990). In addition to modulating Ras signaling, loss of Nf1 also reduces cAMP/PKA levels and impacts G protein–coupled receptor signal transduction (Guo et al. 1997; Hannan et al. 2006; Ho et al. 2007; Anastasaki and Gutmann 2014; Xie et al. 2016). Importantly, *Drosophila* express an Nf1 ortholog, which shares 60% amino acid homology and conserved Ras GAP functionality with humans (The et al. 1997; Williams et al. 2001; Walker et al. 2006). The *Drosophila* NF1 model mimics a range of morphological and behavioral features of NF1, including increased metabolic rate, reduced body size, altered circadian rhythms, decreased sleep, changes in social behavior, increased grooming, and altered synaptic transmission (The et al. 1997; Williams et al. 2001; Bai and

Sehgal 2015; King et al. 2016, 2020; Bai et al. 2018; Moscato et al. 2020; Botero et al. 2021; Dyson et al. 2022; Brown et al. 2023). Nf1 deficiency alters behaviors through effects on different sets of neurons (Guo et al. 2000; Buchanan and Davis 2010; King et al. 2020; Moscato et al. 2020; Georganta et al. 2021; Dyson et al. 2022), which are detailed further below.

*Drosophila nf1* mutants show impaired learning and memory, particularly in olfactory classical conditioning (a commonly used associative learning paradigm) (Guo et al. 2000; Ho et al. 2007; Buchanan and Davis 2010; Gouzi et al. 2011; Qin et al. 2012; Georganta et al. 2021). This is reminiscent of NF1 in humans, which increases the incidence of learning disabilities (North et al. 1995). Learning and memory deficits in *Drosophila* result from alterations in MB function, with contributions from several cell types. In KCs, Nf1 is required for the acquisition of olfactory associative memory (Buchanan and Davis 2010). Rescue of wild-type Nf1 protein in a subset of MB neurons—the α/β neurons—restores normal memory (Buchanan and Davis 2010). Further, Nf1 interacts with cAMP/PKA signaling in the MB (Buchanan and Davis 2010). In addition to the KCs, Nf1 modulates memory via actions in a set of inhibitory GABAergic neurons that innervate the MB. Loss of Nf1 increases GABAergic circuits innervating the MB, contributing to learning deficits (Georganta et al. 2021). Rescuing Nf1 expression in these circuits restores normal memory (Georganta et al. 2021). This occurs via regulation of Ras in the GABAergic neurons, and signaling upstream of Ras contributes as well. The receptor tyrosine kinase anaplastic lymphoma kinase (Alk) is an upstream regulator of Ras that colocalizes with Nf1 in the nervous system and modulates the Nf1 learning phenotype (Gouzi et al. 2011; Bai and Sehgal 2015; Georganta et al. 2021). Thus, learning and memory are modulated by both cAMP and Ras signaling (Guo et al. 1997; Ho et al. 2007), with cAMP-dependent effects in KCs (Buchanan and Davis 2010) and Ras-dependent effects in the GABAergic neurons that innervate the MB (Georganta et al. 2021). This represents one example in which Nf1 deficiency in one set of cells can act via Ras and potentially affect another set of cells via cAMP/PKA signaling to produce a phenotype (Georganta et al. 2021). A similar interaction of different signaling pathways across cell types regulates the growth phenotype in *Drosophila nf1* mutants (Walker et al. 2006) and optic glioma growth in mice (Pan et al. 2021).

Nf1 regulates circadian rhythms and sleep via its function in the MB. Loss of Nf1 disrupts the normal circadian rhythms of locomotor activity in *Drosophila*, along with reducing sleep (Williams et al. 2001; Bai and Sehgal 2015; Bai et al. 2018). Mutations in Alk also alter sleep because of effects in the MB, where Alk and Nf1 interact (Bai and Sehgal 2015). Circadian rhythms drive oscillations in gene expression in the MB, which are dependent on Nf1 and cAMP/PKA signaling (Almeida et al. 2021). Nf1 also acts downstream from the circadian clock and outside the MB, with the pars intercerebralis being one major site of action (Bai et al. 2018). In addition to its effect on sleep quantity, Nf1 modulates sleep quality (sleep depth) and the interaction of sleep with metabolic state (Brown et al. 2023). Like many other animals, flies exhibit a set of sleep states (Hendricks et al. 2000; Shaw et al. 2000). Loss of Nf1 fragments sleep and prevents flies from entering deep sleep (Brown et al. 2023). Further, it alters the interaction of sleep with metabolic state. When animals sleep, they normally suppress their metabolic rate. Yet flies with Nf1 mutations do not exhibit this suppression of metabolism during sleep (Brown et al. 2023). The sleep–metabolism interaction is not known to map to the MB. Yet reminiscent of the learning deficits, it relies on GABAergic circuitry. Nf1 is required in neurons that express the $GABA_A$ receptor Rdl, suggesting that circuitry immediately postsynaptic to GABAergic circuits regulates sleep–metabolism interactions (Brown et al. 2023).

Related to the learning and sleep phenotypes described above, loss of Nf1 in flies drives ASD-like behavioral changes, such as increased grooming (King et al. 2016, 2020) and altered social behavior (Moscato et al. 2020). Although the focus of this review is on MB effects, it is noteworthy that Nf1 modulates ASD-like phenotypes via actions outside the MB. In addition to those noted above, the grooming phenotype maps to cholinergic, Oct–Tyr receptor-expressing neurons in the ventral nerve cord (King et al. 2020). This effect is Ras-dependent and includes a developmental contribution (King et al. 2020). Additionally, social behavior alterations result from Nf1 function in adult chemosensory cells (ppk23+ neurons) and are also Ras-dependent (Moscato et al. 2020). Thus, the loss of Nf1 alters different behaviors via actions on different circuits. In some cases, the effects are likely additive across multiple neurons/circuits (King et al. 2020).

Therapeutic development to date has focused intensively on the mitogen-activated protein kinase (MAPK) signaling pathway (Ras/MEK/ERK). This pathway is important for some phenotypes in the *Drosophila* NF1 model. Increases in phospho-ERK accompany Nf1-dependent changes in body size, synaptic growth, and learning (Walker and Bernards 2014; Georganta et al. 2021). Metabolic alterations in *nf1* mutants are dependent on Ras and likely involve ERK (Botero et al. 2021). In addition to MEK/ERK, other signaling pathways downstream from Ras are dysregulated in NF1 (Anastasaki et al. 2022). Among these, mTor has been implicated in other animal models of NF1, including modulating memory (in mammals) via effects on presynaptic neurotransmitter release (Asati et al. 2016; Choi et al. 2016). Whether/how this pathway contributes to *Drosophila* phenotypes is currently unknown. Future studies will be needed to understand how signaling pathways such as cAMP/PKA and PI3K/AKT/mTor modulate NF1 phenotypes, as well as how these pathways interact with MAPK signaling (such interactions occur in other model systems/phenotypes) (Anastasaki and Gutmann 2014). Ras signaling alterations also contribute to the circadian rhythm, grooming, and social behavior phenotypes (Williams et al. 2001; King et al. 2020; Moscato et al. 2020).

Molecular dissection of the signaling pathways downstream from Ras and cAMP will likely aid the development of therapeutic strategies. Similar to FXS, current treatments for NF1 are palliative and symptom-specific. Some patients experience multiple symptoms, and no single treatment addresses all of them (Walker and Upadhyaya 2018). A pharmacological inhibitor of MEK, selumetinib, is used to treat pediatric plexiform neurofibromas (effects of this pharmacological intervention have not been tested in *Drosophila*) (Gross et al. 2020). Another strategy involves the use of statins to inhibit Ras. Lovastatin, an HMG-CoA reductase, improves learning and attention in mice (Li et al. 2005). Another HMG-CoA reductase, simvastatin, rescues quantal size deficits at the *Drosophila* neuromuscular junction (Dyson et al. 2023). However, statins have not shown efficacy in clinical trials with children suffering from NF1 (Li et al. 2005; Payne et al. 2016). New approaches to treating NF1 may involve small molecules focusing on the regulation of Ras and/or cAMP signaling pathways (Walker and Upadhyaya 2018), as well as molecules targeting downstream effects on neuronal excitability (Pan et al. 2021; Dyson et al. 2023).

## Other diseases modeled in the MB

Although this review focuses on four commonly studied diseases that alter the MB circuit, other diseases have been modeled as well. For instance, Angelman syndrome is a rare neurodevelopmental disorder that is characterized by delayed development, seizures, and intellectual disabilities. The disease is caused by

mutations in *Ube3a*, which encodes a ubiquitin ligase (Kishino et al. 1997). Although the loss of the *Drosophila* homolog, *dube3a*, does not induce seizures, significant deficits were identified in long-term memory, climbing, and circadian rhythms (Wu et al. 2008). Similar to FXS, the fusing of β lobes is present along with the loss of α lobes in *dube3a* mutants (Chakraborty et al. 2015). Outside of the MB, mutant larvae exhibit morphological characteristics that are shared with mammals, including alterations in dendritic arborizations (Dindot et al. 2008; Lu et al. 2009). These dendritic alterations appear to be cell autonomous, and are dependent on expression level (Lu et al. 2009). In larval dendritic arborization (multidendritic) sensory neurons, Ube3a is responsible for proper pruning (Furusawa et al. 2023). The transport of Ube3a to presynaptic dendritic terminals is dependent on the kinesin motor and functions by maintaining the BMP signaling (Furusawa et al. 2023). For further information on Angelman syndrome, see Maranga et al. (2020).

Another well-defined class of neurodegenerative disorders that has been modeled includes the polyglutamine (polyQ) diseases. There are nine different polyQ diseases, including Huntington's, spinocerebellar ataxia types 1, 2, 3, 6, 7, and 17, spinobulbar muscular atrophy, and dentatorubral–pallidoluysian atrophy (Xu et al. 2015). Each of these is caused by a CAG repeat leading to a glutamine track forming somewhere in the protein-coding region of the gene (Macdonald et al. 1993). The number of these repeats varies significantly across the different diseases (Koide et al. 1994; Deka et al. 1995; Ikeuchi et al. 1995a,b; Komure et al. 1995). These polyQ repeats lead to a protein aggregation formation that precedes neurodegeneration. A multitude of transgenic models corresponding to each of the nine polyQ diseases have been generated as tools to identify the underlying pathophysiology (Fernandez-Funez et al. 2000; Chan et al. 2002; Takeyama et al. 2002; Warrick et al. 2005; Pandey et al. 2007; Nedelsky et al. 2010; Nisoli et al. 2010; Napoletano et al. 2011). Although many screens use S2 cells, or the eye, to investigate aggregation/neurodegeneration, significant loss in the α, β, and γ lobes of the MB has also been observed (Agrawal et al. 2005; Zhang et al. 2010; Song et al. 2013; Tandon and Sarkar 2023). This selective degradation is also found in the human neuropathology of each of the nine diseases (Tandon et al. 2024). For an extensive review on polyQ current research and therapeutics, see Tandon et al. (2024).

## Overview and outlook

The *Drosophila* MB has functioned as a key source to identify the fundamental mechanisms of several distinct neurological disorders. The insights garnered from the model have shed light on the etiological identification of aberrated molecular mechanisms underlying multiple aspects of disease states. Although current genetic sequencing has identified many monogenetic mutations that cause disorders, many associated risk factors have yet to be discovered. Advancements in patient-derived sequencing will further personalize the therapeutic potential associated with many risk factors. These advancements, coupled with a comprehensive *Drosophila* connectome (Scheffer et al. 2020), will enable further dissection of how diseases alter biology (Scheffer et al. 2020). Further genetic studies are necessary to identify and characterize the full breadth of pathways that underlie and modulate brain disorders, and the MB provides an anatomical node to examine their effects on anatomy and complex behavior. From the forward genetic approaches that have identified foundational gene function to developmental and behavioral studies and detailed circuit studies, significant contributions have been made into disease mechanisms at the genetic, molecular, cellular, circuit, and behavioral levels. These discoveries are likely to continue and accelerate as fundamental nervous system function is more thoroughly dissected.

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