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Beyond vertebrates: *Drosophila melanogaster* as a model to study negative symptoms of schizophrenia

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Schizophrenia is a complex neuropsychiatric disorder characterized by positive, negative, and cognitive symptoms. While positive symptoms have been extensively studied, negative symptoms—such as anhedonia, social withdrawal, and apathy—remain challenging to model and treat. Vertebrate animal models for schizophrenia have provided insights into some of the underlying mechanisms associated with this disorder. Recently, *Drosophila melanogaster* has emerged as a valuable model due to its genetic tractability, conserved neurochemical pathways as compared to vertebrates, and suitability for high-throughput behavioral analyses. Mutations in genes such as *dysb1*, *Rim*, and *Neuroligins* have been linked to behaviors in flies resembling negative symptoms of schizophrenia, supporting the relevance of this animal model in psychiatric research. Moreover, behavioral paradigms aimed at assessing social interaction, motivation, and anhedonia in *Drosophila* are being refined to better capture schizophrenia-related deficits. The use of *Drosophila* enables precise investigation of neural circuits and molecular pathways underlying negative symptoms of schizophrenia, research that has the potential to lead to novel therapeutic targets.

KEYWORDS

***Drosophila*, schizophrenia, negative symptom, dysbindin-1 (DTNBP1), Rim1, neuroligin**

Introduction

Schizophrenia is a complex and multidimensional neuropsychiatric disorder, affecting approximately 1% of the global population, which exhibits a higher prevalence in males (1–3). Globally, costs associated to schizophrenia are estimated between US$94 and US$102 billion annually. This represents an economic burden equivalent to 0.02% to 1.65% of a

country's gross domestic product (GDP), with indirect costs—such as lost productivity and social security expenses—accounting for 50% to 85% of that total (4, 5). This is relevant as the health, social, and economic burden associated to this disorder is substantial, impacting patients but also families, caregivers and society at large.

By 1908, Eugen Bleuler first introduced the term "schizophrenia", describing personality, perception, and cognitive symptoms in a group of patients (6). Schizophrenia was later categorized into positive (hallucinations, delusions) and negative symptoms (blunted affect, avolition, anhedonia, asociality, and alogia) (6–8). It is currently known that schizophrenia also involves cognitive impairment, including alterations in language, executive function, verbal memory, spatial memory, among other features (9, 10) (Figure 1).

On the other hand, non-classical symptoms, such as olfactory impairments (11) and circadian disruptions (12), have been observed in 80% of schizophrenia cases (12–14), and have gained attention as prodromal symptoms or markers of this disorder (Figure 1).

The study of schizophrenia has largely focused on positive symptoms due to the effectiveness of antipsychotics on them (15, 16). However, although negative symptoms seem critical in determining the loss in the quality of life of people with a diagnosis of schizophrenia, they remain a major therapeutic challenge.

Negative symptoms of schizophrenia

Negative symptoms involve behavioral features that are absent or undermined in patients. They are classified into two primary domains: abulia/apathy and diminished emotional expression (17, 18). The first domain is understood as deficits in motivation and pleasure. It involves reduced motivation and goal-directed behavior and decreased pleasure when facing positive experiences (17). Thus, this domain includes individual symptoms (or subdomains) of abulia, asociality, and anhedonia (19).

The second domain involves a decrease in the external expression of emotions (blunted affect) and speech (alogia) (18). Blunted affect or affective flattening is linked with diminished quality of life, depressive symptoms, poor social functioning, emotional withdrawal, negative self-evaluation, and suicide ideation (20), while alogia has been associated with cognitive deficits, such as alterations in semantic memory (21).

Importantly, negative symptoms of schizophrenia are little responsive to dopaminergic agents, which are more effective towards positive symptoms of this disorder (22). Thus, there is a need for a better comprehension of the mechanisms underlying the negative symptoms of schizophrenia, in the search for new treatments and therapeutical approaches.

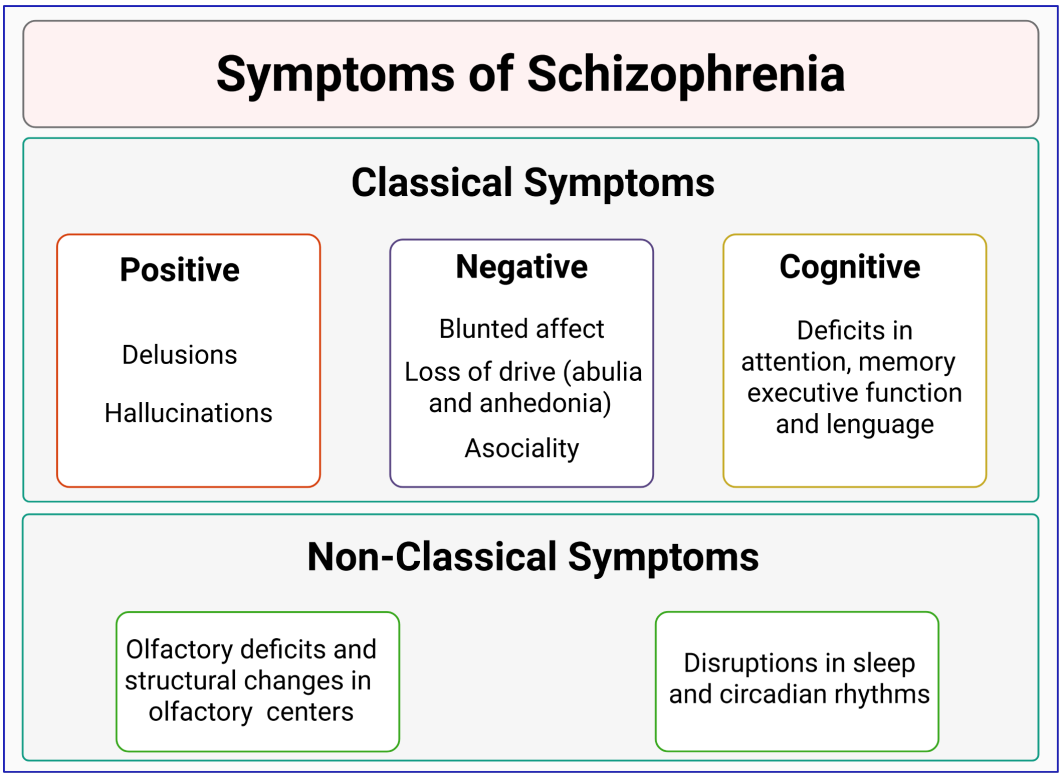

FIGURE 1
Classification of schizophrenia symptoms. Schizophrenia is characterized by positive symptoms (such as delusions and hallucinations) and negative symptoms (including blunted affect, poverty of speech, and anhedonia). Cognitive impairments, such as deficits in language, memory, and executive function, are also common. Non-classical symptoms, involving olfactory discrimination deficits and sleep/circadian disruptions, are emerging as potential prodromal markers of schizophrenia.

Schizophrenia etiology and negative symptoms

The etiology of this disorder involves multifactorial elements ranging from genetic features to risk factors in brain development to environmental influences, which accumulate and interact to produce a wide range of symptoms, mainly in adolescence and youth (23, 24).

Several genetic linkage and GWAS studies have tried to identify genes that could play a role in the disorder, and some of these reports have pointed out a genetic contribution to negative symptoms. Thus, for instance, a strong link has been found between negative symptoms of schizophrenia and chromosome 22q11 microdeletions, as well as with alterations in the *NKAIN2* gene, which encodes a protein that interacts with subunits of the sodium/potassium ATPase (25). Additionally, these studies have identified an association between haplotypes of the *DTNBP1* gene (Dystrobrevin Binding Protein 1, also known as Dysbindin-1), and cognitive and negative symptoms of the disorder (26–28). Notably, dysbindin-1 deficiency affects glutamatergic, GABAergic, and dopaminergic neurotransmission (29, 30), some of the neurochemical systems mostly associated with schizophrenia etiology (31). Similarly, haplotypes and polymorphisms in the gene that encodes COMT, an enzyme involved in dopamine metabolism, have been linked to the severity of schizoaffective negative symptoms (32–35).

The serotonergic system plays a well-established role in regulating mood and affect, some of the features associated with negative symptoms of schizophrenia. Considering this, it was proposed that the serotonergic neurochemical system could play a role in these symptoms and early studies supported this idea (36). Accordingly, pharmacological treatments targeting serotonin receptors have been shown to prevent the loss of gray matter typically observed in schizophrenia patients and to improve cognitive and negative symptoms of this disorder (37, 38).

Importantly, most of these studies support that the interaction of genetic and environmental factors during early neurodevelopment contributes to brain vulnerability and predisposition to develop schizophrenia (31, 39). However, what is the contribution of genes and environment, or what are the exact mechanisms responsible for this effect, is an open question that is difficult to study in humans. In this regard, animal models seem better suited to advance on this issue (40).

Animal models in the study of negative symptoms of schizophrenia

Despite the inherent limitations of studying a complex human disorder like schizophrenia in vertebrate animal models, research in non-human primates, rodents, and zebrafish has provided valuable insights into the cellular, molecular, and circuit-level underpinnings of some behavioral features of schizophrenia (41–43). Positive symptoms, for example, are often modeled through non-verbal indicators such as hyperlocomotion or stereotypy, while negative symptoms are inferred from behaviors like impaired thigmotaxis, reduced exploration, or diminished social interaction (44).

Rather than replicating the full disorder, animal studies focus on isolating specific symptoms or symptom clusters to explore their underlying causes (45, 46). This strategy has been instrumental in identifying or understanding environmental, genetic, and pharmacological factors contributing to schizophrenia, helping to dissect the complex interplay of elements involved in its pathophysiology (Figure 2).

Genetic models in mice to generate schizophrenia-like symptoms include mutants for the DISC1, DTNBP1, and COMT genes (47–50), as well as deletions in the equivalent to 22q11.2 region, among others (51, 52). Most of these tools have been successful in modeling some of the positive symptoms of the disorder.

Environmental models primarily focus on neurodevelopmental disruptions, such as prenatal and postnatal stress paradigms, including maternal exposure to adverse conditions that elevate corticosterone levels, maternal malnutrition during gestation, and maternal separation, resulting in behavioral alterations and schizophrenia-related symptoms in the offspring (53–55).

Pharmacological models offer another widely used approach, employing acute or chronic exposure of animals to specific compounds. For instance, administration of methamphetamine or amphetamine induces hyperlocomotion and stereotypy in rodents, mimicking positive symptoms of schizophrenia and providing support for the dopaminergic hypothesis of this disorder (56, 57). However, these models poorly replicate negative symptoms of the disorder (58, 59). To overcome this limitation, researchers have used NMDA receptor antagonists, such as phencyclidine (PCP) and MK-801, which can induce negative-like symptoms, including social withdrawal, reduced social interaction, and increased immobility in the forced swim test (60–62).

Another pharmacological approach to model negative symptoms of schizophrenia is based on the serotonergic hypothesis for this disorder. This is based, as stated above, on the fact that serotonin dysregulation induces behavioral features that resemble negative symptoms of this disorder and that serotonergic agents show some efficacy against schizophrenia's negative symptoms (37, 38). Thus, serotonin receptor antagonists, alone or in combination with glutamatergic antagonists or dopaminergic agonists, have been used to generate rodent models for negative symptoms of schizophrenia (63–65) (Figure 2).

Although vertebrate models have provided valuable insights into the neurobiological basis of schizophrenia, many of these approaches, particularly pharmacological and neurodevelopmental models, carry the risk of inducing widespread, non-specific alterations in several body organs, multiple neural circuits, and signaling pathways (66–68). Thus, if the goal of these animal models is to understand the contribution of specific circuits or neurochemical systems to the disorder, these global approaches might hinder the precise dissection of the mechanisms contributing to the onset and progression of schizophrenia. Moreover, they might lead to the misidentification of contributing factors. In this regard, the use of models that allow for a

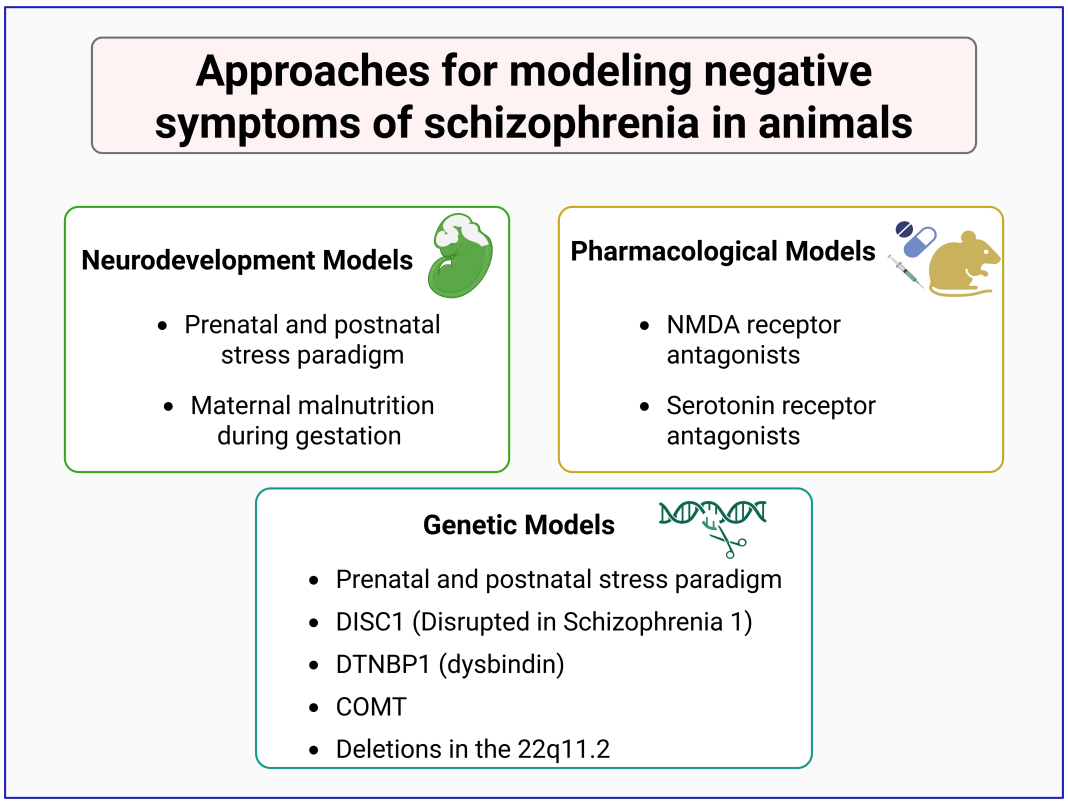

FIGURE 2
Animal models in the study of negative symptoms of schizophrenia. Experimental models are categorized into three main approaches: neurodevelopmental, pharmacological, and genetic models. Neurodevelopmental models involve prenatal and postnatal stress paradigms or maternal malnutrition during gestation. Pharmacological models utilize NMDA receptor and serotonin receptor antagonists to induce schizophrenia-like phenotypes. Genetic models include mutations in schizophrenia-associated genes such as DISC1, DTNBP1 (dysbindin), COMT, and deletions in the 22q11.2 region. These models contribute to understanding the neurobiological basis of schizophrenia and its negative symptoms.

more precise spatial and temporal dissection of neural activity and dysfunction is necessary.

Drosophila models for schizophrenia and the study of negative symptoms

In the study of complex human disorders, the use of invertebrate models including *Drosophila melanogaster*, has gained increasing attention. *Drosophila* offers several advantages as an animal model for the study of disorders, including its fully sequenced genome (69), its short life cycle, the possibility to obtain and study a large number of animals, and a high proportion of conserved genes when compared to the human genome (70, 71). Notably, approximately 75% of human disease-related genes have functional orthologs in *Drosophila* (70, 71), including many implicated in schizophrenia. Although exist evident anatomical and structural differences between the brains of flies and vertebrates, the basic principles that govern their development and operation are conserved. Moreover, *Drosophila* connectomics, which has been well established and refined (72, 73), further support using this animal in modeling anatomical and functional features of complex psychiatric and neurodevelopmental disorders like schizophrenia. Furthermore, several binary expression systems have enabled the study of human gene homologs linked to this disorder in *Drosophila* (70, 71). This animal model is particularly valuable because it encompasses the same major neurochemical systems associated with schizophrenia in humans, including dopaminergic, serotonergic, GABAergic, and glutamatergic systems, although some differences in their respective enzymes, receptor subtypes, transporters, and metabolizing proteins need to be considered (74, 75).

Several *Drosophila* models for schizophrenia have been developed and characterized, exhibiting key features observed in other animal models of the disorder and patients. These include altered circadian rhythms, hyperlocomotion, and some cognitive deficits, such as impaired learning and memory (76–80). These models have become valuable tools for exploring the cellular and molecular processes underlying the pathophysiological aspects of schizophrenia, including its negative symptoms, and have provided important information on the human disorder.

Thus, for instance, one of the first studies that explored the molecular underpinnings underlying schizophrenia pathophysiology in *Drosophila* was that of Sawamura et al. (77). In this work, authors generated transgenic flies expressing the human gene *Disrupted in schizophrenia 1*, *DISC1*, which resulted in alterations in sleep

homeostasis. Importantly, it was demonstrated that *DISC1* modulates CRE-mediated gene transcription by interacting with ATF4/CREB2 (77), an important factor in a broad range of brain conditions (81–83).

Other studies used *Drosophila* to provide further support to the dopamine ontogenic hypothesis for schizophrenia (76, 84). In these works, activation of the dopaminergic system in specific early developmental windows resulted in behavioral alterations in adult animals, including changes in sleep patterns, and behavioral responses to mechanic and visual stimuli, which could reflect an effect on salience allocation, a characteristic of the positive symptoms of schizophrenia (85).

These and other studies demonstrate the validity of *Drosophila* models to assess the mechanisms underlying complex human disorders including schizophrenia. Nevertheless, one of the challenges in schizophrenia research is the difficulty in replicating negative symptoms in animals -including *Drosophila*- to study the molecular, cellular, and circuital underpinnings underlying their onset. Importantly, new tests and social and cognitive paradigms have been developed over recent years to assess complex behavioral, social, and cognitive functions in *Drosophila* relevant to neurological and psychiatric conditions. For instance, the flies' clustering behavior, which consists of flies aggregating in groups, has been linked to social coordination and has provided insights into collective behavior dynamics (86). In addition, *Drosophila* exhibits attention-like processes, allowing them to prioritize certain stimuli above others, an aspect of cognition observed in more complex organisms (87). Research has further revealed that *Drosophila* engages in goal-driven behavioral adaptations, modifying their actions based on environmental conditions or experiences, a process akin to motivation, learning, and behavior modifications seen in vertebrates (88). Furthermore, *Drosophila* has been tested in their ability to make choices, which somehow resembles basic decision-making processes (89). These findings highlight the potential of *Drosophila* as a model for studying multifaceted brain processes underlying complex behaviors and foster support that it is possible to study the mechanisms underpinning schizophrenia negative symptoms in this animal.

In this regard, our lab advanced the previous characterization of the hypomorphic mutant $dysb^1$, which represents a loss-of-function mutation in the fly orthologue of *DTNBP1/Dysbindin-1* (90, 91). Our findings revealed several behavioral phenotypes reminiscent of schizophrenia's negative symptoms in humans. In particular, $dysb^1$ flies exhibit increased social spacing compared to controls (92). This is in agreement with previous studies in the "sandy" mouse (mutant for dysbindin-1) (93) and in schizophrenia patients, which demonstrate alterations in social distance (94, 95), supporting the notion that social space is a good marker or probe for negative symptoms of schizophrenia.

We further showed neurochemical alterations in the $dysb^1$ mutant flies, including reduced serotonin levels and a two-fold increase in *dSERT* expression (92). Interestingly, the administration of 4-MTA, a serotonin-releasing agent, effectively increased social behaviors in control flies but failed to elicit the same effect in *dysb1* mutants, providing further support for the idea that the serotonergic system plays a role in the expression of negative symptoms of schizophrenia (92).

In a different work (80) we investigated the role of the orthologue for the Rab-3 interacting molecule-1 (*RIM1*) gene, called *Rim* in *Drosophila*, to some of the behavioral anatomical and functional phenotypes observed in schizophrenia patients. In this work, *Rim* mutants displayed impaired social behavior, which is similar to the social impairment described in RIM1α−/− mutant mice (96, 97). Moreover, the *Rim* mutant flies showed impaired olfactory acuity and circadian defects, including a loss of circadian rhythmicity and decreased period length phenotypes, that mapped to the pacemaker ventral lateral clock neurons. Importantly, haloperidol, a typical antipsychotic, efficiently rescued *Rim* mutant deficits to normal levels further validating the *Drosophila* model for investigating the mechanisms underlying schizophrenia-related behaviors (80). Other studies have used *Drosophila* to assess the role that could play alterations in Neuroligins (NLGs) to schizophrenia symptoms. NLGs are a family of proteins that form protein-protein complexes essential for the proper formation, maturation, and functional adjustment of chemical synaptic connections between neurons (98, 99). Several alterations in genes coding for NLGs have been associated with changes in social behavior in disorders such as autism and schizophrenia (100). Specifically, mutations in orthologs for these genes in *Drosophila* (*dlng2* and *dlng4*) have shown alterations in the sleep rhythms, altered acoustic communication signals, as well as a reduced tendency to form groups and social interactions (101–103), phenotypes that parallel negative symptoms observed in schizophrenia.

Recent studies have expanded the scope of *Drosophila* schizophrenia models to study endophenotypes, heritable and quantifiable traits that serve as intermediate markers linking genetic risks to clinical symptoms of a disorder. For instance, Foka et al. (104) demonstrated that *Drosophila furin1* mutants exhibit defective habituation to repeated stimuli, a phenotype that mirrors impaired habituation observed in schizophrenia patients (105). In that work, it was also demonstrated that the deficit observed in flies can be reversed by antipsychotic treatment, validating the translational relevance of this model (104). Likewise, Schiöth et al. (106) provided the first evidence of prepulse inhibition (PPI) for visual stimuli in adult *Drosophila*, an endophenotype sensitive to NMDA receptor antagonists in flies that has been reported in people with this disorder (107).

Conclusion

Drosophila melanogaster has proven to be a valuable model for investigating some of the neurobiological underpinnings of schizophrenia, particularly its negative symptoms, which remain one of the most challenging aspects to study in this disorder. These

findings not only affirm the relevance of these genes to the disorder but also underscore *Drosophila* as a model system for investigating the mechanisms involved in psychiatric conditions. Moreover, the development of new behavioral paradigms, such as sucrose preference to assess anhedonia (108), and the forced swim test to measure despair-related behavior (109), further expands the utility of this model. As research continues to refine these approaches, *Drosophila* holds significant potential for deepening our understanding on the cellular and molecular mechanisms driving schizophrenia and for identifying new therapeutic targets to alleviate its debilitating negative symptoms.

Author contributions

ME-R: Writing – review & editing, Writing – original draft. SH: Writing – review & editing. JC: Funding acquisition, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be considered a potential conflict of interest.

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Publisher's note

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