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# *In vivo* experimental models of schizophrenia: mechanisms, features, advantages, disadvantages

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## Abstract

The experimental models of human diseases are indispensable research methods which are undesirable to be tested on humans. It is inevitable for researchers who continue their careers in the field of anatomy to be aware of these methods. Here, experimental schizophrenia models that can be used to reveal brain functions and also pathophysiology of schizophrenia are discussed. It is aimed to give general information about the features of the experimental schizophrenia models that can be used by researchers in morphological sciences; therein the references should be considered for the setup of the experimental schizophrenia models. In this review, *in vivo* model of schizophrenia used on etiopathogenesis, pathophysiology, drug discovery and behavioral analysis are represented. And also we briefly indicate the molecular mechanisms of the experimental models that mimic schizophrenia-like symptoms and its behavioral outputs.

**Keywords:** animal models; experimental models; mental disorders; schizophrenia

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## Introduction

Morphological sciences have been mostly concerned with describing the structural features of organisms. As research techniques have been developed today, the scope of research in anatomy, which is one of the main branches of morphology, has also expanded. The experimental animal models developed based on evolutionary relationship of the human and other species have begun to be used in research to understand function of organism and pathology of illness. *In vivo* and *in vitro* experimental models are indispensable way for applying methods that are undesirable to be tested on humans. To be aware of these methods is inevitable for researchers who continue their careers in the field of anatomy. Here, experimental schizophrenia models that can be used to reveal brain functions and pathophysiology of the illness are discussed. It is aimed to give general information about the features of the experimental models; therein the references should be considered for the setup of the experimental schizophrenia models.

In this review, we represent the *in vivo* model of schizophrenia for researches on etiopathogenesis, pathophysiology, drug discovery and behavioral analysis. In addition, we briefly indicate the molecular mechanisms of the experimental models that mimic schizophrenia-like symptoms and its behavioral outputs.

## *In Vivo* Models of Schizophrenia (General Characteristics of Schizophrenia)

Schizophrenia is a serious and complex mental illness that has neurodevelopmental origin. It affects approximately 1% of the general population and is thought to result from interplay between genetic and environmental factors. It is unclear that how these risk factors collectively contribute to pathology. As multiple etiological factors contribute to the schizophrenia spectrum, altered symptomatology can be observed as the condition progresses. Symptoms of schizophrenia is classified primarily into three: positive, negative, and cognitive symptoms.[1–3] Positive symptoms (hallucinations, delusions, disorganized thought processes, disorganized or catatonic behavior, etc.) have an acute

onset, respond to antipsychotics and are composed of biochemical dysregulations.[4] Negative symptoms (affective flattening, alogia, apathy, anhedonia and asociality, attention disorders, etc.) respond to antipsychotics weakly, can be seen in combination with cognitive and behavioral disorders which also contain abnormal involuntary movements.[1,4] Cognitive symptoms (attention disorders, memory deficits, executive functioning, etc.) respond poorly to drugs and have negative effects on illness processes, quality of daily life.[1,5]

Although the pathophysiology of schizophrenia is not identified completely, it is well recognized that it has a complex structure. As a result, rather than relying on a single approach to explain schizophrenia, a combination of different approaches such as chemical, environmental, genetic, and structural components may be more helpful in understanding schizophrenia's pathogenesis.[3,6]

Alterations in neurotransmitters are one of the most important aspects of schizophrenia pathophysiology.[7,8] Reduced plasma dopamine metabolites are a sign of dopaminergic dysregulation in patients with a poor prognosis and social impairments. Higher dopamine metabolites, on the other hand, are detected mostly in patients with positive symptoms.[9] Glutamatergic hypofunction,[10] serotonergic dysregulation (as 5-HT1A receptor overexpression),[11] and changes in prefrontal cortex gamma-aminobutyric acid (GABA) neurotransmission (such as GABA-A receptor upregulation) have all been reported in the neurotransmitter researches.[12]

The researches on the brains of schizophrenic subjects are focused mainly on temporal cortex, frontal cortex, striatum, thalamus, hippocampus.[13–15] In these researches, decrease in temporal cortex, hippocampus, amygdala and parietal cortex volume are reported.

Genetic predisposition, because of the strong link with schizophrenia etiogenesis, is a crucial issue for most of the researches:[16] DISC1,[17] and dystrobrevin binding protein 1 (DTNBP1), dysbindin,[18] NRG1, ErbB4,[19] GAD, BDNF[20,21] are some of the mostly studied genes in the schizophrenia researches. Furthermore, environmental factors that include physiological, pharmacologic and psychological events have an influence on schizophrenia etiopathogenesis.[22]

In present review, we provide a brief overview of five animal models of schizophrenia. Also, we summarized common pathways involved in schizophrenia-like brain and behavioral abnormalities, which are specific to the animal model of interest.

At least twenty animal models of schizophrenia have been using in researches, and new ones are created in line with purposes of the researches. In this review, we focused on prevalently used animal models:

- pharmacologic animal models,
- lesion animal models,
- neurodevelopmental animal models,
- genetic-epigenetic animal models,
- combinations of animal models

## Pharmacologic Animal Models

In 1950's first animal model of schizophrenia was developed in the basis of amphetamine. Psychosis that stimulated with amphetamine is used to mimic positive symptoms.[23] Pharmacologic animal models are based on the dysregulations in neurotransmitters. However, these models have constructive validity, they maintain limited information about cognition and thought processes.[24–38]

**Serotonergic approach:** Serotonergic (5-HT) neurotransmission is reported as an important issue for schizophrenia: Indolamines' (LSD: lyseric acid diethylamide) and phenethylamines' (mescaline), two main hallucinogenic drugs, effect mechanisms are mentioned to be mediated by 5-HT2A receptors.[38] On the other hand decrease in 5-HT2A receptor and increase in 5-HT1A receptor in the prefrontal cortex[39] are reported, and also the neuroendocrine respond to 5-HT2A receptor agonists is found to be weaker in schizophrenic individuals then healthy subjects.[40] In dopaminergic and glutamatergic animal models and also in human subjects, LSD mechanism on startle habituation and pre-pulse inhibition (PPI) are shown to act directly via 5-HT2A receptor stimulation.[41] Similarly phencyclidine (PCP) acts via indirect activation of 5-HT2A receptors and impairs PPI.[42] 5-HT5A receptor antagonist ASP5736's (N-(diaminomethylene)-1-(3,5-difluoropyridin-4-yl)-4-fluoroi-soquinoline-7-carboxamide (2E)-but-2-enedioate) therapeutic effects on positive and cognitive symptoms of schizophrenic individuals are mentioned as a validity for serotonergic approach.[11]

**Dopaminergic approach:** In dopaminergic approach, it is assumed that dysregulation in dopamine (DA) neurotransmission leads to the manifestation of the disorder. Positive symptoms are proposed to be thrived as a consequence of hyperactivity in mesolimbic dopaminergic neurons.[25] On the other hand, hypo-dopaminergic processes in fronto-cortical areas are proposed to lead negative symptoms.[26]

Locomotor hyperactivity and stereotypic behaviors can be induced after a single amphetamine administration in the animal models. Repeated amphetamine administration may cause impairment in locomotor activity and hyperac-

tivation in striatum dopaminergic neurotransmission, however alterations in social interaction may not observed in this animal model of schizophrenia. As a conclusion it is claimed that DA based animal models have limited constructive validity.[23,27]

**Glutamatergic approach:** Despite the amphetamine model, through the glutamatergic approach cognitive deficits, negative and positive symptoms, can be mimicked in the same animal model.[28–30] N-methyl-D-aspartate receptor (NMDAR) inhibitors like PCP, dizocilpine and kethamine are reported to induce schizophrenia like symptoms (hallucination, delusion, etc.) in healthy subjects.[28,29,31,32] Especially PCP is mentioned as an effective inducer of positive symptoms together with its influence on negative and cognitive symptoms.[28,33] PCP treatment to animals can mimic several behavioral and neurochemical abnormalities reported in schizophrenic patients, including hyperlocomotion, impairments in pre-pulse inhibition,[41] social interaction, working memory, and cognition.[35,36] Chronic PCP administration has been linked to a decrease in social contact. The acute treatment of haloperidol and clozapine are reported to reverse social interaction in the same study. As a result of those findings researchers concluded that this model mimics social withdrawal which is a negative symptom of schizophrenia.[33,39] The effects of PCP on gene expression in the brain are explored, and the expression levels of 146 genes (associated with apoptosis, neurological disorders, and schizophrenia-related genes) are found to be altered. Analyzing the signalization pathways reveal an increase in calcium signaling and long-term synaptic potentiation. These findings also support the use of PCP injection as a schizophrenia animal model.[37]

**GABAergic approach:** In prefrontal cortex γ-aminobutyric acid (GABA) neurons receive synaptic inputs from dopaminergic terminals, on the other hand they have inhibitory control over excitatory outputs of the pyramidal neurons, and also they have regulatory effects on developmental alterations that are seen in late adolescence. This mechanism makes GABAergic, dopaminergic and glutamatergic interactions a considerable issue in schizophrenia researches.[43,44]

Increase in GABA-A receptor expression[45] and decrease in glutamic acid decarboxylase 67 (GAD67) expression in prefrontal cortex[46] reflect GABAergic alterations that consist in pathophysiology of schizophrenia. After a decrease in calcium flux as a result of NMDAR hypofunction, GAD67 downregulation has been reported as a result of interneurons' response to NMDAR antagonism.[47] The decrease in PPI after injection of the GABA-A receptor antagonist picrotoxin to the rat medial prefrontal cortex[48] and the decrease in parvalbumin-containing GABAergic interneurons after prenatal MAM injection[49] have both been demonstrated in animal studies.

Risk factors like early life stress and trauma are shown to increase psychosis risk and accomplish subjects more vulnerable to hippocampal hyperactivity in their late life by impairing developing GABAergic neurons.[50] Hippocampal hyperactivity is associated with cognitive dysfunction[51] and impairment in perceived reality.[52] In schizophrenic individuals hippocampal hyperactivity level[52] or glutamatergic dysregulation leads to decrease in hippocampal volume which is used to mimic hippocampal dysfunction in developmental animal models of schizophrenia.[51]

## Lesion Animal Models

Because of the prefrontal cortex's executive functions in attention, working memory, social interaction and emotional processes, prefrontal cortical lesions are widely used in schizophrenia researches.[53] Behavioral experiments support the prefrontal cortex's regulatory role on subcortical DA activity.[54] Increase in amphetamine induced stereotypic behavior and continuous hyperexcitability with stress exposure are reported after prefrontal cortex lesion in adult rats.[55]

Hippocampal formation plays a key function in prefrontal cortex modulation and has direct control over the dopaminergic system.[56] Because of these features, lesions of hippocampal formation are used in researches: Excitotoxic lesions of dorsal and ventral hippocampus are found to stimulate different behavioral profiles. Lesions of dorsal hippocampus are not found to be effective in amphetamine induced locomotor activity.[57] However by kainic acid administration, neural loss is reported in dorsal hippocampus, and this model is proposed as a neurodegenerative animal model of schizophrenia.[58] On the other hand, lesions of ventral hippocampus by DA agonists are found to stimulate locomotor activity.[57]

Because of its importance in filtering sensory information, the thalamus is being addressed in researches. Abnormalities in corticothalamic limbic system are proposed as a useful target for studying sensorimotor deficits.[57] To sum up, although lesion models have face and predictive validity, dimensions of lesions and adult nature have limiting impacts on construct validity.

Lesions of ventral hippocampus are developed to mimic pathological conditions including ventricular enlargement and hippocampal atrophy. Abnormal behaviors after adolescence are reported to be induced by excitatory toxin ibotenic acid microinjection as a neonatal

lesion of ventral hippocampus. This model is shown to be resulted in behavioral alterations in different developmental stages: Spatial and working memory deficits are reported on postnatal day 25, however increase in social withdrawal and aggression are seen on postnatal day 35. Increase in sensitivity to dopaminergic and glutamatergic agonists, impairments in PPI and reward mechanisms and increase in drug sensitivity are reported around postnatal day 56.[13]

## Neurodevelopmental Animal Models

Weinberger (1986) was the first to propose the neurodevelopmental hypothesis, stating that brain developmental defects that occur early in life increase the chance of clinical symptoms later in life.[13] Neurodevelopmental animal models consist of prenatal exploration to environmental risk factors or toxic compounds. Based on schizophrenia epidemiology neurodevelopmental animal models of schizophrenia have construct and face validity.[59,60]

There are several methods that are used to induce inflammation: polyriboinosinic-polyricocytidylic acid [poly(I:C)],[61] methylazoxymethanol asetat (MAM)[62] and bacterial endotoxin lipopolysaccharide (LPS).[63,64] On the other hand multiple environmental stressors can be used alone or together to induce molecular processes related with schizophrenia: Social isolation,[65] maternal separation,[66] water stress.[55]

Usage of two different stress factors in different developmental stages are proposed to be more effective to mimic schizophrenia spectrum, which is also called two-hit animal model of schizophrenia:[67] Prenatal LPS administration with juvenile stress or prenatal polyI:C with neonatal LPS.

**Polyriboinosinic-polyricocytidylic acids [poly(I:C)]:** Multiple proinflamatuar cytokines are released through the binding of poly(I:C) to its receptor, tool-like receptor (TLR) 3.[68] This viral compound has several influences on rodents: After its prenatal administration pups are reported to have increased locomotor sensitivity to psychostimulants, impaired pre-pulse inhibition and new object recognition, social withdrawal in their late life (in their adolescence or young adulthood). However, spatial memory impairments are not reported in researches.[61,69,70] Together with those behavioral abnormalities neurochemical alterations like decrease in DA and glutamate levels in prefrontal cortex and hippocampus are shown.[70] Increase in striatal and accumbal D1 and D2 receptors' function, increase in D2 receptor function in frontal cortex, decrease in DA and increase in tyrosine hydroxylase in striatum are demonstrated.[71]

**Bacterial endotoxin lipopolysaccharide (LPS):** Bacterial endotoxin LPS has its action through TLR4 receptors on macrophages and other immune cells. After binding to its receptor, it triggers several signal transduction cascades like release of proinflamatuar cytokines, activation of transcription factors (like kappaB) and anti-inflammatory modulators (cytokines, proteins, etc.).[72]

Multiple behavioral deficits are also reported as a consequence of LPS administration: increase in locomotor activity, decrease in sociality, impairment in PPI and memory, anxiety like behaviors.[69]

It is demonstrated that LPS administration leads to dysregulation of dopaminergic signalization: Increase in accumbal and striatal DA, decrease in striatal and frontal DA, decrease in frontal 3,4-dihydroxyphenylasedic acid (DOPAC), increase in frontal and decrease in striatal homovallinic acid levels.[71,73]

**Methilazoxymethanol asetat (MAM):** Prenatal MAM administration leads to developmental damage in fetal brain because of DNA synthesis inhibition during mitosis. This abnormal brain development results in multiple behavioral deficits like impairment in sociality, PPI, spatial cognition.[62] In another study increase in accumbal DA levels is reported. Increase in ventral tegmental DA activity and locomotor sensitivity to amphetamine are reversed by the injection of tetrodotoxin to ventral hippocampus.[74]

**Environmental stress:** Multiple environmental stress factors can be applied in different developmental stages acutely or chronically, alone or in combination: Social isolation, restrainer, noise, light, water. Sociality is reported to be critical for normal developmental processes of rats; they have socially active nature which also has hierarchical rules.[59] For this reason any kind of social deprivation can resulted in abnormal brain development which also leads to locomotor hyperactivity, impaired cognition, increased anxiety, depressive like behaviors and aggression which are also reported as schizophrenia symptoms.[59,65]

Stress exposure stimulates the release of stress hormones that resulted in dysregulation of several neurochemical compounds: decrease in DA, DOPAC and homovallinic acid levels,[75] increase in striatal and accumbal, decrease in frontal serotonin levels, increase in corticostriatal noradrenaline level which are related to anxiety and positive symptoms,[76] downregulation in cortical parvalbumin containing GABAergic neurotransmission.[65]

Schizophrenia-like behavioral and neurochemical abnormalities that are generated by using environmental stressors can be reversed by antipsychotics, and this condition is proposed to be sufficient for this model's validity.[77]

## Genetic Animal Models (Knockout & Transgenic)

Genetic studies are identified several specific genes that are associated with schizophrenia disorder.[78–90] Generally, twin studies are shown that schizophrenia is a predominant genetic disorder, with estimates of heritability risk ranging at 50–80%. In researches it is demonstrated that single effects of a major gene are unlikely to mimic schizophrenia's complexity; instead, polygenic models consists of multiple-risk genes can provide the best expression for schizophrenia.[91,92]

**There are several genetic animal models of schizophrenia:** neurodevelopmental candidate genes (reelin, BDNF, GAD37, N-CAM); hyperdopaminergic hypothesis related genes (Akt, PP2A, B-arrestin 2, DARPP-32); hypoglutamatergic approach related genes (NMDR reseptor subunit 1, calciceurin knockout); susceptibility genes of schizophrenia (COMT, NRG1, Dysbindin, DISC1, RGS-4, CHRNA7, NPAS3, PRODH2 [22q11]).[2,78–80,93]

N-methyl-D-aspartat (NMDA) receptor subunits importance in schizophrenia neuropathology is reported in schizophrenic postmortem brain tissues: decrease in NR1 subunit expression,[78] deficits in associative learning processes are linked with NMDAR dependent plasticity.[79] Hyperlocomotion, stereotypic behavior, decrease in social interaction, deficits in cognition and abnormal brain development, impairment in working memory, anhedonia and anxiety,[2,80] impairment in spatial memory, hyperactivity in novel environment and depression[81] are reported in NR1 mutant animal models of schizophrenia. These behavioral anomalies are not seen if NR1 subunit deficiency is generated in adolescence.[2]

DISC1's influence on neuronal migration, synaptic plasticity, neurogenesis together with its effect on mechanisms in schizophrenia onset, is demonstrated in multiple researches.[82–84] Schizophrenia like behavioral deficits are reported in genetic models of DISC1: Hyperactivity in novel environment, immobility in forced swimming test, impairment in pre-pulse inhibition,[85] hyper or hypolocomotion, impairment in cognition and alterations in brain morphology which are also compatible with schizophrenic subjects' symptoms.[86,87]

In multiple studies, it is reported that "dysbindin1", coded by DTNBP1, has an influence in regulation of exocytosis and vesicular genesis during neurotransmitter release. In addition, it has a role in dopaminergic and glutamatergic neurotransmissions. On the other hand it is shown that DTNP1 associates with prefrontal and cortical functions of schizophrenic individuals, whereas episodic and working memory of healthy individuals. Decrease in dysbindin1 mRNA and protein expressions are reported in postmortem brain tissues of schizophrenic subjects.[1,88] Sand (Sdy) mice have DTNBP1 homozygote mutations that lead to lack of dysbindin1 protein expression.[88]

Schizophrenia like behavioral alterations as increase in locomotor activity, cognitive deficits, decrease in social interaction, and impairment in PPI and response adaptation to sensory stimulus are demonstrated.[89] Sdy mice can be used to investigate dysbindin's potential pathways: decrease in mGluRI signalization and its association with synaptic plasticity are shown. Heterozygote mutants are also used in researches.[88]

## Combinations of Animal Models

To generate an animal model, combination of multiple animal models that includes several molecular mechanisms is suggested to mimic the complex mechanisms of schizophrenia. Animal models consist of multiple parameters can be more useful in understanding mechanisms of schizophrenia and generating more effective therapeutic strategies.[83,84,90,91] For instance, measuring the adult behavioral alterations in dominant-negative N-terminus human DISC1 (DN-DISC1) expressing transgenic mice is used with the combination of neonatal[83] and prenatal[84] poly(I:C) injection. Deficits in hippocampus dependent fear memory, working memory, object recognition memory, decrease in sociality, aggressive behavior are reported in neonatal poly(I:C) injected DN-DISC1 mice.[83] To determine the efficiency of animal models, behavioral alterations are investigated by using four different experimental groups: *(1)* control group, *(2)* standard genetic group *(3)*, environmental group, *(4)* gene × environment group. Behavioral paradigms are found to be worsening in gene × environment group, and these kind of models are suggested to be critical for animal model's validity.[91]

## Behavioral Parameters and Their Testing Methods

Clinical symptoms and related behavioral parameters in animal models of schizophrenia:

**Positive symptoms:** In animal models hyperlocomation in novel environment and as a response to stress are linked with psychomotor agitation, delusion, hallucination and psychosis which are seen in human subjects. Stereotypic behaviors, hyperlocomation and vulnerability to stress can be investigated by open field test. In animal models hyperactivity can be measured and observed as postural disorders, climbing behavior, stereotypic movements (repeated sniffing, licking, etc.). Instead of catatonia, the term "catalepsy" is used for animals and can be measured by wire grids and bar test.

**Negative symptoms:** Anhedonia, lack of motivation are seen as an increased immobility in animal models and can be measured by forced swimming and sucrose preference tests. To identify mood disorders, elevated plus maze, light/dark box and open area tests can be used. Social withdrawal which is seen in schizophrenic individuals can be measured by social interaction tests in animal models. There are several protocols for social interaction tests: 3-Chamber social interaction and social novelty preference paradigm are commonly used.

**Cognitive disorders:** In animal models schizophrenia-like cognitive deficits can be evaluated by multiple parameters, that consist of working memory, long term memory, spatial learning memory, executive functions by using cognitive tests: Barnes maze, Radial arm maze, Morris water maze, T or Y maze, attentional set shifting task, 5- choice serial-reaction time test, radial arm maze.

## Conclusion

There are multiple animal models of schizophrenia (**Table 1**), targeting specific mechanisms of interest. Recent researches are focused on the animal models that consist of multiple mechanisms and researchers are mentioned the requirement for the combination of multiple models to mimic this spectrum.

Animal models can reflect one or more symptoms of schizophrenia, however this disorder has much more of that. For instance animal model of amphetamine can reflect hyperactivity as a response to striatal dopaminergic activity, however other symptoms like cognitive deficits can not be observed by this animal model.[27] On the other hand in the model of glutamatergic hypofunction, hyperactivity and worsening in positive symptoms are demonstrated.[30] It is shown that prefrontal glutamatergic hypofunction leads not only positive symptoms, but also negative symptoms together with cognitive deficits.[28,29]

In researches it is demonstrated that preference of animals' strain, developmental stages for any administration (like LPS, etc.) or any environmental stressors that will be applied, is critical for the studies' purpose and results.[62] For instance after single or repeated PCP administration, decrease in sociality is reported,[30] whereas social deficits as a response to amphetamine administration is contradictory. Prenatal administration of MAM and poly (I:C) are reported to lead decrease in sociality, however preadolescent administration of MAM also results with social deficits.[74] As a response to neonatal lesion of ventral hippocampus, decrease in social interaction together with the increase in aggression is shown.[14] Repeated administration of PCP is found to induce anhedonia like behavior,

**Table 1**
Results of the measurements (n=55).

| Animal model | Approaches | Clinical symptoms* | Schizophrenia like symptoms | Behavioral task |
|---|---|---|---|---|
| Pharmacological | Serotonergic<br>Dopaminergic<br>Glutamatergic<br>GABAergic | *Positive* | Hiperlocomotion<br>Climbing behavior<br>Stereotypic movements<br>Postural disorders | Open field test<br>Wire grids<br>Bar test<br>PPI |
| Lesion | Hippocampal<br>Thalamic | | | |
| Neurodevelopmental | Poly(I:C)<br>LPS<br>MAM<br>Stress | *Negative* | Social interaction<br>Novelty preference<br>Explorative behavior | 3-Chamber SI & NP<br>Resident intruder<br>Social play<br>Self grooming |
| Genetic | Knock out<br>Transgenic | | | |
| Combined models | Env × Env<br>Env × Gene<br>Gene × Gene<br>Gene × Env × Env | *Cognitive* | Social cognition<br>Memory<br>Executive functioning<br>Attention | Morris water maze<br>Barnes maze<br>Radial arm maze<br>Latent inhibition<br>5-CSRTT<br>Attentional set shifting<br>T/Y maze |

*Type of clinical symptom of schizophrenia depends on the animal model that was chosen and developmental stage of the animal model that was formed. Animal model may include one, two or all of the symptoms. **5-CSRTT:** five card sorting reaction time test; **Env:** environmental; **Gene:** genetic; **LPS:** lipopolysaccharide; **MAM:** methilazoxymethanol asetat; **NP:** novelty preference; **Poly(I:C):** polyriboinosinic-polyricocytidilic acid; **PPI:** pre-pulse inhibition; **SI:** social interaction.

however single administration of PCP is reported to be insufficient.[28,39]

Requirement of generating novel animal models that mimic positive, negative and cognitive disorders together in one model are demonstrated. That kind of models can include multiple molecular mechanisms like the schizophrenia spectrum itself. Thus, by using combination of multiple animal models, all forms of validity can be maintained which can also leads to investigation of better therapeutic strategies and better understanding of schizophrenia's etiopathogenesis.[94] By this point of view, combining the interaction of two or more impact factors, as environment × gene, gene × gene, environment × environment, environment × gene × environment are proposed to be useful for modeling schizophrenia.[6,95,96]

As a result, according to their research hypothesis researchers need to decide which experimental animal model or models to choose. This review aimed to provide a perspective to researchers who will conduct research on the physiopathology or treatment of schizophrenia.

### Conflict of Interest

The authors declare that there are no conflicts of interest.

### Author Contributions

ZMA: study design, systematic search and screening of literature, drafting the manuscript, edits; AA: systematic search and screening of literature, commenting on drafts and the final version of the manuscript; EA: senior author, supervising work, commenting on drafts and final version of the manuscript.

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