

Brain in flames – animal models of psychosis: utility and limitations

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Abstract: The neurodevelopmental hypothesis of schizophrenia posits that schizophrenia is a psychopathological condition resulting from aberrations in neurodevelopmental processes caused by a combination of environmental and genetic factors which proceed long before the onset of clinical symptoms. Many studies discuss an immunological component in the onset and progression of schizophrenia. We here review studies utilizing animal models of schizophrenia with manipulations of genetic, pharmacologic, and immunological origin. We focus on the immunological component to bridge the studies in terms of evaluation and treatment options of negative, positive, and cognitive symptoms. Throughout the review we link certain aspects of each model to the situation in human schizophrenic patients. In conclusion we suggest a combination of existing models to better represent the human situation. Moreover, we emphasize that animal models represent defined single or multiple symptoms or hallmarks of a given disease.

Keywords: inflammation, schizophrenia, microglia, animal models

Introduction

Over the past 20 years, an increasing amount of evidence supports the involvement of inflammatory processes in the pathophysiology, and more recently in the etiology of schizophrenia. High levels of proinflammatory cytokines are found in the blood and in the cerebrospinal fluid of schizophrenia patients.^{1,2} Current treatments with classical or atypical antipsychotics have significantly improved the life quality of affected individuals; however, these medications have often severe side effects, especially when taken over a long period of time.³ Moreover, existing antipsychotic drugs, including clozapine, treat only a subset of the symptoms. Existing drugs have little (or no) efficacy against the cognitive and negative symptoms that are responsible for much disability.⁴⁻⁶ The second-generation antipsychotic drugs have far less tendency than the older drugs to cause serious motor system side effects. But the newer drugs carry their own burden of serious side effects, such as significant weight gain and elevated levels of glucose and lipids.⁷⁻⁹ In clinical trials, minocycline, an anti-inflammatory antibiotic has been used with positive outcomes on the negative and cognitive symptoms.¹⁰⁻¹²

A growing body of literature also supports an increased appreciation for the integrated role of microglia in psychiatric disorders research. Microglia cells are the resident immune competent cells and phagocytes of the brain. Recently, microglia have been identified as potential pathological key player in schizophrenia.¹³ Evaluating postmortem tissue, an increase in reactive microglia density has been reported in distinct subtypes of schizophrenia and different brain regions.¹⁴ Using a ligand for the peripheral benzodiazepine receptor and PET (positron emission tomography) scans, a state of neuro inflammation in vivo in schizophrenic patients have been confirmed.^{15,16}

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Interestingly, microglial activation has also been found in animal models such as the maternal immune activation (MIA) that mimics a plethora of schizophrenia-like symptoms and hallmarks. The use of the antibiotic minocycline in animal models of schizophrenia proved the efficacy of treatments targeting microglia, the primary source of reactive oxygen species and proinflammatory cytokines in the brain, on schizophrenia-like manifestations.^{17–20} Minocycline is also able to decrease glutamate release through the interaction with voltage-dependent Ca^{2+} and Na^{+} channels, and this mode of action may also participate in the outcome of such a treatment in this pathology.²¹

Microglia orchestrates neuroinflammation and thus might become a new target of anti-inflammatory treatments. We here review present animal models in connection to either microglial activation and/or anti-inflammatory treatment outcome to see whether inflammatory processes are bridging the heterogeneous pool of animal models of schizophrenia. In addition, identifying a common inflammatory pattern would rationalize the use of anti-inflammatory drugs as an adjunctive therapeutic option.

When it comes to the development of animal models for a given neuropsychiatric condition, three main validity domains are usually screened to assess the strength of the model in reproducing a given human condition: construct validity, that is how the model was developed in terms of fidelity toward the given natural causes of the disease in humans; face validity, which describes a model's reliability in terms of symptom array and biological changes pertinent to the disease being studied; predictive validity, how well the model responds to present medication used to treat the given disorder in comparison to how human patient responds and therein how valid the model is for testing of new compounds and biological targets for future research.²² The models described in this review will be addressed to as “models of schizophrenia”. However, schizophrenia is a complex human disorder with a yet unclear etiology and pathophysiology; it is therefore not reproducible in animals. The models used up to date all express several of the known neurochemical and behavioral abnormalities related to the human clinical picture of schizophrenia. Every time we refer to “models of schizophrenia” here, we actually address only a distinct manifestation of symptoms, hallmarks, and traits of the human disease, which will be discussed in detail for each model.

Genetic models

Schizophrenia has been linked to many different gene variants and mutations. Nevertheless, it is more probable

that susceptibility genes together with environmental factors influencing the epigenome bring about the neurodevelopmental process leading to a schizophrenic phenotype.^{23–25} In order to study the effect of genes in the pathophysiology of schizophrenia, many different transgenic mouse models have been developed. Because of the large number of schizophrenia-related transgenic mice, we refer here to the works of Miyamoto and Nitta²⁶ and van den Buuse,²⁷ which thoroughly reviewed the vast array of genetic models in this regard. We decided to discuss briefly only one of the most studied group of genetic mouse models of schizophrenia, the DISC1 (disrupted in schizophrenia-1) transgenic mice. The dominant-negative DISC1 mouse has a forebrain-specific expression of dominant-negative truncated DISC1 under the promoter for calcium/calmodulin-dependent kinase II in C57BL/6 mice, which shows the typical cellular and morphological changes observed in patients, such as decreased parvalbumin (PV)-expressing interneurons and enlarged ventricles. As reviewed by van den Buuse,²⁷ though, not all DISC1 transgenes do show a clear-cut schizophrenic phenotype in terms of sensorimotor deficits, hyperlocomotion, and other symptoms. This reflects the fact that genetic changes in one gene are probably not enough to reproduce the complexity of this disease, and the outcome of any DISC1 transgene may depend on the applied truncation or deletion in the exons of the mouse *Disc1* gene.^{27,28} Changes in microglia cell phenotype and function in this mouse would be of particular interest in light of the fact that DISC1 is expressed in microglia cells (and also the other glia cells, astrocytes, and oligodendrocytes) in both humans and rats.²⁹ In summary, the discovery of susceptibility genes has helped scientists to understand which biological pathways are possibly perturbed in schizophrenic endophenotypes. It is therefore conceivable that the same pathways or genes can be altered also in the absence of genetic mutations, eg, by environmental challenges against which cells respond via epigenetic mechanisms to adapt to changed conditions.²³ One example is the changes in reelin expression observed in schizophrenic patients, which prompted scientists to develop reelin KO-mice as a model of schizophrenia, while schizophrenic patients do not present a full deletion of the reelin gene.³⁰ On the other hand, the adult offspring of PolyI:C-challenged pregnant dams (discussed later in the review) presents a naturally diminished reelin expression following MIA, a known environmental risk factor for developing schizophrenia.^{31,32} In the same line, it appears that prenatal MIA is able to also alter the expression of

DISC1 in the hippocampus of adult offspring.³³ A final remark on genetic models is the lack of studies testing antipsychotic treatment on the behavioral features displayed by this pool of models. Future research should aim at validating these models for predictive validity so as to assess the effect of antipsychotics on the genetic component of this disease. Table 1 summarizes the major behavioral deficits found in the DISC1 mouse for a better overview.

Pharmacological models

Pharmacological models are a valuable tool through which specific underlying causes of schizophrenia can be reproduced. One example is the induction of glutamatergic hypoactivity observed in schizophrenic patients by injecting NMDA receptor antagonists into adult mice or rats.^{34–36} The most widely used and explored NMDA receptor antagonists are phencyclidine (PCP), ketamine, and dizocilpine (MK-801). The use of these compounds to reproduce schizophrenic-like symptoms such as psychosis came from the observation that humans administered with or without abusing these compounds develop features of a wide array of symptoms matching many of the positive, negative, and cognitive symptoms of schizophrenia. Moreover, schizophrenic patients administered with NMDA receptor antagonists experience a worsening of symptoms.^{37,38} The strength of this model is the simplicity in producing it and the possibility to quickly test new pharmacological interventions. The downside of the model is that it lacks the neurodevelopmental component that is thought to be the basis for the structural and cytoarchitectural abnormalities that result in the symptomatology of schizophrenia.³⁰ On the cognitive symptoms side, ketamine administration has been reported to induce working memory deficits in the Y-maze, but no impairments were observed in the novel object exploration test.^{39,40} On the negative symptoms side, ketamine increases immobility in the forced swim test, decreases social interaction, and increases anxiety-like behaviors. Signs of positive symptoms include deficits in PPI (prepulse inhibition), PCP/MK-801-induced hyperlocomotion, and disrupted latent inhibition (LI). Comparable to the human clinical situation, atypical antipsychotics are more effective than the typical ones in treating the negative symptoms in this model. Haloperidol (a typical antipsychotic) seems to have no effect on the negative and cognitive symptom manifestations in this model, but it is efficacious against the positive ones, while clozapine (an atypical antipsychotic) has been found to revert both symptomatology, which means that this

model has a good predictive validity to test the efficacy of novel compounds in different symptom domains pertinent to schizophrenia pathology.^{39–43} PCP induced a huge array of cognitive manifestations, namely, deficits in novel object recognition, attentional set shifting, and T-maze delayed alternation and reversal learning. Moreover, it disrupted working and short-term memory. As for the positive-like symptoms, hyperlocomotion, disrupted PPI and LI have been reported along with negative symptoms such as impaired social behavior and enhanced immobility in the forced swim test. Similar to the ketamine model, haloperidol is able to reverse positive but not cognitive or negative symptoms, whereas clozapine showed positive effects on most behavioral abnormalities.^{44–52} The same cognitive, negative, and positive symptoms manifestations have also been found upon administration of MK-801, with very similar outcomes of antipsychotic treatment.^{53–58} In summary, although NMDA antagonism does not represent the perfect construct validity as a model, it shows a very good face validity in terms of schizophrenia-related behavioral abnormalities and an appreciable predictive validity according to the studies testing present antipsychotics.

NMDA antagonism causes acute and reversible miswiring of brain areas involved in schizophrenia, leading to schizophrenia endophenotypes and also indirectly to dopaminergic derangements.^{35,59} Nevertheless, the fact that minocycline pretreatment prevents the induction of positive, negative, and cognitive symptoms associated with NMDA antagonism implies that some form of inflammation may also be involved in this model.⁴⁰ It has been reported that NMDA antagonism can, depending on the dose and number of administrations, damage neurons and lead to apoptosis and inflammatory responses.^{39,45,60} This in turn may lead to microglial activation and cytokine production in a brain region specific fashion. In fact, Zhu et al⁴⁴ reported microglial activation following chronic PCP administration. In this regard, minocycline can be beneficial in two different ways: one is through minocycline's neuroprotective and antiapoptotic action,^{61,62} and the other is the prevention of microglial activation.^{63,64} A study reported necrotic cortical neurons even with a dose of 1 mg/kg of MK-801, with intracellular vacuolization associated with reactive microglia. At higher doses (5 and 10 mg/kg), this response was even more evident.⁶⁵ Monte et al⁴⁰ reported that minocycline treatment was efficient in both preventing and treating the ketamine-induced cognitive, negative, and positive schizophrenia endophenotypes. Zhang et al⁶⁶ showed that minocycline treatment can attenuate MK-801-induced hyperlocomotion and PPI deficits, showing here too that

Table 1 Behavioral abnormalities that match schizophrenia symptoms and their treatment

Model	Positive symptoms	Negative symptoms	Cognitive symptoms	Antipsychotic treatment	MN treatment
DISC1 (129S6/SvEv mouse strain)	Hyperlocomotion, PPI deficits. ²⁷	Increased immobility in the forced swimming and tail suspension test. ²⁷	No deficits in the Y-maze test for working memory. ²⁷	ND	ND
NMDA antagonists	Hyperlocomotion, PPI deficit (not sustained, only upon repeated administration of any of the NMDA antagonists), and latent inhibition deficits. ³⁷⁻⁵⁶	Social withdrawal, forced swimming immobility, increased anxiety-like behavior. ³⁷⁻⁵⁶	Deficits in: novel object recognition, attentional set shifting, and T-maze delayed alternation and reversal learning along with working memory and visuospatial memory deficits in the Morris's water maze. ³⁷⁻⁵⁶	TAP had no effect on the negative symptoms. Haloperidol reverses hyperlocomotion and novel object recognition deficits. AAP reverses all the mentioned deficits. ³⁷⁻⁵⁶	Pretreatment with MN, prior to NMDA-antagonist injection, prevents the outbreak of positive cognitive and negative manifestations. Treatment with MN post NMDA-antagonist administration reverses the latter symptoms. ^{38,46,64-66}
nVHL	PPI deficits, drug-induced hyperlocomotion, increased aggression, higher risk taking behavior, and disrupted latent inhibition. ^{83,85-88}	Social withdrawal enhanced immobility in forced swimming test when administered PCP. ⁸⁴	Deficits in working and spatial memory. ^{85,89,90}	AAP have no effect on social withdrawal but reversed amphetamine-induced hyperlocomotion. ^{86,91} TAP restored increased aggression. ⁸⁸ AAP are able to rescue PPI deficits, but not TAP. ⁸⁸	MN treatment prior to lesion prevented the phenotype outbreak completely. ⁹⁵ Chronic MN treatment starting at P42 rescued all behavioral abnormalities in the LPS induced nVHL. ¹⁰²
PolyI:C	Drug-induced hyperlocomotion, deficits in PPI, and latent inhibition. ^{116,117}	Social withdrawal, decreased sucrose preference, increased immobility in the forced swimming test, and tail suspension test. ^{122,144-146}	Deficits in: working memory, intentional set shifting along with spatial memory deficits, and impaired object-in-place recognition memory. ^{119,145,147,148}	AAP reverses deficits in working memory and latent inhibition, the latter also rescued by TAP. No tests have been carried for screening on the negative symptoms. ^{143,149}	MN restored PPI deficits and social withdrawal. No test has been carried out on other behavioral abnormalities. ^{116,158}
LPS	Psychostimulant-induced hyperactivity, PPI deficits. ^{175,181,182}	Increased despair in the forced swimming test. Decreased social behavior and increased anxiety. ^{176-178,180}	Impaired object-recognition memory and spatial learning. ^{175,179}	TAP and AAP reverse the PPI deficits and chlorpromazine the drug-induced hyperactivity. ^{171,183}	ND

Notes: The table summarizes the main behavioral abnormalities that best match positive, negative, and cognitive symptoms of schizophrenia displayed by the animal models described in this review. Moreover, the table reports the effect of present antipsychotic treatment and anti-inflammatory minocycline intervention on the behavioral manifestations.

Abbreviations: MN, minocycline; DISC1, disrupted in schizophrenia 1; NMDA, N-methyl-D-aspartate; PCP, phenylcyclidine; TAP, typical antipsychotics; AAP, atypical antipsychotics; nVHL, neonatal ventral hippocampal lesion; PPI, prepulse inhibition; P42, postnatal day 42; ND, not determined; LPS, lipopolysaccharide.

treatment after the administration of NMDA antagonists is effective. Finally, Fujita et al⁴⁸ found that minocycline treatment successfully improved the cognitive deficits induced by chronic PCP administration. It is believed that oxidative stress is also part of the pathophysiology of schizophrenia.^{67,68} It is therefore inferable that minocycline acts on other aspects besides the anti-inflammatory action, considering it has scavenger and anti-apoptotic properties and modulating glutamatergic neurotransmission. Table 1 summarizes the major behavioral deficits found in this group of models and the outcome of the various treatments.

Lesion and developmental models

While pharmacological models of schizophrenia were created based on early observations of the neurochemical changes in brains of schizophrenic patients, subsequent models focused more on the theory of a neurodevelopmental hypothesis of schizophrenia. One of the first attempts to reproduce a possible developmental perturbation was the neonatal ventral hippocampal lesion (nVHL) model in rats. In this model, an excitotoxic lesion is provoked in the ventral hippocampus (VH) on postnatal day 7 (P7) by local and bilateral administration of either ibotenic acid (permanent lesion) or tetrodotoxin (temporary inactivation of the VH).^{69,70} The rats show features of positive, negative, and cognitive correlates of symptoms observed in schizophrenia as they reach late puberty. This is more alike the human clinical situation and hypothesis of a neurodevelopmental course of the disease than the pharmacological induced models.⁷¹ In the adult brain, the VH is functionally connected to the striatum, nucleus accumbens (NAc), prefrontal cortex (PFC), and amygdala. The nVHL will result in an aberrant development of connections between the VH and these areas, leading to an aberrant development of the PFC. The latter region will then result to be disinhibited in the adult lesioned rats.^{72–74} This is believed to be the net result of an absent maturation of dopamine (DA) receptor 2 (D₂ receptor)-mediated control of fast-spiking interneurons within this structure, which should occur by the end of puberty. The connections between the aforementioned areas are not fully functional until early adulthood, and it is believed that other areas take over until then, so that any developmental misconnection within these circuits will not appear symptomatically until these areas, in early adulthood, are functionally implemented in the circuitry.^{75,76} Alterations in the dopaminergic system have been reported in the lesion model, mainly in the form of increased DA levels in hippocampus and an increase in its metabolite dihydroxyphenylacetic acid in the

mPFC (medial prefrontal cortex).⁷⁷ Flores et al^{78,79} further reported increased binding of DA receptor 3 (D₃) in limbic subregions and also increased binding of D₁ and D₂ receptors in the striatum, suggestive of dopaminergic hyperactivity in this limbic region. Furthermore, decreased binding of glutamate was found along with alterations of the dopaminergic and glutamatergic neurotransmission in adult rats with postnatal ibotenic acid hippocampal lesion.⁸⁰ Finally, the GABA (γ -aminobutyric acid)ergic interneuron system has also been found to be altered.^{81,82} Changes in the cortical GABAergic interneuron system have been proposed to play a pivotal role in many aspects of the symptomatology of schizophrenia, since aberrations in this system seem to contribute to the cortical miss-wiring and disinhibition observed in these patients; hence, these findings highlight an important similarity of this model to the clinical picture.^{30,83} The nVHL model also displays cytoarchitectural abnormalities congruent with the findings in human studies on schizophrenic patients.³⁰ Flores et al⁸⁴ reported decreased spine density and dendritic length in PFC and NAc medium spiny neurons, in line with the cytoarchitectural abnormalities known in schizophrenia pathology. Also, decreased spinogenesis and neuronal atrophy have been found in the NAc, PFC, and basolateral amygdala of the nVHL rats.⁸⁵ As the lesioned animals reach early adulthood, they show features of negative symptoms in the form of social withdrawal in the sociability test and enhanced immobility in the forced swimming test when administered with PCP.⁸⁶ As signs of positive symptoms, they show amphetamine- and PCP-induced hyperactivity, deficits in sensory and sensorimotor gating, increased aggressive behavior and higher risk-taking behavior in the elevated plus maze, and also disrupted LI.^{85,87–90} The lesioned animals have been found to have deficits in working and spatial memory as measured in the Morris's water maze and T-maze.^{91–93} The lesion model is mainly applied in rats, and recently, Naert et al⁸⁷ carried out a large behavioral screening of this model in C57B1/6J mice. They showed that lesioned mice present with higher spontaneous and amphetamine-induced activity and higher risk-taking behavior in the elevated plus maze. Further, they found deficits in working memory assessed by means of Y-maze (spontaneous alternation) and *t*-test (online storage of information). Working memory in these tasks is dependent on proper PFC function, and these deficits can be related to the known aberrant PFC function in nVHL rats. Nevertheless, the mouse model of nVHL did not display deficits in spatial memory assessed with the Morris's water maze, and also the social behavior was intact. Furthermore, these mice had an intact sensorimotor

gating and LI. These results show that the mouse model differs from the rat model which seem to segregate more symptom domains as compared to the mouse model.⁸⁷ One major advantage of the nVHL mouse model conceived by Naert et al⁸⁷ is that it can be combined with genetic mouse models of schizophrenia endophenotypes in order to encompass more etiological factors. The lesion model has, in general, good face validity, encompassing many symptom domains of schizophrenia with a neurodevelopmental component and a postpubertal manifestation of symptoms. As for the predictive validity, the outcome of antipsychotic testing has been quite mixed. So far, clozapine and haloperidol have been shown to be able to reverse drug-induced hyperactivity.⁹⁴ Becker et al⁹⁰ showed that haloperidol did not restore the deficit in social behavior but decreased the aggressive behavior, which is more related to the positive symptoms of schizophrenia. On the other hand, clozapine did not have any effect on the aggressive behavior but restored a normal social pattern. This is in contrast with the results of another study in which neither clozapine nor risperidone (another atypical antipsychotic) managed to restore a normal social interaction.⁸⁸ Nevertheless, clozapine, risperidone, and olanzapine improve the deficits in sensorimotor gating, while haloperidol has no effect in this positive symptom-like measure, which is not what is expected in terms of treatment efficacy, considering the human clinical picture.⁹⁵ Levin and Christopher⁹⁶ showed that clozapine can worsen the already impaired learning and memory functions in this animal model. The construct validity of this model may be questionable, since schizophrenic patients do not display a direct and profound lesion in the anterior hippocampus, which is the corresponding VH in rodents.⁹⁷ Somehow, this model shares a component with the viral and bacterial developmental models of schizophrenia (discussed later). The immune response in the mother and consequently in the fetal brain may represent the spark of an initial damage directed against neurodevelopmental processes involving, among other regions, the hippocampus. In this regard, these models have one thing in common: microglia activation and ongoing inflammatory processes that may be the basis of the developmental perturbation leading to the postpubertal outbreak of symptoms. In line with the theory implicating developmental neuroinflammation in the pathophysiology of schizophrenia, Drouin-Ouellet et al⁹⁸ analyzed in a recent study the role of microglia cells in the nVHL. They reproduced the postpubertal impairments showed by others in this model, including amphetamine-induced hyperlocomotion, deficits in PPI, impaired social interaction, and spatial

working memory deficits. They could detect microglial activation following ibotenic acid injection from early after the injection until P35, long after ibotenic acid treatment, but not in adulthood (P56); moreover, interleukin-1 beta (IL-1 β) was upregulated in the hippocampus until P14. Interestingly, they observed a selective induction of the metabotropic glutamate receptor 5 only in activated microglia, implicating the glutamatergic system in this immune response. Finally, they showed that treatment with minocycline 12 hours and 30 minutes prior to ibotenic acid administration and for 3 days following surgery prevented microglial activation, the raise in IL-1 β , and the outbreak of the aforementioned symptoms. Interestingly, it also preserved to a certain extent the VH neuronal loss following ibotenic acid injections.⁹⁸ They basically show that microglial activation is largely responsible for the short- and long-term consequences of nVHL with ibotenic acid. Two recent studies confirm these findings, further linking developmental neuroinflammation and microglial activation in the development of a schizophrenic endophenotype in this model. Feleder et al⁷³ combined the lipopolysaccharide (LPS)-induced developmental model (discussed later) with the nVHL model by injecting LPS bilaterally in the VH at P6–P7 in rats. The rationale behind this model is to have a construct that implements a local inflammatory perturbation without any severe and destructive lesion. The authors showed that this kind of LPS challenge does not lead to changes in hippocampal morphology. Then, they demonstrated an increase in IL-1 β and IL-2 in the hippocampus, PFC, and NcA, which was persistent and detectable also in adulthood.⁷³ Interestingly, the same persistent increase in brain cytokines has been found in postmortem tissue from schizophrenic patients, suggesting that if any developmental perturbation occurred in pre- or perinatal stages of their lives, it may have given rise to a persistent increase in proinflammatory mediators.^{99–101} In a recent study, Zhu et al¹⁰² reproduced this model, demonstrating that nVHL challenge with LPS also leads to negative and cognitive manifestations in the adult rats which show deficits in social interaction and novel object recognition. Furthermore, they displayed PPI deficits as a sign of positive symptoms, but no locomotor hyperactivity. Here the authors found a marked increase in microglia density in the VH, thalamus, and cortex of the adult rats injected in the VH with LPS at P7. These rats were treated with minocycline and risperidone either alone or in combination, starting from P42 for 14 consecutive days. The authors report that both compounds, either alone or in combination, managed to rescue all the behavioral abnormalities and also the increase

in microglia density in the aforementioned brain areas.¹⁰² This study shows that minocycline is effective in this model as a treatment and not only as a pretreatment as demonstrated earlier by Feleder et al.⁷³

Both studies demonstrate that a persistent lesion is not required to reproduce a valid schizophrenia endophenotype with neonatal perturbation of the VH, as also demonstrated by the transient VH inactivation model with tetrodotoxin. In conclusion, the latter three studies carried out by Drouin-Ouellet et al,⁹⁸ Feleder et al⁷³ and Zhu et al¹⁰² implicate microglia density and inflammatory processes in the developmental course of this animal model, suggesting that anti-inflammatory intervention can prevent the outbreak of schizophrenia-like symptoms when administered early and also when administered in later pubertal stages. Further studies may address the questions as to why inflammatory processes and microglia cells are activated in regions far from the actual site of lesion/LPS injection, and how this activation can be so persistent. Table 1 summarizes the major behavioral alterations found in this group of models and the outcome of the various treatments.

Maternal immune activation models Prenatal PolyI:C

Epidemiological studies revealed a correlation between certain viral and bacterial infections during pregnancy and the development of schizophrenia in the offspring.¹⁰³ This finding was further strengthened by more recent serological studies conducted on the blood samples collected during pregnancy from mothers of children who developed schizophrenia.^{104,105} Fatemi et al¹⁰⁶ during the early nineties showed that inoculation of human influenza virus in pregnant rodent dams caused the offspring to develop naturally a schizophrenia endophenotype as they reached early adulthood, with changes in various gene expression profiles in the brain, affecting also schizophrenia-related symptoms. The model was further developed using more practical means of evoking MIA by avoiding human pathogens. Instead of actual viruses, the double-stranded synthetic RNA PolyI:C is used nowadays.¹⁰⁷ Double-stranded RNA is a product of viral replication for most kinds of viruses, and it is recognized by toll-like receptor 3 (TLR3) as a viral component, thereby evoking an innate antiviral immune response that includes the production of proinflammatory cytokines such as IL-1 β , IL-6, TNF- α , and type I interferons: INF- α and INF- β .¹⁰⁸ It is believed that the maternal immune response interferes with the correct development of the fetal brain in sensitive time-windows of pregnancy.¹⁰⁹ In rodents, MIA at gestational day (G)15 gives rise to a reliable schizophrenia-like

phenotype in the adult offspring, which will present hallmark structural changes found in schizophrenic patients, including enlarged ventricles and thinning of the hippocampus, which can be blocked by administering atypical antipsychotics during the asymptomatic period in adolescence.^{110–112} Although G15 is a commonly used gestational day, MIA at G9 and G17 also gives rise to schizophrenia endophenotype pathological components.^{113,114} To analyze the exact outcome of prenatal PolyI:C on the many different gestational days used is beyond the scope of this review; nevertheless in the discussion that follows, we will specify the day of MIA when relevant in the context of major phenotypical differences. Additionally, the last trimester of pregnancy in humans corresponds to P2–P6 in rodents, and in this case the animals are injected postnatal and the PolyI:C is given once a day for these 5 consecutive days.¹¹⁵ We decided not to elaborate on the neonatal PolyI:C model since it lacks the maternal immune response–fetal interface that reproduces the reported risk factor in a biologically more congruent way.

The adult offspring of dams challenged with PolyI:C (also referred to here as PolyI:C animals) have been found to present many histopathological and neurochemical hallmarks of schizophrenia in regions implicated in this pathology: limbic DA hyperactivity in striatal slices from adult brain, along with structural histopathological abnormalities in hippocampal CA (cornu ammonis) 1 and CA3 regions (PolyI:C at G15),¹¹⁶ increased DA turnover and decreased D₂-like receptors binding in the striatum (PolyI:C at G12–G17),¹¹⁷ and reduction in reelin- and PV-expressing prefrontal neurons.¹¹³ This is of particular relevance to the PFC disinhibition features also shown by the nVHL model and schizophrenic patients thought to be caused, at least in part, by a malfunctioning GABAergic system.¹¹⁸ Following this line, an increased immunoreactivity for GABA-A receptor in the limbic system¹¹⁹ and reduced expression of glutamic acid decarboxylase 65 and 67 (GAD65/67) isoforms in the PFC and dorsal hippocampus (PolyI:C at G17) were reported in this model, which may contribute to GABAergic dysfunction. GAD is the rate-limiting enzyme in GABA biosynthesis; therefore, we could infer that a challenge in late gestation may decrease GABA levels at least in PFC and dorsal hippocampus.¹²⁰ Soumiya et al¹²¹ also reported decreased GAD67 expression in the upper cortical layers together with decreased synaptophysin immunoreactivity. Winter et al¹²² screened the content of several neurotransmitters in brain regions relevant to schizophrenia (PolyI:C at G9). They found that this offspring showed in adulthood increased DA levels and its major metabolites in

the lateral globus pallidus and PFC and decreased serotonin and its metabolite in the hippocampus, NAc, and lateral globus pallidus. Nevertheless, central glutamate and GABA contents were unchanged. On the other hand, another study reported decreased DA, glutamate, and GABA levels in the PFC and hippocampus (PolyI:C Cat G17).¹²³ These two studies reveal that different neurotransmitters are differentially affected in adult PolyI:C offspring, depending on the timing of MIA. Nevertheless, it has to be stressed that dysfunctions in specific neurotransmitter systems may manifest in the form of altered receptor or receptor subunit expression pattern independently of the gestational day of MIA. For instance, a study conducted by Roenker et al¹²⁴ revealed marked glutamatergic hypofunction in the offspring of dams challenged at G14, which was manifested through decreased NMDA receptor function and elevated extracellular glutamate levels in the PFC. Besides the changes in serotonin and glutamate levels, changes in receptor expression for these two neurotransmitters have also been shown. Holloway et al¹²⁵ demonstrated that MIA with PolyI:C leads to increased expression of the serotonin receptor 5-HT_{2A} and a decrease in metabotropic glutamate receptor 2 in the frontal cortex of adult offspring. Similarly, Dalton et al¹²⁶ showed an increase in 5-HT_{1A} receptor in the brain of adult PolyI:C animals, and the increase was greater if these animals were exposed to a cannabinoid during adolescence. These findings are of particular relevance since serotonergic dysfunctions have been described in this disease and medications acting on the serotonergic system are being screened as a possible new treatment strategy.¹²⁷ Another neurotransmitter system found to be impaired in both human schizophrenic patients and the PolyI:C model is the cholinergic system, with particular focus on the nicotinic receptor system.^{128–131} Particular focus has been put on the $\alpha 7$ nicotinic receptor system, with agonists being tested for their efficacy in bettering cognitive symptoms of schizophrenia.^{130–132} Interestingly, Wu et al found that following MIA with PolyI:C, there was an increase in *Chrna7* gene expression, which is the gene encoding for the nicotinic acetylcholine receptor $\alpha 7$ subunit in the fetal brain.¹³³ This was paralleled by an increase in IL-6 expression. Furthermore, *Chrna7*^{+/-} mice were more susceptible to MIA and displayed a higher increase in fetal brain IL-6.

In addition to the neurochemical changes, cytoarchitectural abnormalities have also been reported in mPFC and dentate gyrus of the hippocampus of PolyI:C animals. These abnormalities consisted of decreased complexity and density of the dendritic spines (PolyI:C at G9.5).¹³⁴ Interestingly, Soumiya et al¹²¹ reported increased presynaptic structure

density in the upper cortical layers and a decreased number of synaptophysin- and GAD67-positive puncta surrounding the neuronal bodies in the upper cortical layers, suggestive of an imbalance between excitatory and inhibitory synapses. Therefore, prenatal PolyI:C may determine aberrant spine-density development in a brain region specific way, and dendritic spine pathology is indeed a feature of the pathophysiology of schizophrenia.¹³⁵ Studies conducted with human material from schizophrenic patients revealed that structural abnormalities are not restricted to dendritic spines but are also reported to include white matter abnormalities in the PFCs and in the tracts linking the PFC to limbic regions, as reviewed by Najjar and Pearlman.¹³⁶ Importantly, changes in white matter structure correlated with microglial activation, changes in GAD65/67 immunoreactivity, and increased mRNA for IL-1 β and IL-6 in different regions of the PFCs. Higher density of neuronal nuclear antigen immunoreactive cells was found at the sites of inflammation as compared to controls, suggesting that correct development and cellular density organization were not properly shepherded.¹³⁶ White matter pathology in schizophrenic patients and in PolyI:C mice has also been shown in vivo using diffusion tensor imaging, which is a particular kind of magnetic resonance imaging often used to analyze white matter structural integrity.¹³⁷ Using this method, Alvarado-Alanis et al¹³⁸ and Li et al¹³⁹ found white matter abnormalities in frontostriatal–limbic tracts in the adult PolyI:C mice, reflecting the human abnormalities especially in treatment-naïve first-episode patients.

Finally, it has been shown that maternal PolyI:C challenge at G15 impairs neuronal synchrony between the mPFC and the hippocampus, and this is a major basis for thought disorder and for deficits in PPI.^{140,141}

The adult offspring of PolyI:C-challenged dams presents with correlates of phenomena pertaining to the positive, negative, and cognitive symptoms of schizophrenia. As signs of positive symptoms, PolyI:C mice display psychostimulant-induced hyperlocomotion, deficits in PPI, and LI.^{116,117} Concerning the negative symptoms, they have been shown to have deficits in social behavior, decreased sucrose preference (anhedonia), and also increased behavioral despair in the forced swimming test.^{123,142,143} Zhang and van Praag¹⁴⁴ found, moreover, increased immobility in the tail suspension test. The offspring of PolyI:C mice show compromised working memory and also intentional set shifting deficits along with spatial memory deficits in the Morris's water maze and object-in-place recognition memory deficits.^{120,145–147} Furthermore, impairments in hippocampal

dependent behavioral tests along with decreased hippocampal neurogenesis have also been reported.¹⁴⁴ Chronic clozapine treatment has been shown to revert impairments in working memory.¹⁴⁸ Zuckerman et al¹¹⁶ found that both clozapine and haloperidol could revert the deficits in LI. Moreover, as reviewed by Dickerson and Bilkey,¹⁴⁰ clozapine treatment could efficiently restore the deficits in PPI and the aberrant neural synchrony between the mPFC and the hippocampus. So far, no study has been carried out to test the present antipsychotic treatment on the negative symptoms part in this MIA model. Behavioral outcomes with PolyI:C prenatal exposure seem to be highly dependent on the dam's individual immune response. Missault et al¹⁴⁹ discovered that pregnant dams that lost weight after PolyI:C administration had the highest serum TNF- α levels, and the offspring displayed the most severe behavioral deficits. On the other hand, the offspring of dams that gained weight and showed a minor rise in TNF- α after PolyI:C showed a more blunted phenotype. This may account for some variability in reporting certain behavioral deficits in this model, and perhaps, it may even be a decisive factor for the penetrance of this risk factor in humans, given that the immune response of pregnant mothers can vary. After PolyI:C injection in the mother, there is a rise in several proinflammatory cytokines and chemokines in the fetal brain.^{150–152} Microglia expresses the TLR3 to which PolyI:C binds, evoking an innate immune response in both rodents and humans, and besides being able to respond to PolyI:C, they are able to sense changes in cytokine levels.¹⁵³ It is known that microglia during fetal development are controlling and guiding neural precursor cells and axonal and dendritic outgrowth by active phagocytosis.^{154,155} They may, therefore, not be ready for an immune challenge yet. The interesting part is that this early activation seems to permanently change microglial phenotype throughout development, as highlighted by a study in which they showed that following PolyI:C prenatal challenge in regions relevant to schizophrenia, cytokines follow a precise expression pattern from P0–P60 and that MIA with PolyI:C disrupts this program.¹⁵⁶ In this regard, IL6 seems to play a major role in the PolyI:C-induced neurodevelopmental derangement.^{142,151} In the absence of IL-6 (IL-6 knockout mice), the phenotype will not develop despite PolyI:C injection.¹⁴² There are evidences that microglia cells persist in an activated phenotype in the adult PolyI:C animal.^{18,19,157,158} This is in line with in vivo PET scan studies conducted on schizophrenic patients using the binding of a ligand to the peripheral benzodiazepine receptor as a measure for neuroinflammation. Activated microglia increase the expression of the peripheral benzodiazepine

receptor. Thus, the measure of the ligand binding in the brain can be used as an in vivo correlate for microglia activation.^{15,16} As we reported earlier, anti-inflammatory treatment with minocycline has been proven efficacious in human studies, especially in improving cognitive and negative symptoms, which are the most resistant to present treatment.^{159,160} Minocycline has been applied in some studies to PolyI:C animals with promising preclinical results. Our group tested it successfully in a chronic treatment regimen, whereupon we showed a restoration of the deficits in PPI accompanied by decreased mRNA levels of IL-1 β and TNF- α in microglia cells freshly isolated from the hippocampi of PolyI:C rats. This was accompanied by a restored adult hippocampal neurogenesis.¹⁹ Meyer et al¹⁴⁸ also showed that PolyI:C animals have decreased hippocampal neurogenesis, but clozapine treatment did not ameliorate the decrease, while we proved that minocycline did while decreasing microglial proinflammatory cytokine production. Van den Eynde et al¹⁵⁷ observed that PolyI:C offspring showed increased microglial density in the chronic stage of the model (P180), accompanied by hypolocomotion and social defeat. Minocycline intervention restored social defeat.

A final remark on this model regards its phenotypical similarities to autism spectrum disorders. As reviewed by Brown¹⁰³ prenatal immune activation can also confer risk for developing autism spectrum disorders. In fact, some components of the negative and cognitive symptom scales are overlapping with aspects of the autism spectrum.^{103,161} Likewise, behavioral abnormalities in the MIA models, for instance, increased stereotyped behaviors (eg, grooming), increased anxiety, and social defeat, along with several cognitive dysfunctions and PPI deficits, are considered also as correlates of phenomena observed in autism.^{161,162} As we discussed earlier, microglial activation following MIA may participate in the aberrant formation of brain systems, and they are also a component of the adult aspect of the disease in schizophrenic patients. Given that autism and schizophrenia share an environmental risk factor and some symptoms, they may even have in common persistent microglial activation.^{163–165} Table 1 summarizes the major behavioral deficits found in this model of schizophrenia and the outcome of the various treatments.

Prenatal LPS

Since bacterial infections during pregnancy have also been linked to the development of schizophrenia in the offspring, some groups use LPS as a “primary hit” during the same time windows.¹⁰⁴ LPS binds to TLR4 in immune cells, thereby inducing a systemic innate immune response similar to

PolyI:C in terms of proinflammatory cytokine release such as IL-1 β , IL-6, and TNF- α , although lacking the interferon-like response typical of viral immune challenge.¹⁰⁸ It is difficult to directly compare the PolyI:C- and the LPS-exposed offspring since the studies conducted vary significantly and are inconsistent in the time point, the dose, and the amount of PolyI:C and LPS injections. Meyer¹⁰⁷ recently compared in a direct way the general behavioral outcome of, among others, LPS and PolyI:C MIA models, and we refer to this review for a direct LPS vs PolyI:C comparison. As we will discuss, the phenotype of the adult offspring of dams challenged with LPS (also referred to as LPS animals) will present many similarities with the PolyI:C offspring, with several features matching a schizophrenic endophenotype.

Baharnoori et al¹⁶⁶ and Santana et al¹⁶⁷ demonstrated that LPS offspring display decreased D₂ receptor binding potential in PV-positive GABAergic interneurons in the PFC. This is comparable to the lack of maturation in D₂ receptor-mediated control of the GABAergic interneuron system in the PFC found in the nVHL model.^{73,75} Moreover, these findings are conformant with what Meyer¹⁰⁷ found in the PolyI:C model. Baharnoori et al¹⁶⁶ also showed altered DA transporter binding in limbic regions, a sign of dopaminergic malfunction. Further evidence of anomalies in the DAergic system in this model comes from Borrell et al¹⁶⁸ who found increased tyrosine hydroxylase immunoreactivity in the NcA of these animals, along with the findings of increased DA levels in the NcA and increased dihydroxyphenylacetic acid in the striatum by Romero et al.¹⁶⁹ In this study, the authors also report increased immunoreactivity for synaptophysin in the frontal cortex and hippocampus, a clear sign of synaptic reorganization in these two areas in adult offspring from LPS challenged dams.¹⁶⁹ Further cytoarchitectural abnormalities are found in the pyramidal neurons in the mPFC and CA1 region of the hippocampus.¹⁷⁰ Dendritic arbor was found significantly decreased in both the regions, at different postnatal time points, including adulthood, and as we mentioned earlier, dendritic spine pathology is a recognized feature in schizophrenic patients.¹⁷⁰ Golan et al¹⁷¹ reported an increase in hippocampal pyramidal and granular cells with a shrinkage in cellular size, restricted to the pyramidal cells, further highlighting the sensitivity of the hippocampus to prenatal inflammatory insult. This model also presents with aberrations in the GABAergic system as it is the case in schizophrenic patients, the nVHL and the PolyI:C models. Basta-Kaim et al¹⁷² recently showed diminished total number of PV- and GAD67-positive neurons in the mPFC of adult LPS female animals, while the same changes occurred in

the hippocampus of the males, although a decrease in PV-positive axon terminals of GABAergic cells was reported in the mPFC of both sexes. On the other hand, Wischhof et al¹⁷³ showed a decrease in PV-positive neurons in the mPFC, hippocampus, and entorhinal cortex in both adult male and female LPS animals. The difference between the two studies may be due to the fact that Basta-Kaim et al¹⁷² administered LPS every second day, starting from G9 until delivery, whereas Wischhof et al¹⁷³ administered two injections at G15 and G16. Furthermore, Li et al,¹³⁹ Wischhof et al,¹⁷³ and Alvarado-Alanis et al¹³⁸ also show impaired myelination in cortical and limbic regions in these mice, reflecting the abnormalities previously reported in the PolyI:C model and in schizophrenic patients.

LPS mice also display several schizophrenia endophenotype-related behaviors which show up in early adulthood. Adult LPS mice show negative-like symptoms in the form of increased sensitivity to stress and increased despair in the forced swimming test, and also decreased social behavior and increased anxiety in the elevated plus maze test (Table 1).^{174–177} Wischhof et al¹⁷³ demonstrated the presence of cognitive deficits in the form of impaired object recognition memory and also PPI deficits. Impaired spatial learning in the Morris's water maze was also shown by Chlodzinska et al.¹⁷⁸ Moreover, besides the PPI deficits, another sign of positive symptoms found in the LPS rodent model is the psychostimulant-induced hyperlocomotion, as shown by Basta-Kaim et al¹⁷⁹ in a study in which they also demonstrate a hyperactive hypothalamic–pituitary–adrenal axis, which might be the reason for the altered stress responsiveness observed in this model by Lin et al.¹⁸⁰ When it comes to the predictive validity of this model, only one study has shown that haloperidol treatment reverts the deficit in PPI, as did clozapine but not chlorpromazine, which decreased the amphetamine-induced hyperlocomotion, however.^{169,181} The LPS model of schizophrenia has till date not been thoroughly investigated in terms of inflammatory processes and microglial activation. We could find two studies addressing this topic, both carried out by Graciarena et al.^{182,183} These studies showed that prenatal LPS leads to activated microglia cells in the hippocampus of adult offspring, and this is accompanied by a decrease in transforming growth factor beta 1, lower adult hippocampal neurogenesis (in line with what we reported in the PolyI:C model), and deficits in the novel object recognition test.^{182–184} Furthermore, Cunningham et al¹⁵⁵ demonstrated that microglia cells from the embryonic day 15 onward play a fundamental role in regulating the number of neuronal precursor cell (NPC) pool that are meant

to build the cerebral cortex by active phagocytosis of the NPCs. LPS challenge in pregnant dams between G15 and G16 can significantly decrease the number of neural precursor cells possibly due to a significantly increased proportion of inducible nitric oxide synthase-positive microglia cells in the subventricular zone. These effects were ablated by anti-inflammatory treatment with doxycycline, a tetracycline, and a close derivative of minocycline.¹⁵⁵ This particular function of microglia has been shown to be important also in the adult regulation of neurogenesis in the hippocampus. Therefore, it is not surprising to find decreased neurogenesis in the adult offspring of PolyI:C- and LPS-treated dams, and also that treatment with minocycline improves neurogenesis, as we demonstrated.^{184–186} For an overview of the major behavioral deficits found in this model of schizophrenia and the outcome of the various treatments we refer to Table 1.

Conclusion

Overall, the construct validity of the MIA models with LPS and PolyI:C show great reliability, being based on human epidemiological observations. Moreover, there is no manipulation in terms of lesions, administration of psychotropic drugs, or knockout/in of genes. On the contrary, they show a natural postpubertal outbreak of symptoms as observed in humans, suggestive of a neurodevelopmental course. As reviewed by Meyer,¹⁰⁷ the PolyI:C model seems to have the widest array of schizophrenia-like behavioral aberrations. Moreover, as far as we could find in the literature, it has been more thoroughly characterized as compared to the LPS model. As for the face validity, both MIA models show structural, neurochemical, and behavioral abnormalities, which share a lot of common hallmarks with the human clinical picture. A growing body of evidence is associating schizophrenia to microglial activation and inflammation, with promising outcome of anti-inflammatory intervention. The studies carried out so far in the PolyI:C model show that microglia activation is also a feature of this model, with the neurodevelopmental component and a proven efficacy of minocycline at least in the aspects screened up to date. One major limitation of this model is the fact that full organogenesis, including the brain, is completed after birth, while in humans it occurs in utero, and it is difficult to match the right trimester of rodents and humans.³² To our knowledge, the best way of getting around this issue has been proposed by Ratnayake et al³² by utilizing the spiny mouse strain, which has a complete organogenesis at birth with a gestational term of 39 days. The outcome of maternal PolyI:C exposure seems to be quite the same as for the other mice strain utilized for the purpose, including

microglia cell reactivity. Nevertheless, as we mentioned earlier, some groups prefer to inject PolyI:C in early post-natal days (P2–P6) to specifically target the corresponding early second trimester of pregnancy in humans.¹⁸⁶ This is normally done in mouse strains that do not reach complete organogenesis at birth. As adults, the treated mice will display behavioral and neurochemical changes similar to those of the prenatally challenged animals, and it is therefore a model worth deeper characterization.¹⁸⁶ However, these mice are directly exposed to PolyI:C and therefore lack the interface between MIA, placental and amniotic fluid alterations in cytokine expression, and, consequently, fetal brain changes in cytokine production that characterize the risk factor per se.^{187,188} A schizophrenic phenotype is most probably the result of susceptibility genes and environmental factors that disturb normal brain development and wiring.¹⁸⁹ Therefore, studying this interaction would probably be a very good way of completing our understanding of this pathology and also for the development of novel pharmaceutical targets, eg, targeting more specifically microglia activation. Accordingly, in recent times, several groups started to combine the known etiological factors in animal models. One such example is the MIA with PolyI:C in DISC1 transgenic mice. Lipina et al¹⁹⁰ used a heterozygous mutant for a point mutation in the *Disc1* gene, which shows mild behavioral abnormalities reminiscent of schizophrenia and induced MIA at G9 with PolyI:C. The resultant adult offspring presented with intense deficits in social interaction, PPI, and LI, accompanied by reduced spatial object recognition, all stronger than those observed in the mutant mouse alone. Interestingly, the development of these phenotype could be blocked by coadministration of anti-IL-6 antibodies together with PolyI:C, highlighting the importance of inflammatory processes also in the gene–environment interaction, as also shown by Lipina et al¹⁹⁰ and Smith et al¹⁴² in the PolyI:C model alone. DISC1 is also found in adult glia cells, although its function there is not yet known; this model provides a good tool to screen how these cells are affected by an aberrant DISC1 production. Other combinatorial strategies include the “two hit models”, where, eg, a first immunological hit (MIA) is combined with a peri- or a postpubertal second hit, usually involving physical or mental stress. This is based on the observation that the outbreak of schizophrenic symptoms often follows exposure to strong emotional stress that functions as a second hit in predisposed individuals primed earlier in life by either genes or an environmental factor. These studies reveal that the second hit with stress enhances the outbreak of schizophrenia-like symptoms in terms of stress responses,

neurochemical and behavioral changes.^{191–193} These are initial promising studies that pave the way for future research into following models that reproduces more than one etiological factor of schizophrenia, and they may represent the future tool to explore this pathology more in depth. Moreover, animal models will provide us with defined representations of single or multiple symptoms or hallmarks of a given disease. Thus, in the future, we might rather use a combination of different models to mimic a human pathology like schizophrenia in its complexity.

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Disclosure

The authors report no conflicts of interest in this work.

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