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Review

Animal Models of Relevance to the Schizophrenia Prodrome

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ABSTRACT

Patients with schizophrenia often undergo a prodromal phase prior to diagnosis. Given the absence of significant therapeutic improvements, attention has recently shifted to the possibility of intervention during this early stage to delay or diminish symptom severity or even prevent onset. Unfortunately, the 20 or so trials of intervention to date have not been successful in either preventing onset or improving long-term outcomes in subjects who are at risk of developing schizophrenia. One reason may be that the biological pathways an effective intervention must target are not static. The prodromal phase typically occurs during late adolescence, a period during which a number of brain circuits and structures are still maturing. We propose that developing a deeper understanding of which circuits/processes and brain structures are still maturing at this time and which processes drive the transition to schizophrenia will take us a step closer to developing better prophylactic interventions. Fortunately, such knowledge is now emerging from clinical studies, complemented by work in animal models. Our task here is to describe what would constitute an appropriate animal model to study and to potentially intervene in such processes. Such a model would allow invasive analysis of the cellular and molecular substrates of the progressive neurobiology that defines the schizophrenia prodrome and hopefully offer valuable insights into potential prophylactic targets.

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The existence of a prediagnosis prodromal phase of schizophrenia has been clarified in the past few decades (1). While the term "prodromal" is applied retrospectively to those patients who ultimately transition to schizophrenia, clinical tools can identify people who are likely to be in this prodromal phase. These tools include assessing the expression of attenuated schizophrenia symptoms, which, when meeting threshold criteria, is termed an at-risk mental state (ARMS), and/or identifying a family history of schizophrenia coupled with functional decline (2,3). ARMS subjects are commonly identified during late adolescence/early adulthood (3), and approximately 15% to 30% will transition to schizophrenia (4). Unfortunately, many patients with schizophrenia experience long-term disability despite treatment with antipsychotics (5,6), which also cause severe metabolic and movement-related side effects (7,8). An intervention that prevents the transition from prodrome to schizophrenia would represent a significant major step in treating this debilitating disorder.

WHY DO WE NEED ANIMAL MODELS OF RELEVANCE TO THE SCHIZOPHRENIA PRODROME?

Antipsychotics are generally effective at reducing psychosis symptoms in a large fraction of patients with an established diagnosis of schizophrenia (9). These agents have also been trialed in at-risk subjects; however, they have been ultimately unsuccessful in preventing disease onset (10–13). One reason for this failure may be that the biological targets for an intervention therapy—intended to divert a malleable, still-maturing system away from dysfunction—are quite distinct from those designed to ameliorate chronic symptoms in schizophrenia (Figure 1). Animal models of schizophrenia that permit the assessment of disease course are now required to understand where normal trajectories in brain maturation diverge from a healthy pathway toward dysfunction. Animal models of the prodrome also allow rapid trials of novel prophylactic therapies. Such trials are especially difficult in ARMS subjects, given the low transition rate (15%–30%).

WHAT CONSTITUTES AN ANIMAL MODEL WITH RELEVANCE TO THE PRODROME?

Kapur and colleagues (14) posited that an animal model for the schizophrenia prodrome should 1) "be encompassed within a model that has the capacity to show the full-blown phenotype analogous to schizophrenia, 2) embody progression over time, 3) show gradation of pathophysiology rather than an all/none phenotypic outcome, and 4) lead to abnormalities that are analogous to the full-blown phenotype if there are no interventions."

While schizophrenia-relevant symptoms emerge in adults (15), more recent evidence suggests that behavioral and neurobiological dysfunction show a progressive onset that begins in late adolescence. Therefore, we suggest an additional criterion to those above; in a model of the prodrome, animals must also be assessed during the adolescent period, at which point attenuated schizophrenia-relevant phenotypes may be evident.

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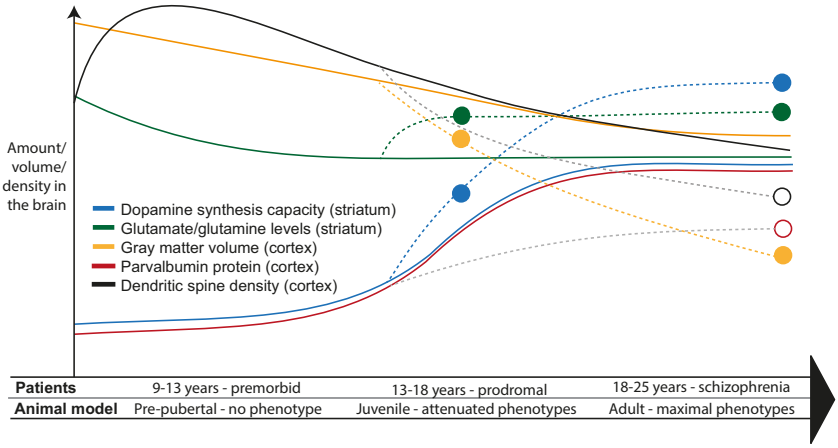

Figure 1. Maturation of schizophrenia-relevant neurobiological systems. Solid lines indicate normal patterns of maturation in healthy people. Dotted lines indicate findings in patients with schizophrenia. Solid circles indicate that evidence has been acquired in prodromal patients or patients with chronic schizophrenia. Open circles indicate data that are only acquired in patients with chronic schizophrenia, and therefore, prodromal dysfunction is only hypothesized.

Can Animal Models Be Used to Recapitulate the Neurodevelopmental Progression From the Prodrome to Schizophrenia?

As the human brain matures during adolescence, it undergoes volumetric changes (16–19), continued synaptic maturation (20–22), and changes in functional connectivity between brain regions (23). There are also changes in key neurotransmitters, including dopamine (24–26), glutamate (27), and GABA (gamma-aminobutyric acid) (28,29), as well as their receptors. Steroids such as testosterone and estrogen also modulate adolescent brain development, leading to sexually dimorphic patterns of maturation (30). Rodents undergo a similar trajectory of behavioral, neurochemical, and hormonal maturation (31). Although the timing varies between species, sex, and strain, adolescence in rodents spans approximately postnatal day (P) 28 to P56 (32). This conserved developmental trajectory allows the use of rodents to map the adolescent onset of phenotypes from early neurodevelopmental exposures. Although it is impossible to model the complexity of schizophrenia in an animal, it is possible to assess analogous behavioral phenotypes (33).

Current models of the prodrome can be classified into two main groups. The first group of models are those designed specifically to replicate aspects of the neurobiology of the prodrome (specifically aspects of dopaminergic dysfunction). The second group of models are those based on environmental risk factors or gene variants, where adult phenotypes are already well established. These models have been reexamined within rodent adolescence (P28–P56) to assess the progressive onset of behavioral or neurobiological phenotypes (Table S1). We have extracted the key trends evident in these models and highlighted their relevance to findings in clinical populations.

NEUROBIOLOGICAL ABNORMALITIES IN THE PRODROME

Dopamine

Positron emission tomography neuroimaging studies indicate that patients with chronic schizophrenia have a robust increase in dopamine synthesis capacity in the dorsal striatum (34). Striatal hyperdopaminergia is also evident in at-risk patients who progress to schizophrenia (35–38). Longitudinal positron emission tomography imaging indicates that the magnitude of this dopaminergic abnormality increases as symptoms worsen (39), suggesting that this may be a target for pharmacological intervention. The dopaminergic system also undergoes substantial refinement during the adolescent period; levels of dopamine in the brain increase from infancy to adulthood (26), and levels of dopamine receptors appear to peak at mid-adolescence, before decreasing to adult levels (24,25).

Models Designed to Recapitulate the Dopaminergic Abnormalities of the Prodrome. Amphetamine-sensitization models—in which adult animals are delivered escalating doses of amphetamine, then challenged with amphetamine after withdrawal (14)—result in schizophrenia-relevant hyperdopaminergia (40). Tenn *et al.* (14) adapted this model by replacing amphetamine with saline for some injections (inducing only partial sensitization) to reflect a reduced or prodromal level of dopaminergic dysfunction. This model was designed to replicate the attenuated phenotypic profile rather than the neurobiology of the prodrome because amphetamine elevates striatal dopamine to nonphysiological levels. Interestingly, this model predates the findings of increased dopamine synthesis capacity in prodromal patients by some years.

The dopamine D_2 receptor (D_2R) overexpression model of schizophrenia increases D_2R density transgenically in the striatum (41). Although increased D_2R density is not a major finding in schizophrenia (42), this model replicates increased striatal dopaminergic transmission, which is a key component of the schizophrenia prodrome. Adult D_2R overexpression mice display a number of cognitive- and negative-symptom phenotypes (43), and juvenile D_2R overexpression animals show deficits in social interaction (44). These findings lend support to the theory that cortical dysfunction (which contributes to the cognitive and negative symptoms of schizophrenia) may be secondary to striatal hyperdopaminergia (45).

Enhanced Dopamine in Prodromal Schizophrenia (EDiPS) is a model described by Petty *et al.* (46) that uses a transgenic construct to increase dopamine-synthesizing enzymes in the

dorsal striatum of rats from adolescence (P35). Adult animals show increased amphetamine-induced dopamine release in this region, reflecting the presynaptic dorsal striatal dopaminergic abnormality evident in the prodrome. Adult EDiPS animals also display increased amphetamine-induced hyperlocomotion and prepulse inhibition (PPI) deficits (46). When assessed longitudinally from juvenile to adult ages, these behaviors show a progressive onset, similar to the progression of symptoms seen in prodromal patients (47). This model can now be used to clarify the downstream effects of increased dopamine synthesis and release during adolescence.

Dopaminergic Dysfunction in Animal Models of Schizophrenia. Studies using maternal immune activation (MIA) (48–52), neonatal brain lesion of the entorhinal cortex or medial prefrontal cortex (mPFC) (53–56), pre- and postnatal stress (57,58), genetic manipulation (59), and the gestational MAM (methylazoxymethanol acetate) model (60) have assessed dopaminergic dysfunction in both adult and juvenile animals. In the dorsal striatum, MIA-exposed and neonatally lesioned animals showed increased extracellular levels of dopamine at baseline and following potassium-induced dopamine release, as well as an increased number of dopamine D_1- and D_2-like receptors as adults, but not as juveniles (compared with age-matched control animals) (48,49,53,54). In juvenile MIA-exposed, neonatally lesioned, and prenatally stressed animals, findings in the nucleus accumbens (NAc) were variable, with levels of extracellular and tissue homogenate dopamine increased (50,57), decreased (51,55), or unchanged (53). However, when assessed as adults, baseline (tissue homogenate) and amphetamine-induced dopamine levels in the NAc were almost universally increased compared with adult control animals (50,51,53,57). Levels of the dopamine transporter were downregulated in the NAc in juvenile MIA-exposed and neonatally lesioned animals but returned to control levels by adulthood (48,52,54). As in the dorsal striatum, D_1 and D_2 receptors in the NAc were typically unaltered compared with control animals in MIA-exposed and neonatally lesioned animals as juveniles but were increased in adulthood compared with control adults (48,54). In the PFC, dopamine levels in neonatally lesioned and genetically manipulated animals were unaltered in juveniles (compared with age-matched control animals). However, in contrast to striatal findings, PFC dopamine was decreased in adult animals from these models (53,59). One exception was the PFC lesion model, for which dopamine levels were decreased at P30, P45, and P60, relative to age-matched unlesioned control animals (55,56). Finally, in the MAM model, dopamine neuron activity in the ventral tegmental area was normal in juvenile animals (compared with age-matched control animals), but increased in adulthood (60). In contrast, stress during adolescence (from P31 to P40) induced an increase in ventral tegmental area dopamine neuron activity when assessed 1 to 2 weeks later, whereas stress during adulthood resulted in decreased dopamine neuron activity in the ventral tegmental area (58). Overall, most dopaminergic factors were normal in juveniles but were abnormal (generally increased) by adulthood compared with age-matched control animals.

Glutamate/Glutamine

Proton magnetic resonance spectroscopy (^{1}H-MRS) studies have revealed elevated levels of glutamate and/or its precursor glutamine in the striatum and medial temporal lobe of patients with schizophrenia (61), although these findings may be affected by treatment and/or disease course (62). ARMS subjects who later transition to schizophrenia show elevated levels of glutamate in the dorsal striatum (63,64) and hippocampus (65) [but not the medial temporal lobe (66)] in comparison with ARMS subjects who do not transition and with healthy control subjects. As far as we are aware, no study has performed ^{1}H-MRS longitudinally in ARMS patients. ^{1}H-MRS studies in healthy people indicate that levels of glutamate are stable through adolescence in the basal ganglia (67) but decline in cortical areas during this time (27).

Glutamatergic abnormalities have also been examined in preclinical models of the prodrome. A study using longitudinal ^{1}H-MRS found no difference in levels of glutamate or glutamax (glutamate+glutamine) between MIA-exposed offspring and control animals in the PFC at any age (68). Upregulation of NMDA receptor subunits was seen in the PFC of adult but not juvenile MIA-exposed animals compared with age-matched control animals (69). In addition, increased NMDA-mediated excitation of pyramidal cells was seen in the PFC of adult, but not juvenile, neonatally lesioned animals, compared with unlesioned, age-matched control animals (70). These findings may reflect an attempt at compensatory upregulation of NMDA signaling, which would be consistent with the hypofunction of NMDA receptors seen in patients with schizophrenia (71). Given the region-specific abnormalities seen in clinical studies, we also await analysis of striatal (rather than cortical) glutamate in these models.

Structural Abnormalities

Longitudinal studies indicate that as prodromal subjects transition to schizophrenia, normal structural changes (decreasing cortical gray matter volume, increasing lateral ventricle volume) are evident earlier and progress more rapidly compared with healthy control subjects and compared with those at-risk subjects who did not transition (72,73). There is also evidence that the normal trajectory of white matter maturation is disrupted in ARMS subjects who later transition, including an accelerated reduction in corpus callosum volume during early adulthood, compared with healthy control subjects (74). Finally, there is evidence that hypermetabolism in the hippocampus may contribute to structural changes in this region in ARMS subjects (75), indicating a potential link between brain activity and structural abnormalities.

Progressive alterations in brain structure are also evident in preclinical models of the prodrome. Two studies in MIA-exposed animals used longitudinal magnetic resonance imaging to assess the progression of brain structural abnormalities. The first study found that juvenile MIA-exposed animals showed reduced cortical gray matter volumes and enlarged ventricles compared with juvenile control animals and that these abnormalities worsened as animals matured (76). However, a more recent study found that while early trajectories of structural development were altered between P38 and

P60, in MIA-exposed mice, many of these volumetric abnormalities normalized by P90 (77). Importantly, this second study also found an association between volumetric abnormalities and behavioral phenotypes in juvenile MIA-exposed animals, which was absent in adulthood. Decreased white matter volumes have also been shown in juvenile MIA-exposed and genetically manipulated animals, and these animals showed accelerated white matter volume reduction (compared with maturing control animals) (78,79). Therefore, these models can reflect certain progressive volumetric changes evident in prodromal patients.

NEUROCHEMICAL ABNORMALITIES IN PATIENTS WITH CHRONIC SCHIZOPHRENIA THAT MAY BE RELEVANT TO THE PRODROME

Some cellular and molecular factors can only be assessed in postmortem tissue, which to date has come mainly from patients with chronic schizophrenia. However, evidence acquired from healthy people (and healthy rodents) indicates that neurotransmitter systems undergo profound remodeling during adolescence. Therefore, the dysfunction apparent in patients with chronic schizophrenia may have its origins during the prodrome.

Parvalbumin Interneurons

Parvalbumin (PV) interneurons are an important class of GABAergic (gamma-aminobutyric acidergic) interneurons that regulate cortical function. Decreased PV interneuron density is one of the most well-replicated cortical cellular abnormalities in patients with schizophrenia (28,80). Because the number of PV interneurons increases in early postnatal life (28) and PV interneuron firing properties continue to mature into adulthood (81), this cellular abnormality may originate in the prodrome. Animal models have been used to explore this possibility. The number of PV^+ cells and the abundance of PV protein was found to be decreased in the hippocampus and PFC at both juvenile and adult ages (relative to age-matched control animals) in the MAM (82,83), prenatal MK-801 (dizocilpine) (84,85), and neonatal MK-801 (86) models. In addition, a stress model found that the number of PV^+ cells was unchanged immediately following 9 days of adolescent stress exposure (at P41) but was decreased from P51 into adulthood (P75) (58). In contrast, when adult animals were exposed to the same stress paradigm, no decrease in PV^+ cells was seen. Given the critical role of these interneurons for normal brain development, early changes in the PV system may contribute to downstream neurobiological and structural abnormalities evident in the prodrome. Interestingly, in two genetic models of schizophrenia—*Disc1* knockdown (59) and a model of *22q.11.2* deletion (87)—the number of PV^+ cells was decreased in adult but not juvenile animals (relative to age-matched control animals) in the mPFC and hippocampus, respectively. Whether these changes in PV expression reflect changes in PV firing properties is unknown.

Synaptic Pruning/Dendritic Morphology

A number of studies (primarily in postmortem tissue) indicate that patients with schizophrenia show decreased presynaptic and/or dendritic spine density in cortical areas (88–90). Pruning of synapses and maturation of dendritic morphology continues in the cortex during adolescence and into adulthood (21), and altered spine density or morphology may therefore be evident in the prodrome. In preclinical models, disruption of the normal maturation of synaptic density and dendritic morphology was seen in juvenile and adult MIA-exposed offspring (91) and animals exposed to prenatal stress (92,93). In a genetic model of schizophrenia in which *C4A*, a complement gene, was constitutively overexpressed, synaptic density in the mPFC was decreased in adult animals (P60), but not in juveniles (P40) compared with age-matched control animals (94). Therefore, changes in synaptic density and/or spine morphology may be evident even prior to schizophrenia diagnosis.

IMMUNE RESPONSE

Mounting evidence suggests that elevated neuroinflammation is a feature of chronic schizophrenia (95,96). However, there is contradictory evidence from neuroimaging studies regarding whether microglial activity (a marker of neuroinflammation) is increased in ARMS subjects (97,98). This is further complicated by potential limitations of the neuroimaging tracers used in vivo (96). In preclinical studies, immune factors have been assessed in both juvenile and adult animals predominantly in MIA-exposed offspring. These studies have found evidence of increased microglia activation throughout the brain (99), specifically in the hippocampus, mPFC (100), and striatum (101) in both juvenile and adult animals, compared with age-matched control animals. Altered levels of proinflammatory cytokines have also been seen in the brains of both juvenile and adult MIA-exposed animals (99,100,102–104). However, because the MIA model specifically induces an inflammatory response, studies in models that do not target the immune system would provide stronger evidence for the centrality of neuroinflammatory abnormalities in the schizophrenia prodrome. Oxidative stress, a correlate of neuroinflammation, has also been seen in a number of animal models in adulthood (105). However, to our knowledge, the effects of oxidative stress on juvenile animals in these models has not yet been assessed.

PROGRESSION OF SYMPTOMS IN THE PRODROME

Attenuated cognitive and negative symptoms are typically evident in prodromal patients prior to the expression of attenuated psychosis symptoms (106). In preclinical studies, negative symptom– and cognition-relevant phenotypes are poorly assessed (25 of 103 studies examined in Table S1) and have been reported in juvenile animals from some but not all models. Because these symptom domains are highly sensitive predictors of functional outcomes for prodromal patients (107,108), this is a critical omission.

Positive symptoms are often absent or minimal prior to a subject fulfilling ARMS criteria. This pattern is also observed in preclinical models; phenotypes relevant to psychosis are typically absent (or attenuated) when assessed at pre- or peripubertal stages, only to emerge by adulthood (Table S1). This convergent pattern suggests two potential mechanisms. First, early adverse exposures may create some hidden lesion or dysconnectivity for which the malleable adolescent brain can compensate. This becomes unmasked or decompensated once the animal matures and these plastic circuits can no

Box 1. Current Animal Models Most Relevant to the Schizophrenia Prodrome

1. Models specifically designed to recapitulate the dopaminergic dysfunction of the prodrome
   a. Partial amphetamine-sensitization model: Uses a modified amphetamine-sensitization protocol to induce a prodromal level of dopaminergic dysfunction
   b. Dopamine D_2 receptor overexpression model: Uses a transgenic manipulation to increase levels of the D_2 receptor in the striatum, reflecting striatal hyperdopaminergia
   c. Enhanced dopamine in prodromal schizophrenia model: Uses a genetic construct to increase levels of dopamine-synthesizing enzymes in the nigrostriatal pathway
2. Neurodevelopmental models of schizophrenia, retrospectively assessed at juvenile ages
   a. Maternal immune activation models (e.g., PolyI:C [polyinosinic:polycytidylic acid] model)
   b. Neonatal lesion models (e.g., neonatal hippocampal lesion models)
   c. Prenatal neurotoxin (e.g., MAM [methylazoxymethanol acetate] model)
   d. Genetic manipulation (e.g., 22q.11 deletion models)
   e. Drug-induced (e.g., neonatal dizocilpine [MK-801] administration)

longer be recruited. Second, an early adverse exposure may leave circuitry intact but change some undetermined chemical or hormonal signal that the brain does not require until puberty. These concepts are not mutually exclusive and have been discussed in greater detail in a recent review (109).

PROGRESSION OF ENDOPHENOTYPES IN THE PRODROME

Deficits in PPI and mismatch negativity (MMN) are considered endophenotypes for schizophrenia (110) and have also been found in ARMS cohorts (111,112). Furthermore, PPI deficits worsen in ARMS subjects who transition to schizophrenia (113), and MMN abnormalities are associated with transition likelihood (112). In preclinical models of relevance to the prodrome, PPI deficits generally appear postpubertally (21 of 35 studies), suggesting that the circuitry underlying PPI is resilient to early developmental insults. Although MMN has been assessed in adult animals across a range of models (114), to our knowledge it has not yet been assessed in juvenile animals from these models. Because MMN may be a useful predictor of transition to schizophrenia, this is a significant gap in the field.

OUTCOMES OF INTERVENTIONS IN CURRENT MODELS OF THE PRODROME

In a number of models of the prodrome, transient intervention with antipsychotic drugs during adolescence prevented the appearance of schizophrenia-relevant behavioral (15,115–118), structural (119), and neuropathological (120) phenotypes in adult animals, even after drug washout. Nonantipsychotic compounds also showed efficacy in reducing the expression of schizophrenia-relevant phenotypes (60,116,121–132). This suggests that compounds that do not depend on dopamine blockade may be viable alternatives to current antipsychotic drugs. However, as discussed above, antipsychotic-based interventions in ARMS cohorts have not been effective at preventing transition to clinical schizophrenia or improving symptoms long term (133). This discontinuity in treatment efficacy between preclinical models and clinical cohorts suggests that 1) these models are not accurate representations of the neurobiology underlying transition to schizophrenia, 2) the behavioral phenotypes are inadequate reflections of clinical symptomology, or 3) the timescales at which animal models are assessed do not accurately reflect longer-term brain remodeling abnormalities in ARMS subjects. Some of these studies also revealed that chronic antipsychotic treatment during juvenile development can result in adverse outcomes in control animals (116,121,122), highlighting the need to find new, nontoxic prophylactics.

SUMMARY OF ANIMAL MODELS THAT ARE RELEVANT TO THE PRODROME

One convergent finding across models of the prodrome (Box 1) is evidence of dopaminergic dysfunction (and deficits in dopamine-related behaviors) that is generally (although not exclusively) apparent in adult, but not juvenile, animals. This robust finding is consistent with the postpubertal appearance of positive symptoms in patients, which are believed to be

Box 2. Limitations of Current Animal Models for the Prodrome

1. Limits of the translatability of current behavioral tests to the attenuated symptoms of the prodrome
2. Inadequate comparison of sex differences in the progression of neurobiological dysfunction
3. a. Limited focus on behavioral symptoms/endophenotypes associated with transition, such as negative and cognitive symptoms and mismatch negativity
   b. Difficulties of models of adolescent risk factors that are related to transition risk
4. Limited longitudinal repeated testing, especially of neurotransmission/brain function with simultaneous behavioral studies

Box 3. Criteria for an Optimal Animal Model of Relevance to the Prodrome

1. Allows longitudinal testing of neurobiology and behavior
2. Displays trajectory of normal juvenile/adolescent to abnormal adult brain circuits/cells/processes
3. Shows schizophrenia-relevant phenotypes in adulthood
4. Testing negative and cognitive symptoms as well as positive
5. Includes both male and female animals
6. Examines putative biomarkers (e.g., mismatch negativity response, inflammatory markers from blood)

mediated by dopaminergic dysfunction (9). Importantly, phenotypes relevant to negative and cognitive symptoms, as well as nondopaminergic neurobiological abnormalities, show greater variability between models. However, this may simply reflect the fact that these factors have been examined in fewer models. Further studies are clearly warranted to determine how the robust deficits in subcortical dopamine systems may interact with other brain regions and neurotransmitters.

LIMITATIONS AND THE FUTURE OF ANIMAL MODELS FOR THE PRODROME

Limitations of current animal models for the prodrome are presented in Box 2.

Translatability of Behaviors

A pervasive limitation of all preclinical models of schizophrenia is the difficulty in assessing positive-symptom phenotypes in rodents. Current tests—responsivity to psychotomimetic compounds and measures of sensory gating—likely do not accurately reflect the neurobiology underlying the positive symptoms of schizophrenia (134). Novel signal detection tests may permit a more valid assessment of psychosis in rodents (135); however, such tests can require extensive training and are therefore unsuited to time-sensitive analyses during adolescence. Regardless, there is a clear need to reassess the behavioral tasks used to represent the positive symptoms of schizophrenia. Diminished symptom severity as seen in the prodrome should also be reflected in preclinical models reflecting a phenotype magnitude intermediate between control animals and that observed in mature animals from the same model rather than simply the presence or absence of phenotype.

Sex Differences

Epidemiological studies suggest that the prevalence of schizophrenia is sexually dimorphic, with a male-to-female ratio of approximately 3:2 (136). Men also show an earlier average age of onset (137). This may be the consequence of altered maturational events that vary in timing dependent on sex (138,139). These findings suggest that the neurobiology and course of the prodrome (and therefore also biological targets for intervention) may also be sex specific. Although a growing number of animal models include both male and female animals (Table S1), making this a standard practice would

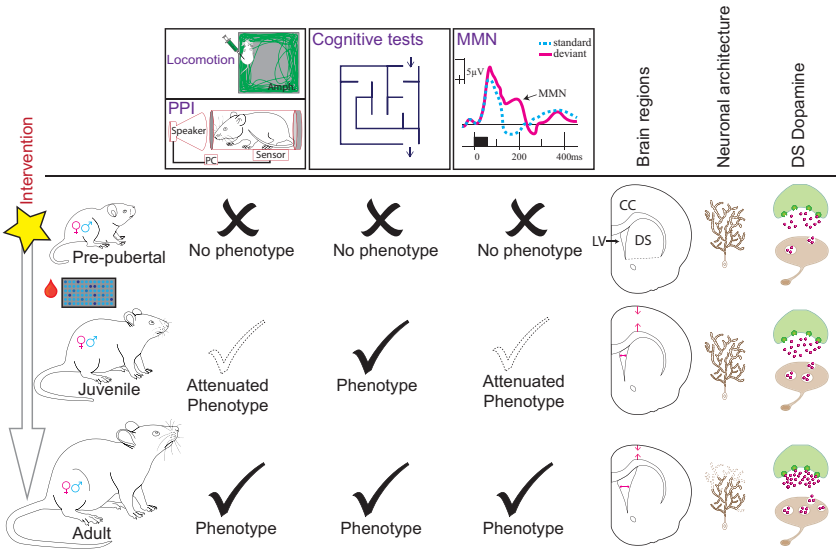

Figure 2. Summary of the ideal model of the schizophrenia prodrome. Animals (both male and female) would be assessed longitudinally for both behavioral and biological outcomes relevant to schizophrenia. Such an animal model would show phenotypes relevant to the positive symptoms of schizophrenia (drug-induced locomotion and impairments in PPI) in adulthood and attenuated expression of these phenotypes as juveniles. These animals would show cognitive deficits as both juvenile and adult animals. Based on clinical data, we expect these animals would show an attenuated MMN deficit as juveniles and robust MMN deficits in adulthood. The ideal animal model would also include progressive changes in brain structure, including accelerated cortical thinning, ventricular enlargement, enhanced synaptic pruning, and an increase in dopaminergic release in the dorsal but not ventral striatum. To assess putative biomarkers, blood samples would be acquired from these animals before any phenotype onset. A range of analytes (including neuroinflammatory markers) would then be correlated to adult outcomes (behavioral and/or neurochemical) to determine their value in predicting adult dysfunction. Finally, the ideal animal model of the prodrome would be used to trial interventions at a range of developmental stages to determine whether it is possible to rescue the abnormal maturation of the brain and prevent or delay onset of adult phenotypes. CC, cerebral cortex; DS, dorsal striatum; LV, lateral ventricle; MMN, mismatch negativity; PC, personal computer; PPI, prepulse inhibition.

allow a robust assessment of sexually dimorphic neurobiological and phenotypic patterns in these models.

Identifying Transition Likelihood

Pinpointing markers of transition likelihood would be invaluable for early identification of ARMS subjects who will progress to schizophrenia. Although patterns of blood-based analytes can suggest those subjects most likely to transition to schizophrenia (140,141), these tests are currently insufficiently sensitive and/or specific for diagnostic application (142). Animal models may offer a solution; MIA-exposed adult animals can be clustered into two groups that show either the presence or absence of schizophrenia-relevant phenotypes (143). Analyzing blood samples from these animals as juveniles may reveal putative biomarkers for transition.

Factors including adolescent stress and cannabis use have been shown to increase the likelihood of transition to schizophrenia (107). However, in preclinical models of these risks, the manipulation/treatment typically occurs during adolescence, with animals being assessed either in adulthood or immediately following cessation of the manipulation/treatment (normally in late adolescence). Such a study may therefore simply reflect the acute effects of the model, rather than its pervasive effects on neurobiology. For this reason, these studies were not included in this review. However, the neurobiological processes on which such factors act are likely crucial to schizophrenia onset.

Technical Limitations

Analysis of neurobiology alongside behavior is key to understanding the schizophrenia prodrome. Neuroimaging techniques are highly translatable and permit longitudinal analyses. However, these techniques are often limited in spatial and/or temporal resolution. Older in vivo techniques to examine neurotransmitter function cannot be used longitudinally owing to the tissue damage. Technical advances, such as the development of ultrafine fast scan cyclic voltammetry recording electrodes (144), genetically encoded sensors for dopamine signaling (145), and soft cortical "windows" into the brain (146), may allow longitudinal analysis of schizophrenia-relevant neurobiology during the critical adolescent period.

CONCLUSIONS

A well-defined preclinical model of the schizophrenia prodrome (Box 3 and Figure 2) is now required to follow disease course, understand the neurobiology and circuits behind transition, and trial potential prophylactics. In addition, such a model may provide answers to currently intractable questions such as the following:

1. Why do negative and cognitive symptoms precede the subacute psychotic symptoms of the prodrome?
2. What is the neurobiological basis for the temporal differences in prodromal onset between men and women?
3. What are the biomarkers that could predict transition?
4. Is there a pharmacological agent or bioactive molecule that could delay symptom onset, diminish symptom severity, or ultimately prevent transition to the neurobiological and behavioral phenotypes relevant to schizophrenia?

Data from brain imaging modalities and emerging clinical observations from the ARMS subject groupings will help to refine future animal models with relevance to the schizophrenia prodrome in an iterative cycle. We must continue to improve animal models of psychiatric disorders while considering the adage from statistician George Box: "all models are wrong, but some are useful" (147).

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