Commentary

Biological Psychiatry: GOS

Limitations and Value of Animal Models of Relevance to the Schizophrenia Prodrome

Alison R. Yung

In the current issue of *Biological Psychiatry: Global Open Science*, Petty *et al.* (1) discuss animal models of relevance to the schizophrenia prodrome. These models are essentially rodent models of schizophrenia in which the animals are assessed during adolescence and early adulthood. This is the period in which brain structures and networks are changing in both rodents and humans and is the age range of highest risk for onset of schizophrenia in humans. How useful are these animal models for research and clinical work in humans? As I discuss herein, both animal and human factors affect their usefulness.

A first obvious limitation of animal models is that the behaviors seen in rodents are imperfect representations of the symptoms seen in humans. Positive symptoms in patients with schizophrenia, such as passivity phenomena, delusions, and hallucinations, are thought to be linked to subcortical hyperdopaminergia. Enhanced dopaminergic activity in rodents—for example, through giving rodents methamphetamine—results in increased locomotor activity. This behavior is also seen in neurodevelopmental animal models, such as maternal immune activation models. This has led to the assumption that increased locomotion is relevant to positive symptoms and is the equivalent of psychotic agitation.

However, positive symptoms such as having a feeling that one's thoughts are being read by others, believing that there is a conspiracy against one, and hearing voices when there is no one around are impossible to assess in nonhumans. Further, positive symptoms are heterogeneous. Factor analyses have found 3-factor (bizarre experiences, persecutory ideas, and magical thinking), 4-factor (bizarre experiences, persecutory ideas, perceptual abnormalities, and either magical thinking or grandiosity), and 5-factor (hallucinations, delusion, paranoia, grandiosity, and paranormal beliefs) models (2). These different types of positive symptoms may have different underlying pathologies, and increased locomotion in rodents cannot reflect all of these subtypes of psychotic symptoms. Further, positive symptoms are strongly influenced by environmental stressors, and a high and cumulative load of environmental risk factors (for example, life events and substance use) can result in positive symptoms even with a low level of genetic risk for schizophrenia (3). Some animal models involve stressing an animal or providing it with a substance such as cannabis, with the resultant neurobiological changes possibly relevant to positive symptoms with an environmental stress component. However, the ethics of repeated stressing of an animal are dubious, especially as positive symptoms may not be the most important feature of schizophrenia, as discussed below.

Another issue is that we are not yet able to identify all the manifestations of the schizophrenia prodrome in humans with a high degree of predictive power. The best that we can do is to identify those who are at high risk of developing a psychotic disorder. The criteria for doing this were developed more than 25 years ago (4) and have variably been called the at-risk mental state, ultra high risk (UHR) criteria, or clinical high risk criteria. About 36% of individuals meeting these criteria develop a psychotic disorder (or "transition to psychosis") 3 years after initial identification (5). Thus, more than 60% of UHR individuals do not develop a psychotic disorder. Some may not have been truly at risk (so-called false positives) and others may have been prevented from transitioning by some treatment or a change in circumstance (false false positives). This means that the animal models of schizophrenia prodrome likely do not apply to many people meeting UHR criteria, and treatments tested in such models would not be effective in reducing symptoms in many UHR individuals.

Further, some individuals who transition from a UHR state to a psychotic disorder will not have schizophrenia. The criteria for transitioning are based on the individual's positive symptoms changing from an attenuated level to a level considered fully psychotic. For example, someone changes from having a sense that others may wish him harm to being convinced about the hostile intentions of others, or changes from hearing indistinct murmuring or whispering to hearing clearly discernible voices when there is no one around. The threshold positive symptoms also need to be present for at least 1 week. These criteria for transition were developed in order to identify those in need of specific treatment for their positive symptoms, probably by prescription of antipsychotic medication (4). However, having at least 1 week of fully threshold positive psychotic symptoms is not the same as having schizophrenia. A meta-analysis reported that 73% of UHR individuals who transitioned developed a schizophrenia spectrum disorder according to DSM-IV or ICD-10 criteria (6). But even these criteria may not identify someone with what many would consider to be "core" schizophrenia. A person can meet the DSM-IV criteria for schizophrenia by having 2 threshold psychotic symptoms for less than a month if successfully treated, having poor functioning, and having 6 months of prodromal symptoms. Many individuals in a clinical service for UHR individuals will have had at least 6 months of attenuated psychotic symptoms before presenting for help, will be functioning poorly (indeed this is a necessary condition to be considered at risk in some services), and at time of transition will often have at least 2 threshold positive symptoms. In other words, it is not hard for a person who has met UHR criteria and then

SEE CORRESPONDING ARTICLE ON PAGE 22

https://doi.org/10.1016/j.bpsgos.2022.08.004
ISSN: 2667-1743

Table 1. Limitations and Value of Models of the Schizophrenia Prodrome

Models	Limitations	Value
Animal Models	Behaviors do not represent the complexity of positive symptom psychopathology Few models of negative symptoms and cognitive impairment	Increase understanding of neurobiology of the schizophrenia prodrome Enable development of novel treatments and their effects on brain and behavior over time
UHR Model	UHR concept has low positive predictive power for detecting schizophrenia Individuals with negative symptoms and cognitive impairment without positive symptoms are not identified	

UHR, ultra high risk.

transitioned to meeting the DSM-IV definition of schizophrenia. The presence of any negative symptoms or cognitive impairment is not necessary in the DSM-IV definition of schizophrenia, yet it is these phenomena that identify the fundamentality of schizophrenia. This concept of fundamental, core, or nuclear schizophrenia was common in early descriptions of the illness and in European psychopathology (7). It has recently been reflected in a call to view schizophrenia as primarily a cognitive illness (8). If we conceptualize schizophrenia as an illness characterized primarily by negative and cognitive symptoms, then it is likely that many individuals in the prodromal phase of illness are not being detected, as without positive symptoms they will not be captured by the UHR criteria.

The modern manifestation of core schizophrenia is best approximated by the deficit syndrome, which is characterized by persistent primary negative symptoms and cognitive impairment. Compared to nondeficit schizophrenia patients, deficit schizophrenia patients have white and gray matter abnormalities and high levels of inflammatory markers (9). The rodent models, especially the neurodevelopmental models, will likely be relevant to core schizophrenia. Some animal models relevant to schizophrenia and the schizophrenia prodrome show the structural brain abnormalities and increased immune response characteristic of deficit syndrome. Petty *et al.* (1) stated that there needs to be a greater focus on negative and cognitive symptoms, as they associated with transition in UHR individuals. I would argue that we need to focus on these phenomena in their own right. More animal models of negative symptoms and cognitive impairment are needed, as they would enable us to determine risk factors for core schizophrenia and to examine the onset and trajectory of negative and cognitive symptoms, allowing investigation of preventative treatments.

Despite the above considerations, the different models of the schizophrenia prodrome described by Petty *et al.* (1) are still of great value to researchers and clinicians involved with UHR individuals. First, they increase our understanding of the neurobiological basis of schizophrenia, or probably more accurately the different types of schizophrenia, including through use of invasive techniques to assess brain and molecular changes that would not be possible in humans. The models may lead to the detection of biomarkers that index a high risk of development of schizophrenia. If these can be applied to UHR individuals, we may be able to identify those who are more versus less likely to develop schizophrenia. Such stratification will enable different pathways of care. For example, those with high biomarkers and a high risk of developing schizophrenia could be considered for early specific treatment such as clozapine. And while exercise is good for everyone, given that it seems to improve cognitive function in people with schizophrenia (10), those at high risk of schizophrenia could be targeted with funded specialized programs that ensure that they achieve the required "dose" of exercise and that they remain engaged with such activity.

Animal models of the schizophrenia prodrome will also enable testing of novel therapies that target the underlying pathologies and take into account brain maturation. The animal studies can assess the mechanisms by which new treatments work and follow their effects on brain and behavior over time. This may lead to the ultimate goal of schizophrenia research: to find a treatment that modifies disease progression. If applied early enough it could even prevent onset of this often-devastating illness. Table 1 summarizes the above discussion.

Acknowledgments and Disclosures

ARY is supported by a National Health and Medical Research Principal Fellowship. The funding source had no role in the content of this commentary.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

From the Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, Victoria, Australia; and School of Health Sciences, University of Manchester, Manchester, United Kingdom.

Address correspondence to Alison R. Yung, M.D., at alison.yung@deakin.edu.au.

Received Aug 15, 2022; accepted Aug 17, 2022.

References

1. Petty A, Howes O, Eyles D (2023): Animal models of relevance to the schizophrenia prodrome. Biol Psychiatry Glob Open Sci 3:22–32.
2. Wigman JTW, Vollebergh WAM, Jacob N, Wichers M, Derom C, Thiery E, *et al.* (2012): Replication of the five-dimensional structure of positive psychotic experiences in young adulthood. Psychiatry Res 197:353–355.
3. Taylor MJ, Freeman D, Lundström S, Larsson H, Ronald A (2022): Heritability of psychotic experiences in adolescents and interaction with environmental risk. JAMA Psychiatry 79:889–897.
4. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A (1996): Monitoring and care of young people at incipient risk of psychosis. Schizophr Bull 22:283–303.
5. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, *et al.* (2012): Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 69:220–229.

6. Fusar-Poli P, Bechdolf A, Taylor MJ, Bonoldi I, Carpenter WT, Yung AR, McGuire P (2013): At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophr Bull 39:923–932.
7. Parnas J (2011): A disappearing heritage: The clinical core of schizophrenia. Schizophr Bull 37:1121–1130.
8. Kahn RS, Keefe RSE (2013): Schizophrenia is a cognitive illness: Time for a change in focus. JAMA Psychiatry 70:1107–1112.
9. Goldsmith DR, Haroon E, Miller AH, Strauss GP, Buckley PF, Miller BJ (2018): TNF-α and IL-6 are associated with the deficit syndrome and negative symptoms in patients with chronic schizophrenia. Schizophr Res 199:281–284.
10. Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, *et al.* (2017): Aerobic exercise improves cognitive functioning in people with schizophrenia: A systematic review and meta-analysis. Schizophr Bull 43:546–556.