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PSYCHOSIS (R GUR AND B CLEMENTZ, SECTION EDITORS)

Animal Models of Psychosis: Current State and Future Directions

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Abstract Psychosis is an abnormal mental state characterized by disorganization, delusions and hallucinations. Animal models have become an increasingly important research tool in the effort to understand both the underlying pathophysiology and treatment of psychosis. There are multiple animal models for psychosis, with each formed by the coupling of a manipulation and a measurement. In this manuscript we do not address the diseases of which psychosis is a prominent comorbidity. Instead, we summarize the current state of affairs and future directions for animal models of psychosis. To accomplish this, our manuscript will first discuss relevant behavioral and electrophysiological measurements. We then provide an overview of the different manipulations that are combined with these measurements to produce animal models. The strengths and limitations of each model will be addressed in order to evaluate its cross-species comparability.

Keywords Psychosis · Animal model · Behavior · Electroencephalography · Transgenic mice · Pharmacological manipulation

Table of Contents

Table of Contents 1
Abstract 1
Introduction 2
  Definition of Psychosis 2
  Definition of an Animal Model 2
Measurements 2
  Behavioral Measures 2
    PPI 3
    Latent Inhibition 3
    Conditioned Avoidance Response 3
    Stereotypy 3
    Hyperactivity 4
    Strengths and Weaknesses 4
  Electrophysiological Measures 5
    Event Related Potentials 5
    Mismatch Negativity 5
    P300 6
    Strengths and Weaknesses 6
Manipulations 6
  Pharmacological Manipulations 6
  Genetic Manipulations 6
  Developmental Manipulations 7
  Environmental Manipulations 7
    Strengths and Weaknesses 7
Manipulations to Neurotransmitter Systems 8
  Dopamine 8
    Theory 8
    Pharmacological 8
    Genetic 9
    Strengths and Weaknesses 9
  Glutamate 10
    Theory 10
    Pharmacological 10
    Genetic 10
    Strengths and Weaknesses 11
  GABA 11
    Theory 11
    Genetic 11
    Strengths and Weaknesses 11
  Serotonin 12
    Theory 12
    Pharmacological 12

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Genetic 12
Strengths and Weaknesses 12
Future Directions and Conclusion 12
Acknowledgements 35
Figure Legends 36
References 37

Introduction

Psychosis is a brain disease characterized by an abnormal mental state and a loss of contact with reality. In an effort to produce viable treatment options for psychosis, animal models have become increasingly important. Animal models are extremely useful and serve as an essential tool for investigating mechanisms and treatments for a variety of human disorders, including psychosis. In this manuscript, we summarize both the current state and future research directions of animal model approaches for studying psychosis.

Before delving into the topic of modern models of psychosis, it is important to note that this article will discuss psychosis in a holistic sense as it relates to several disorders. As such, this article will not discuss models limited to the pathophysiology of schizophrenia, bipolar disorder, or any other related diseases. It will focus purely on models related to psychosis. Furthermore, when a model is discussed in the context of a specific disorder, the model will only be discussed with reference to psychosis and not to the other aspects of that disorder and model, such as cognition and social function. The models of psychosis that will be discussed in this article involve both a manipulation and a measure. We will focus on a behavioral or physiological outcome, coupled to the manipulation that induced the psychotic state as the formation of a viable animal model.

Definition of Psychosis

Psychosis is a mental state characterized by a distortion of reality. Patients diagnosed with psychosis may present with one or more of the following symptoms: hallucinations, delusions, catatonia, disordered thoughts, or impaired social cognition. Psychosis is commonly seen in patients suffering from schizophrenia, bipolar disorder and Parkinson's disease. Furthermore, some surgery patients have brief episodes of post-operative psychosis. A study by van der Mast et al. reported that post-operative psychosis occurred in 13.5 % of cardiac surgery patients [1].

Definition of an Animal Model

An animal model is an approximation of a specific human condition or disease. They are used in order to gain insight into the etiology of the disease or to develop treatment options. A model is formed by the combination of a manipulation and a measurement. The manipulation induces the state and the measurement offers a way to qualify or quantify the results of this induced change.

In order for an animal model to be a reliable model of a human condition there are several forms of validity that must be met: face validity, construct validity, predictive validity, internal validity, and external validity. Face validity indicates the cross-species comparability. It refers to the similarity between the state induced in the animal model and the symptoms observed in humans [2]. Construct validity refers to the accuracy of a test in measuring what it is proposed to measure [2]. Predictive validity is the capacity of a model to predict the criterion that is being studied. Internal validity refers to both the reliability and replicability of a study; it tests the specificity of models [2]. External validity is the extent to which the results obtained using a particular animal model can be generalized to a real-world population [2].

Cross-species comparability refers to the ability of the results of an animal model to be generalized to the human condition that it is trying to approximate. An animal model must exhibit a measureable similarity with the human ailment in question in order for the model to provide any valuable insight into a particular disease. As such, the cross-species comparability of each measurement and manipulation will be discussed as strengths in the relevant sections of this article.

Limitations, in reference to animal models, refer to any inaccuracies that may occur in the approximation of a specific condition. Despite the cross-species comparability that exists in many of the models presented in this manuscript, there are still many limitations to be addressed, as many of these manipulations and measures are not completely true to the state of psychosis they are attempting to model. These limitations will be addressed as weaknesses in the relevant areas of this manuscript.

Measurements

In this section, we will address both behavioral and electrophysiological measurements of psychosis. These measurements are used to both qualify and quantify effects of a manipulation in an animal model. Several relevant behavioral measurements will be discussed in this section. A comprehensive list will not be presented; rather, the most important examples will be discussed in detail.

Behavioral Measures

Behavioral measures are methods that attempt to quantify and interpret the actions of an animal. The underlying hypotheses

are: that the action being evaluated informs the biology related to psychosis and/or; the animal's behavior is informative about some mental construct or process and/or; altering the animal behavior using a treatment is predictive of effects of that treatment in humans. The validity of these assumptions will be addressed individually within each section.

PPI

PPI is a measurement commonly used in schizophrenia models and is also useful for measurements in animal models of psychosis. In the PPI paradigm, subjects are exposed to a weak, often acoustic pre-stimulus followed 30–300 ms later by a stronger startle stimulus [3]. Physical response to the startle stimulus is measured and compared to the startle response when no pre-stimulus is used (Fig. 1). This difference provides a quantitative measure of motor inhibition that has been theoretically linked to a subject's neuronal inhibitory mechanisms. This link is largely based on the observation that alterations in the dopamine system, such as administration of amphetamine, cause a reduction of PPI. Additionally, PPI deficits observed in schizophrenia patients are correlated clinically with symptoms such as thought disorder and distractibility [3].

Latent Inhibition

Latent inhibition (LI) refers to a process by which non-contingent presentation of a stimulus diminishes the ability to enter into subsequent associations. Thus, the prior experience that a stimulus does not have a consequence makes it less likely that the brain will form an association with that stimulus later. LI is widely considered to relate to the cognitive abnormalities that characterize schizophrenia because it reflects an organism's ability to ignore irrelevant stimuli [4–7]. However, it also has been linked to psychosis based on the observation that medications that effectively treat psychosis, such as clozapine and haloperidol, restore latent inhibition across a variety of conditions [4, 5].

Conditioned Avoidance Response

In the conditioned avoidance response paradigm, an electric foot shock is paired with a conditioned stimulus of a tone or light. This will elicit a learned avoidance response so the animal can escape being shocked [8]. This link between the unconditioned and conditioned response is facilitated by dopamine, although several other neurotransmitters are thought to also play a role [9]. When this dopaminergic pathway is disrupted, one sees a decrease in the normal, appropriate avoidance response (i.e., the animal fails to escape). This assay for a reduction in dopamine activity has been used to determine the efficacy of many dopamine antagonists, including both typical and atypical antipsychotics such as haloperidol and risperidone [10–12]. Although this approach has been instructive in finding therapies that block dopamine type 2 receptors and therefore are effective for psychosis, those very same agents actually impair a normal self-preservation function. Thus, the major limitation to this behavioral model is that its predictive validity is at odds with normal function, as well as lacking construct validity related to psychosis.

Stereotypy

Stereotypy is characterized as repetitive behavior and has been noted in patients with psychosis and also in several

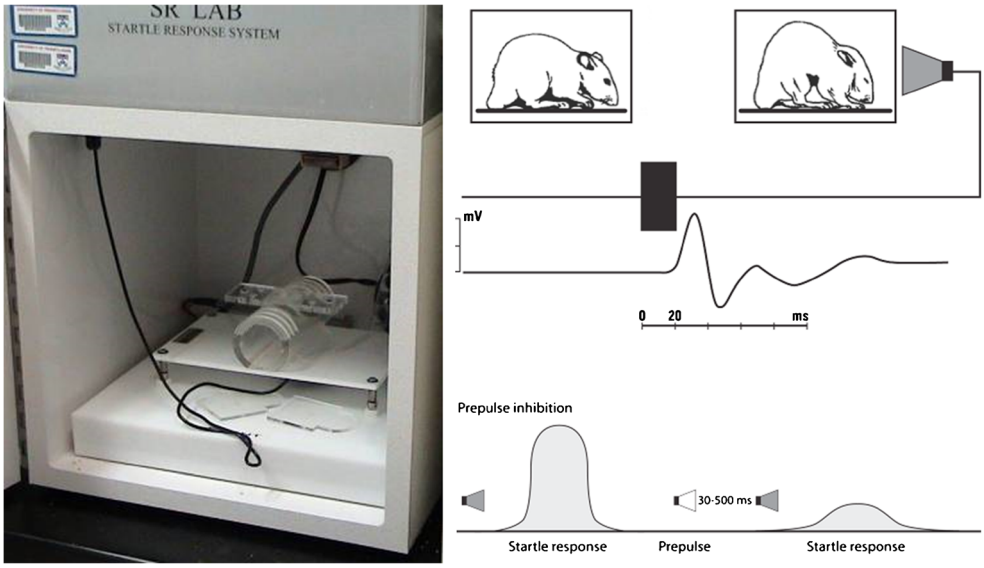

Fig. 1 Example of apparatus used to measure pre-pulse inhibition of startle in rodents

pharmacological human and animal models of psychosis [13–18]. Specific behaviors can vary depending on the drug or animal used and behaviors include, but are not limited to: repetitive licking, chewing, grooming, head movements, sniffing, circling, or climbing [17, 19–22]. The level of stereotypy can be determined through either recorded observation or the use of software programmed with predetermined criteria [17, 18, 22]. Stereotypy thus has been used as both a qualitative and quantitative measure in models of psychosis. For example, quantification of stereotyped behaviors may include rearing, as assessed using locomotor activity monitoring software, or by measuring time spent in repetitive movements [23]. The attenuation of these behaviors can also be used in evaluating the antipsychotic properties of compounds [24–26]. Alternatively, these same measures are likewise used to model motor aspects of schizophrenia such as tardive dyskinesia, as well as medication-induced side effects.

Hyperactivity

Hyperactivity in animal models is a behavioral measurement that has been associated with the agitation and disorganized behavior of psychosis [27]. Many early antipsychotics functioned as dopamine agonists; therefore hyperactivity has been hypothesized to originate from a hyper-dopaminergic state [28]. Hyperactivity, however, remains a consistent measurement even in models where dopamine release is not directly induced. It is suggested that the hyperactivity observed in such models is due to secondary effects on dopamine transmission [28–30]. The maintenance of hyperactivity in models that do not directly influence dopamine supports the idea of elevated dopamine neurotransmission being characteristic of psychosis, but not necessarily the source of psychosis [31–33].

Hyperactivity in mouse models was historically measured through first person observation. Presently, hyperactivity is measured through the use of computer software, yielding greater accuracy. In the former method, experimenters would conduct an open field test in which a grid was drawn on the floor and the experimenter would note every time a grid line was crossed by an animal, in order to calculate an ambulation score for locomotor activity [34]. Locomotor activity can now be measured using a grid of photo-beams at the bottom of a chamber, which is combined with software that determines the number of beam breaks [35, 36]. Increased locomotor activity is often assumed to indicate a general level of hyperactivity [35, 36].

Strengths and Weaknesses

As a whole, behavioral measurements are limited in their ability to translate animal model measurements to humans. This limitation is associated with several factors. The most general limitation stems from the inability to truly interpret the motivation or meaning of the vast majority of animal behaviors. For example, we often ascribe a set of constructs and/or goals to what an animal does, and why it does so. However, there are generally multiple interpretations. Obvious examples of this anthropomorphic fallacy are not limited to psychosis; rather, they are present across a wide variety of studies of normal and abnormal states. For example, the forced swim and tail suspension tests are used to evaluate antidepressant effects. In essence, the animal (generally a mouse) struggles to swim in a chamber filled with water, or climb its tail when attached to the wall with tape. In both cases, increasing the latency to stop trying is associated with an "antidepressant therapeutic" effect. However, in both cases, the animal's motivation and choice to stop trying can be seen in a diametrically different way. Since hanging a mouse by its tail is not harmful, and mice do float, a longer time struggling can also be seen as increasing the latency to learn that struggling is futile and a poor use of energy resources. That is to say, the behavior could just as easily be used as a way to assess for compounds that impair cognition. We will now return to the aforementioned psychosis related behavioral measures in order to describe similar pros and cons.

One of the primary advantages of PPI is its ability to be used similarly in mice, rats, and humans, because it is one of the few tests that is largely conserved across all vertebrate species [37]. There is excellent stability and high test-retest reliability of PPI across time in both rodents and humans, facilitating the use of within-subjects and longitudinal designs. On the other hand, the construct validity between PPI and psychosis is quite limited. As such, its primary value has been as a screening tool for alterations of DA function, and therefore as a screening tool for DA antagonist medications for psychosis. There are also some minor logistical limitations that must be considered. PPI levels vary based on sex, both in humans and in rodents, and it can be difficult to compare within female subjects because PPI fluctuates throughout the menstrual cycle [38]. This however may pertain to multiple behavioral measures and is not specific to PPI.

One of the major strengths of the latent inhibition task is that it can be applied across many mammalian species. Several studies suggest that latent inhibition also fulfills criteria for construct, face and predictive validity in a variety of animal models relevant to schizophrenia [39–41]. Although the construct validity pertains primarily to cognitive deficits, the predictive validity for medication effects on positive symptoms of psychosis is better than for negative or cognitive symptoms [41, 42]. However, predictive validity for negative cognitive symptoms has been notoriously

poor, as no agents to date have shown efficacy for either of these domains in humans.

Electrophysiological Measures

Electroencephalography (EEG) was the first physiological technique used to examine the brain by recording electric field potentials with the capability to reflect both the normal and abnormal electrical activity of the brain. Hans Berger, a German neurologist, recorded the first EEG in 1924. Eventually, EEG evolved into an indispensable method for studying cerebral information processing, particularly due to the introduction of source localization techniques and the decomposition of event-related activity into its frequency components. Conventionally, EEG is recorded from the scalp using electrodes affixed to specific scalp locations and is represented as changes in potential difference. The scalp EEG reflects the summated potentials from a large synchronously activated population of pyramidal cells in the cerebral cortex. These potentials are thought to originate primarily from excitatory and inhibitory neural electric activity, including action potential (AP) and postsynaptic potentials [43].

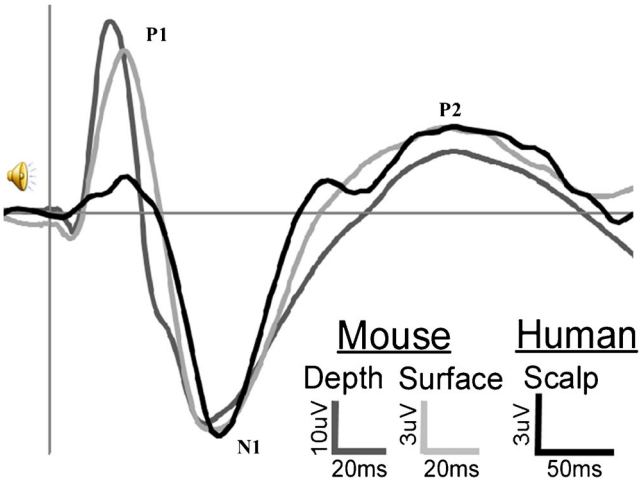

Fig. 2 Representative grand average auditory event related potential recordings from human scalp, mouse surface and mouse depth electrodes. Note that the overall pattern of event related activity is consistent across species and locations, with a prominent P1, N1 and P2 components. These responses are termed "obligatory" as they occur in response to a simple tone or click in rodents, non-human primates or clinical populations. These components occur at 40 % of the human latency in mouse. Thus, the P1 occurs at 20 ms in mouse and 50 ms in human, while the N1 and P2 occur at 40 ms and 80 ms in mouse and 100 ms and 200 ms in human respectively. Studies over the past decade demonstrate that each component in mouse shares psychometric and pharmacological response properties within the corresponding human ERP component, yielding excellent predictive validity

Event Related Potentials

Electroencephalography provides a method to investigate general function of the brain including its reaction to particular stimuli that will be represented as changes in the EEG, globally known as event-related potentials (ERP) or evoked potentials (EP). These event-related potentials are defined as the oscillatory brain responses that are triggered by the occurrence of particular stimuli (auditory, visual, or somatosensory). These voltage fluctuations also allow one to measure distinct stages in neural information processing. Moreover, ERPs reflect sub-cortical and cortical information processing in real time, and thus provide a useful tool for examining cognitive mechanisms in both normal brain function and disorder-related impairments.

EEG recordings analogous to those described above can be obtained from a variety of rodent species. In mice, the characteristic positive and negative deflections of the EEG recording occur at approximately 40 % the latency of equivalent human components [44–46]. Therefore, the P20, N40, P80 and P120 represent ERP deflections in mice analogous to the P50, N100, P200 and P300, respectively, in humans (Fig. 2). Some groups have analyzed P20 and N40 potentials as a single ERP component (termed the P20/N40) in order to examine the effects of pharmacological, genetic and environmental manipulations on the general property of habituation. However, subsequent work has suggested that these two components are subject to independent effects by manipulations such as nicotine and ketamine treatment [44, 47–52].

Mismatch Negativity

The ability to detect, and adapt to, changes in auditory stimulus characteristics is basic as neuronal functions can be measured with ERPs in both humans and animals. Mismatch negativity (MMN) reflects the context-dependent information processing, required to compare a deviant incoming stimulus with the neural representation already stored in transient auditory memory [53]. When a string of tones with a specific regularity (sequence of homogeneous tones) is presented, the brain stores the features of this auditory stimulation in a short-duration neural memory trace [54]. While this echoic memory is still active, each new auditory input is compared to the existing trace for a break of regularity (deviant tone), which generates a neuronal adaptation giving rise to the MMN between 100 and 225 ms in humans [55]. MMN is most frequently elicited in an auditory oddball paradigm. A sequence of repetitive standard stimuli is randomly interrupted by a deviant oddball stimulus, which may differ in stimulus characteristics such as pitch, intensity, or duration. Generators are located in the

auditory and frontal cortices [56, 57]. Of particular importance, MMN is evoked irrespective of attention or awareness (e.g., present in comatose patients) [58]. In clinical neurosciences, MMN has been widely used in various applications, in particular in schizophrenia research, due to its good reproducibility and the ability to assess it without a task [59].

P300

Probably the most extensively studied long-latency ERP component is the P300 (also termed P3), a time-locked positive deflection emerging 250 ms to 500 ms after attending stimulus. First described by Sutton et al. in 1965, P300 is thought to reflect an information processing cascade when attentional and memory mechanisms are engaged [60]. Although related to the process of sensory stimulus mismatch detection, the P300 component represents an attention-driven memory comparison process, in which every incoming stimulus will be revised to detect possible stimulus feature modifications. According to whether changes are present or absent, the electrophysiological recordings will differ. If no change can be detected, only so- called obligate evoked potentials are recorded (N100; P200; N200). If a new stimulus is presented and the subject allocates attentional resources to the target, the neural stimulus representation is altered and the consequent update leads to the generation of P300 [60]. Similar to the MMN, the auditory P300 is elicited in context of an oddball paradigm, but in contrast to MMN elicitation the generation of P300 requires the test-taking person to be attentive and respond physically or mentally to the presented target. Commonly, subjects are instructed to either push a button following the infrequent target or to count deviants.

Strengths and Weaknesses

EEG in general and ERPs in particular are the most readily translatable measure across species. In contrast to behavior, one measures the exact same phenomenon across species and no interpretations of "meaning or intent" are required. Many studies have demonstrated that both mouse and human ERP components are similarly affected by certain pharmacological treatments and stimulus manipulations [61–63]. Thus, recording EEG and ERPs in preclinical studies provides the most translational model system for physiological deficits associated with psychosis.

Although electrophysiological measurements have the highest face and construct validity of any measure, it is less clear how such measures relate to clinical symptoms. Evidence for a link between these measures and cognition is beginning to emerge, but the association with psychosis per se is much weaker. Additionally, studies of the differences in the P300 observed across various patient populations have been highly variable [60]. Despite simplicity of the task, the cerebral mechanisms producing an ERP remain unclear [64–66].

Manipulations

In this section, we will discuss relevant manipulations used in animal models of psychosis, with reference to the different types of validity, generalizability, inconsistencies, and any confounding variables. Molecular mechanisms will be addressed within genetic and pharmacological manipulations, as these are the tools used to address the intra-cellular and inter-cellular signal transduction pathways that contribute to psychosis. As was the case with measurements, this section will not provide a comprehensive list, but rather a discussion of the most important manipulations.

Pharmacological Manipulations

Pharmacological models of psychosis are founded on the current understanding of the effects of drugs on various neurotransmitter systems. They rely on the observation that certain drugs induce behaviors that mimic or predict symptoms of psychosis in humans. Both acute and chronic doses of ketamine are widely used by investigators to disrupt glutamate signaling in order to model psychosis-like effects. For example, both the NMDA receptor-antagonists ketamine and PCP can cause a dissociative state reminiscent of disorganization as well as hallucinations. Similarly, amphetamine can cause a psychotic state in humans and is therefore given to animals to simulate the biological environment present in a psychotic state. Such pharmacological manipulations will be addressed in the following section regarding changes to specific neurotransmitter pathways.

Genetic Manipulations

Genetic models of psychosis are created through the disruption of a molecular genetic pathway that has been linked through association studies to a variety of psychotic states. A host of genetic manipulations have been combined with specific outcome measures to assess the extent to which alteration of a gene or signaling pathway is related to various behaviors and physiological phenomena. For example, alterations of NMDA receptor expression in mice leads to a number of behavioral and physiological changes noted above that are considered relevant to psychosis [62].

Genetic models noted represent both candidate gene and candidate pathway approaches. The former focus on genes that have been identified primarily through human association studies with a specific disease, e.g., schizophrenia. The latter is likely a more informative approach, and represents efforts to use genetic manipulations to dissect signaling pathways that contribute to the physiology of psychosis across a multitude of etiologies. This latter approach offers greater generalizability and is also likely more meaningful with respect to therapeutic development. We will not provide a comprehensive list of candidate gene models for specific disorders as these are discussed in detail elsewhere [67].

Developmental Manipulations

Developmental models of psychosis are founded upon a manipulation during the ontogeny of the animal that affects a developmental outcome, inducing a set of psychosis-related behaviors and physiological changes. The manipulation induces a change that models the state of the human disease in the animal. Prenatal exposure to the cell division inhibitor methlazoxymethanol acetate (MAM) is one example of a developmental animal model of psychosis. Exposure to MAM at embryonic day 17 produces a pattern of brain atrophy in adult animals similar to that seen in human schizophrenia (i.e., cortical and hippocampal atrophy), increasing the face validity for a disease in which psychosis occurs [68]. However, these neural changes overlap with dysfunctions across a wide range of behavioral and cognitive domains affected in humans with schizophrenia, including measures sensitive to mesolimbic dopamine function and cognitive performance. Thus, MAM treated animals display impaired long-term memory, working memory and attentional flexibility, as well as increased responsiveness to measures related to psychosis following amphetamine as adults [69–73].

Lesion models of psychosis, though very limited, are a form of developmental model. This is the case because the lesion tends to be conducted early in development and affects a developmental course. In essence, a part of the animal's brain is lesioned in order to have the desired effect. Neonatal ventral hippocampal lesion (NHVL) is the most prominent example of inducing psychosis-related measures in rats. NVHL in rodents during early life has been shown to produce many of the behavioral measures related to psychotic symptoms in adulthood [74]. Relevant features of this model include amphetamine-induced hyperactivity and deficits in pre-pulse inhibition. These changes occur coincident with schizophrenia-like cellular and neuroanatomical changes, including reductions in parvalbumin expressing GABA-ergic interneurons; exaggerated response to glutamate agonist and antagonists, suggestive of a hypoglutamatergic state. Importantly, most of these changes occur only when the lesion is induced during the neonatal period, and do not occur in adult animals given similar lesions of the ventral hippocampus; suggesting that it is the altered neurodevelopmental environment that is the source of the changes observed in the model.

Environmental Manipulations

Environmental manipulations relevant to models of psychosis include any change to the living conditions of the animal that induce a set of behavioral or physiological measures related to psychosis. Similar to developmental manipulations, environmental conditions that can be linked to psychosis are relatively limited as compared to either pharmacological or genetic ones. However, we will address isolation rearing and stresses as two forms of environmental manipulations that have been relatively well characterized.

Isolation rearing during developmentally critical periods, such as infancy and adolescence, can serve as a stressor that can induce behaviors associated with psychosis [75–77]. The behavioral profile of mice and rats reared in isolation includes hyperactivity in response to novelty, and reduced pre-pulse inhibition. These however are not specific to psychosis, as social deficits, reduced conditioned response, impaired novel object recognition, and elevated aggression are also seen [75, 76, 78–84]. This behavioral profile could be the result of alterations to the HPA axis stress response, and studies have suggested that these alterations to the HPA axis are likely to be mediated by an elevated production of NADPH oxidase-2 in response to the stress of social isolation [85–87]. Isolation rearing has also been shown to alter the signal transduction of glutamate, dopamine, and serotonin, three transmitters whose dysfunction has been implicated in psychosis [87–91]. In some instances this environmental model has been combined with a genetic model or pharmacological model to produce more robust results [77, 92].

A prolonged period of restraint has also been used to induce PPI deficits in mice [93]. Furthermore, adult mice prenatally exposed to stress through the restraint of their pregnant mother exhibited a constellation of psychosis-related and non-psychosis related alterations including hyperactivity, reduced pre-pulse inhibition, social deficits, and impaired fear conditioning [94]. Other studies have modeled prenatal stress by exposing a pregnant mouse or rat to a variable stress paradigm in which the pregnant female is exposed to a range of stressors including restraint, a cold environment, food deprivation, forced swimming, 24 hours of light, an overcrowded cage, and foot shock over an a extended period of time [95–97]. The adult offspring that were prenatally exposed to this variable stress paradigm exhibit

increased AMPH-induced locomotor activity, reduced prepulse inhibition, as well as a host of non-psychosis related behavioral and molecular phenotypes [95–97].

Strengths and Weaknesses

The major strength of the environmental approach is that it has one of the highest levels of translational validity from an etiological perspective. This is based on the current understanding that events that increase stress, and/or directly alter developmental processes lead to persistent psychotic states. The best evidence for this approach comes from epidemiological data showing small, but statistically significant and reliable, increases of psychotic illnesses among populations that experience early life and prenatal stressors, ranging from infection, to famine, death of the father during pregnancy, and war in general [98–101]. There is even stronger evidence that exposure to marijuana prior to and during adolescence can alter the normal developmental trajectory and lead to a permanent state of psychosis, reminiscent of schizophrenia [102, 103]. A major weakness of this approach stems from the nonspecific nature of the insults making it harder to link them to a singular mechanism of action. Both the pharmacological and environmental approaches are more translationally valid than genetic ones, which have offered limited insight into the mechanisms of psychosis after decades of intense effort and investment. Indeed, recent efforts now focus on the task of making sense of the enormous constellation of genetic data that has come out of the previous era of association and candidate gene approaches. Thus, pharmacological models offer the most power presently because they combine the strengths of translational validity and mechanistic clarity. However, genetic factors almost certainly modulate the effects of environmental changes, including exposure to drugs, and will therefore remain a necessary component of preclinical models.

Manipulations to Neurotransmitter Systems

This section will review theories of psychosis developed around specific neurotransmitters across pharmacological, environmental and genetic approaches.

Dopamine

Theory

Many of the models used in the study of psychosis have been based on the dopamine theory of psychosis, which postulates that psychosis arises from the deregulation of the dopamine system. The theory initially arose from the observation that many of the first antipsychotic medications antagonized dopamine receptors [104]. This deregulation could arise from the over-release of the transmitter, limited reuptake, or over-expression of specific dopamine receptors. This theory has been supported by studies in which humans with both pre-existing, and no pre-existing psychosis, exhibit symptoms associated with psychoses after receiving a dopamine agonist [105, 106]. For instance, the indirect dopamine agonist, amphetamine, produces a psychotic state in healthy individuals and exacerbates the symptoms of psychosis in patients [107, 108]. An excess of dopaminergic signaling is hypothesized to cause the positive symptoms of psychosis, particularly those associated with schizophrenia.

Pharmacological

Amphetamine

Amphetamine has been proposed to constitute a model of positive psychosis in general. Featherstone et al. summarize the effectiveness of amphetamine-induced models of schizophrenia as measured by PPI, locomotion and latent inhibition outcomes [71]. Sensitization of amphetamine can induce deficits in latent inhibition and PPI and in some doses causes increased locomotion [71]. Most studies use an escalating dose regimen in order to avoid the neurotoxic effects that could result from an initial high dose of amphetamine [71]. Studies have shown that this gradual increase does not produce neurotoxic effects when a high dose is reached, and therefore remains as a pharmacological modulator, rather than a lesion approach. Amphetamine-induced alterations of the auditory processing abnormalities common to psychotic conditions are well characterized in rodents. It has been consistently reported that amphetamine significantly disturbs ERP amplitude and habituation, in particular diminishing N40 and P80 components [109–112]. Furthermore, normal habituation in rats is disrupted following amphetamine administration. Amphetamine decreases N40 amplitude (the rat correlate of the human N100) and abolishes suppression of the neural response to the second stimulus, resembling the habituation disturbances seen in acutely psychotic, un-medicated patients [113].

Methylphenidate

Exposure to methylphenidate elicits increased locomotive responses as well as focused stereotypies, including repetitive head movements and oral behaviors [114]. These symptoms are also comparable to those seen in amphetamine-induced models of psychosis, as noted above. One key difference between methylphenidate-induced and amphetamine-induced models is that the former does not also elicit observable effects on serotonergic pathways.

Apomorphine

Apomorphine is a non-selective dopamine agonist that is presently used in the treatment of Parkinson's disease. Of note, psychosis is among the known side effects of this agent, supporting the link between increased dopamine activity and psychosis [115]. Apomorphine has also been used in pharmacological studies to evaluate the success of drugs such as haloperidol and risperidone as antipsychotics [116, 117]. Specifically, apomorphine induces emesis in dogs through its dopamine agonist properties in the gastrointestinal system and therefore has been used as a behavioral measure of dopamine function [116]. This model was instrumental in screening compounds that were able to reduce emesis in dogs as potential candidates to reduce psychosis in humans [116, 117]. Although emesis in dogs has very poor construct or face validity for psychosis in humans, its use as a means to assess drugs as in vivo dopamine antagonists was instrumental in developing what remains the only effective treatment approach for psychosis, namely dopamine receptor type 2 (DR D2) antagonists.

Genetic

Dominant-Negative DISC1 Transgenic Mice

Disrupted in Schizophrenia 1 (DISC1) has been identified as a susceptibility gene to schizophrenia [118–120]. Dominant-Negative DISC1 transgenic mice express an altered form of DISC1 under the alpha CaMKII promoter [118]. The mice are characterized by several behavior abnormalities characteristic of psychosis including hyperactivity and disturbance of sensory-motor gating [118]. As a result, DISC1 has emerged as offering a potentially important molecular link in the etiology of psychosis and other related mental conditions, such as schizophrenia [120].

COMT Transgenic Mice

The Catechol-O-methyltransferase (COMT) is a key regulatory enzyme that degrades dopamine and thus controls dopamine availability [121, 122]. In humans, a single nucleotide polymorphism leads to the substitution of a Valine in place of a Methionine at the 158/108 locus [123]. This modification causes a two-fold increase of COMT activity, thereby reducing dopamine levels [124]. Studies in mice with alterations in COMT activity are consistent with human data showing decreased ERP amplitude as well as reduced theta and gamma power among people with psychosis [125, 126]. Specifically, COMT-Val transgenic mice displayed increased N40 latency and decreased P80 amplitude as well as reduced baseline theta and gamma power, indicating that COMT activity specifically alters long-latency components of the event-related response. More recent studies have demonstrated that the effect of COMT in schizophrenia is modified by epistatic interactions with several other genes, such that only a particular subset of genotypes results in dysfunction [127–132].

$G_s\alpha$ Transgenic Mice

$G_s\alpha$ transgenic mice express an isoform of the G-protein subunit $G_s\alpha$ that is constitutively active due to a point mutation (Q227L) that prevents hydrolysis of bound GTP [133, 134]. Expression of the transgene is driven by the CaMKIIα-promoter, which restricts expression to postnatal forebrain neurons. Specifically, in situ hybridization studies indicate that the transgene is expressed in striatum, hippocampus and cortex but not cerebellum, thalamus or brainstem [134]. Previous studies indicate that $G_s\alpha$ transgenic mice have decreased amplitude of cortically generated N40, consistent with forebrain transgene expression and a schizophrenia endophenotype. As such, this transgenic model of sensory encoding deficits provides a foundation for identifying biochemical contributions to sensory processing impairments associated with schizophrenia and psychosis.

Dysbindin-1 Mutant Mice

DTNBP1 is a well-replicated vulnerability gene for both schizophrenia and glutamatergic dysfunction. DTNBP1 encodes the dystrobrevin-binding protein 1 (dysbindin-1) [135–137]. Reduction in dysbindin-1 expression has been found in the schizophrenia population, indicating that reduced dysbindin-1 protein levels may be a disease trait of schizophrenia [136, 138, 139]. Studies in mice with a loss of function mutation in the gene have confirmed that dysbindin-1 is involved in both glutamatergic and dopaminergic transmission in the hippocampal formation, and demonstrated that reduced working memory is replicated in the mouse model [140–143]. Thus, these anatomical and physiological data indicate that disruptions of dysbindin-1 may play a direct role in abnormal hippocampal circuit behavior [135, 138, 141, 143–146]. Several studies have evaluated the selective relationship between dysbindin polymorphisms and psychotic symptoms among people with psychiatric disorders. While one study reported an association with psychosis, the other found only a selective relationship with non-psychotic symptoms [147, 148].

Strengths and Weaknesses

The dopamine hypothesis of psychosis has remained the strongest and most supported theory over the past 60 years. Evidence supports that increased dopamine signaling is necessary and sufficient to create psychotic states in humans. The

bulk of data indicating that a DA signaling deficit is necessary for psychosis relates to the ability to stop psychotic symptoms in schizophrenia using DA antagonists. Similarly, these same compounds (e.g., dopamine antagonists), are highly effective in reducing or eliminating psychotic symptoms across a host of other medical conditions, including post anesthesia delirium, psychotic depression, and epilepsy-related psychosis, just to name a few. Indeed, DA antagonists remain a highly effective treatment for psychosis, regardless of the etiology or primary pathophysiology of the causative state or disorder. Complementary evidence from drug abuse with compounds that augment or mimic DA (e.g., cocaine and amphetamine), as well as treatment of affective (e.g. bupropion) and motor disorders (e.g., ropinirole) with dopamine agonists, also indicate that increased DA availability is sufficient to cause psychotic symptoms.

Glutamate

Theory

Glutamate is the major excitatory (agonist) neurotransmitter in the human brain. NMDAR antagonists as models of psychosis became of great interest because these antagonists cover the complete spectrum of schizophrenia symptoms: positive (paranoia, agitation, and auditory hallucinations); negative (apathy, thought disorder, social withdrawal); and cognitive symptoms (impaired working memory) [149]. NMDA receptor antagonizing drugs have also been reported to induce psychosis-like alteration of event-related potentials, such as reduced P300 and MMN amplitude [150, 151]. In line with human studies, animals treated with NMDAR antagonists exhibit similar electrophysiological alterations, coincident with behavioral changes related to psychosis. Taken together, these aspects prompted researchers to increasingly employ pharmacological NMDAR blockade as a disease model [152]. Thus, the following section describes glutamatergic theories of psychosis based on using ketamine, PCP, and MK801 in humans, non-human primates and rodents.

Pharmacological

Ketamine

Schizophrenia patients treated with ketamine experience an exacerbation of positive and negative systems, suggesting that NMDAR antagonists affect a brain system that is already vulnerable in psychosis [153]. Similar to healthy humans, animals treated with ketamine exhibit behavioral and electrophysiological features that closely resemble psychosis. For example, acute ketamine administration decreases the amplitude of the mouse and rat N40 and P80, mimicking psychosis-like abnormalities on those components in humans [44, 50, 112]. Furthermore, mice undergoing 14 days of daily ketamine administration showed lasting effects, such as decreased N40 amplitude [50]. Reduced ability to detect changes in the auditory environment, as measured by EEG, is a further characteristic of psychosis that results from ketamine in rodents. While some studies have reported that ketamine disrupts cortically generated ERPs, others observed no significant effects [154–156].

MK 801

MK-801 (Dizocilpine) is a noncompetitive NMDA antagonist, like ketamine and phencyclidine, which has been used to induce phenotypes consistent with other animal models of psychosis. One of the most characteristic phenotypes observed with this pharmacological model has been deemed “popping” and denotes the incidents of explosive jumping in mice [157, 158]. MK-801 induced dose-dependent stereotypies in rodents have included repetitive head weaving (lateral head movements), rolling, sniffing, piloerection, rearing, backpedaling and circling [23, 159–161]. Another study concluded that MK-801 treated rats with the circling stereotypy demonstrate face validity with that seen in human psychotic patients [162]. Furthermore, MK-801 treated animals have also shown an increase in locomotor activity and a reduction in sensory ERPs as seen in other models of psychosis [159, 163–165]. Importantly, exposure to NMDAR antagonists leads to increased baseline EEG power in the gamma range (above 30 Hz), and a concomitant decrease in the power of evoked gamma oscillations [166, 167]. This modulation of both resting and evoked gamma power is analogous with the reduced gamma signal-to-noise ratio, and the shift from low frequency to high frequency activity observed in schizophrenia [167].

Phencyclidine

Phencyclidine (PCP) is another non-competitive NMDA receptor antagonist used in creating a pharmacological animal model of psychosis. Similar to previous models discussed, PCP has been shown to induce hyperactivity and reduced prepulse inhibitions in animals [168–170]. As an NMDAR antagonist, PCP induces stereotypies that are similar to those seen in the MK-801 pharmacological model and include: sniffing, rearing, gagging, weaving, backpedaling, grooming, stereotyped searching, circling, and repetitive head movements [171–173]. Studies have also found that PCP inhibits the event related P1 and N1 potentials [174]. Mice have also demonstrated an increase in resting gamma power after an injection of PCP [175].

Genetic

Disturbance of the NRG1 Signaling Pathway

NRG-1 and ErbB2/B4 have both been identified as susceptibility genes for schizophrenia. The NRG-1 gene encodes for the ligand Neuregulin, and the ErbB2/B4 genes encode receptors for this ligand. While the neuronal cell layers of ErbB2/B4 knockout mice appear to develop normally, these mutations cause reduced dendritic spine maturation and reduced transport of glutamate receptors to the neuronal membrane [176]. Disturbance in the NRG-1 gene also has been associated with NMDA receptor hypo-function [177–180]. One study of these transgenic mice utilized auditory ERPs as an electrophysiological measurement [181]. This study used the NRG1 transgenic model in which all three major types of NRG1 have a partial deletion of the EGF-like domain. These NRG1 heterozygote mice displayed disrupted mismatch negativity similar to that observed in psychosis. As such, transgenic models have played a crucial role in determining the function of these gene products, particularly due to the limited availability and usefulness of postmortem human tissues.

NR1 Hypomorphic Mice

NR1 is an obligatory subunit of the NMDA receptor, and therefore reduction of this protein broadly effects NMDAR mediated glutamate transmission. NR1 hypomorphic mice express from 5 % to 10 % of the normal NR1 protein [182]. Several studies have reported behavioral abnormalities in these mice that are also found in both schizophrenia and psychosis. Since then, NR1 hypomorphic mice have been considered as a translation model for these conditions. Of note, NMDAR-hypofunction is thought to contribute to social, cognitive, and gamma (30–80 Hz) oscillatory abnormalities, phenotypes common to these disorders. However, circuit-level mechanisms underlying such deficits remain unclear.

Strengths and Weaknesses

The glutamate hypothesis of schizophrenia has become increasingly popular, largely with respect to treatment-resistant negative and cognitive symptoms. However, these treatment resistant domains are less pertinent to consideration of psychosis per se. Therefore, we will limit the following discussion to the so-called positive symptoms, broadly defined, of psychosis. The strongest evidence that alterations in glutamate signaling can contribute to psychosis comes from the effects of NMDA antagonist drugs of abuse in humans. Specifically, ketamine (Special K) or phencyclidine (angel dust) abuse can result in a lasting state of disorientation and bizarre behaviors that resemble illness related psychosis. Animal models using NMDA antagonists also provide some support for the role of altered glutamate signaling in the psychotic process. However, this is largely limited to hyperactivity following low doses of NMDAR antagonists. Alternatively, there has been virtually no evidence that medications that alter glutamate signaling have any effectiveness for treating psychosis.

GABA

Theory

Most recently, the role of alterations in Gamma Aminobutyric Acid (GABA) signaling has been considered as a contributing factor in schizophrenia. There are several lines of evidence to support this hypothesis. First, a series of anatomical post mortem studies in schizophrenia have demonstrated alterations in the number of GABAergic cells. Additionally, multiple studies have shown that people with schizophrenia have elevated resting (i.e., baseline or default network) brain activity, suggesting a disinhibition phenotype. Furthermore, studies in non-human preclinical models demonstrate that exposure to glutamate antagonists also causes increased network activity. This in turn has been proposed to be due to a selective effect of the NMDAR antagonist drugs on glutamate receptors on GABAergic interneurons. Taken together, these data led to a hypothesis that there is reduced GABA-mediated inhibitory tone, due to a reduction of excitatory drive to interneurons.

Genetic

GAT1 Knockout Mice

A recent study found that GABA transporter 1 (GAT1) knockout mice exhibited behavioral phenotype associated with psychosis. These knockout mice displayed hyperactivity, increased sensitivity to psychotomimetic drugs, exaggerated responses to novel objects, impaired novel object recognition, and reduced pre-pulse and latent inhibition [183].

Strengths and Weaknesses

As noted above, much of the evidence relating GABA to psychosis is based on a constellation of anatomical data in schizophrenia, and interpretation of physiological data. However, there is little if any direct evidence for this hypothesized mechanism, beyond the initial anatomical data. Recent studies, investigating the effects of reduced NMDA receptor expression directly on either GABAergic cells or on excitatory pyramidal cells, suggest that the disinhibition model may not be correct. Specifically, reducing NMDAR mediated glutamate signaling on excitatory pyramidal cells leads to increased network excitability, reminiscent of either schizophrenia or exposure to NMDA antagonists. Thus, it now appears that

directly altering the excitatory inputs on pyramidal (glutamatergic) neurons causes those very neurons to increase their firing rate. This in turn appears to be due to alterations in inherent membrane properties [184]. As such, the longstanding assumptions about disinhibition via GABAergic cells over the previous decade may not be valid [185].

Serotonin

Theory

The potential role of altered serotonin signaling in psychosis stems from the observation that several hallucinogenic compounds, such as Psilocybin (the active compound in mushrooms), mescaline (the active compound in peyote), and Lysergic Acid Diethylamide (LSD), bind to and activate various forms of serotonin receptors. While such observations suggest that selective activations of serotonin systems are capable of inducing psychosis, several of these compounds are also thought to activate dopamine receptors.

Pharmacological

Few specific pharmacological manipulations of the serotonin pathway exist. Pharmacological models of psychosis using solely compounds that modulate 5HT receptors are less ubiquitous than the previously discussed pharmacological models. DOI (2,5-dimethoxy-4-iodoamphetamine) is a 5HT 2A receptor agonist that has been used to induce head twitching in mice as a model with predictive validity for psychosis and hallucination [158]. LSD, DMT (Dimethyltryptamine), mescaline, and psilocybin are also 5HT 2A receptor agonists that have been able to produce positive symptoms of psychosis in humans [186–189]. However, there is not an abundance of studies that have used these compounds to produce animal models of psychosis. One study found that chronic administration of LSD at low doses induced behaviors such as hyperactivity and social deficits [35]. DMT has also caused deficits in mismatch negativity generation [156]. Due to the effects of these compounds on human subjects and the affinity of certain antipsychotics to 5HT receptors, dysfunction in 5HT signaling has been implicated alongside glutamate and dopamine [190–196].

Genetic

5-HT 1A Receptor Knockout Mice

5-HT 1A receptor knockout mice have exhibited relatively increased AMPH-induced locomotor activity. However, this manipulation demonstrated no change in pre-pulse inhibition and a reduction in the effect of the hallucinogen 5-MeO-DMT, making it less fitting as a model psychosis [197].

Alteration to the Serotonin Transporter Gene

The STin2 polymorphism of the serotonin transporter gene (SERT) has been associated with psychosis in humans, while SERT knockout mice have been recognized as a model of impaired emotional control [198, 199]. Impaired SERT function would theoretically result in elevated serotonin in the synaptic cleft and could possibly produce psychotic symptoms similar to those observed with 5HT 2A agonist [187, 200]. Future studies should explore whether this SERT knockout model could be related to psychosis.

Strengths and Weaknesses

As noted above, several lines of research suggest that primary alterations of serotonergic systems can create a psychotic state in humans, or produce animal behaviors that are associated with psychosis in humans. The greatest limitation to the link between serotonin systems and endogenous psychosis in humans comes from the lack of effectiveness of serotoninergic agents in treating the symptoms. For example, multiple agents have been created based on the hypothesis that adding activity at serotonin receptors would improve antipsychotic efficacy. However, this has been clearly disproven, as none of these agents are different (at least not better) than dopamine antagonists that lack serotonergic activity.

Future Directions and Conclusion

Recent years have seen an explosion of effort focused on the non-psychotic symptoms in schizophrenia and related disorders. Yet, there is little understanding of the basic mechanism of psychosis, as well as how those mechanisms relate to other illness domains. There are numerous animal models of psychosis that currently exist and the challenge remains to find common, overlapping mechanisms of psychosis pathophysiology that result from a wide array of etiologies.

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Compliance with Ethics Guidelines

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