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UPDATE ARTICLE

A critical overview of animal models of psychiatric disorders: challenges and perspectives

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Animal models of psychiatric disorders are a challenging but highly relevant issue. Most psychiatric disorders are very heterogeneous syndromes, resulting from multiple and varied causal factors and characterized by symptoms that can only be inferred with significant limitations in non-human models. As constructing a model that reproduces a whole psychiatric syndrome seems virtually impossible, researchers have tried to focus on endophenotypes, i.e., discrete traits that are more proximal to predisposing genes than the whole syndrome. These can be explored in a wide range of approaches, such as in pharmacological, lesion, and environmental models. Another challenge is to understand how genes interact with environmental factors over time to result in the syndromic phenotype. A better understanding of the subcellular mechanisms that enhance or allow brain resistance to environmental influences is required, as is a global thesis compatible with the diversity of diseases sharing similar behavioral and biological traits. With an experimental inventory of the possible causes of minor developmental failures, we may systematically explore their consequences in the adult animal and be able to decide if this will enlighten the understanding of one or another psychiatric disease.

Keywords: Animal models; psychiatric disorders; endophenotype; epigenetics

Introduction

Development of animal models of psychiatric disorders remains a challenge because of our still poor understanding of the etiopathogenesis and pathophysiology of such disorders. This results from the disparity of aims between physicians, whose interest obviously remains based on clinical features, and researchers, who need a biological foundation. There is virtually no objective measure or biological feature that could be used for psychiatric diagnosis. Progress in this field is hampered by the complexity of the human nervous system and the difficulty of studying it in detail in humans. Therefore, experimental models remain of great interest.[1]

A further complication is that most psychiatric disorders are very heterogeneous, probably resulting from multiple and varied causal factors leading to a similar phenotype that allows a syndromic diagnosis. In addition, most psychiatric symptoms (e.g., hallucinations, obsessions, delusions, guilt) are uniquely human and can only be inferred with significant limitations in animal models. It is not necessary or even realistic to postulate that an abnormal rat behavior should or could be analogous to an abnormal human behavior. For all these reasons, there is presently a consensual belief that development of a model that reproduces a whole psychiatric syndrome, such as schizophrenia, bipolar disorder, or major depressive disorder, is virtually impossible in a lower animal.[1] However, we must bear in mind that no animal model of a human disease does so, even for organic diseases such as diabetes, with all its complications.

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Deconstructing mental illness: endophenotypes

As a consequence, researchers have tried to focus on discrete traits that could be studied in laboratory animals and/or be linked to genetic alterations. In this context, the term ''endophenotype'' was largely incorporated into psychiatric research and explored in models under the concept of heritable phenotypic features that reflect discrete components of the pathophysiologic processes more proximal to predisposing genes than the whole syndrome.[2] Examples of tests used as endophenotypes are listed in Table 1. A major limitation of using such traits is that most are not specific to any psychiatric syndrome. For example, prepulse inhibition (PPI), a largely explored endophenotype, is disrupted in schizophrenia, Alzheimer's disease, Huntington disease, and bipolar disorder.[1]

Beyond their obvious role in genetic models of psychiatric disease, these traits serve as dependent variables in a wide range of approaches, such as in pharmacological, lesion, and environmental models of psychiatric disease. Such approaches have a controlled variable, based on a hypothesis about the etiopathogenesis or pathophysiology of the disease, and an endophenotype that is used as the dependent variable. For example, neurodevelopmental models are based on the

Table 1 Examples of tests used as endophenotypes in models of psychiatric disorders

Name of the test	Short description	Property evaluated	Subjects	Main relevant brain area	Limitation	Relevant review
Locomotor effects of dopaminergic agents	Effect of amphetamine on the distance traveled after an initial habituation period	D2 receptor hypersensitivity	Rodents	Mesocorticolimbic system	Rather nonspecific	Swerdlow et al., 2001[3]
Prepulse inhibition of the startle reflex (PPI)	Startle reflex decreased by a stimulus delivered tens of milliseconds before the startling sound	Elementary form of attention	Rodents, humans	Limbic cortex, striatum, pallidum or pontine tegmentum	Nonspecific, parametric dependency	Swerdlow et al., 2000[4]
Latent inhibition (LI)	Slower conditioning to a stimulus that had been repeatedly pre-exposed without consequences	Attention and/or memory	Rodents, humans	Mesocorticolimbic system	Doubtful alteration in patients	Weiner et al., 1997[5]
Dynamics of dopamine release	Extracellular dopamine evaluated by microdialysis or voltammetry	Reactivity of dopaminergic neurons	Rats	Prefrontal cortex, nucleus accumbens	Technically difficult and time consuming	Meyer & Louilot, 2012[6]
Gene expression or mechanisms of gene expression	Uses reverse-transcriptase quantitative evaluation of mRNAs or microarrays	Epigenetic mechanisms possibly sustaining the disease	Any species	Mainly prefrontal cortex	Large diversity of candidate genes/ interpretation difficulty	Kumarasinghe, 2012[7]
Social withdrawal	Video recording of at least two individuals together and coding their interaction (ethological basis)	Escaping from social interplay	Rodents, monkey, humans	Unclear, perhaps prefrontal-parietal interaction	Nonspecific (any uncomfortable situation causes social withdrawal in an animal), lack of cross-laboratory standardization of variables, related to negative or depressive symptoms?	Gururajan et al., 2010[8]
Decreased sucrose preference	Measures the preference for sucrose solution over water in the absence of a sensory or motor deficit	Anhedonia	Rodents	Nucleus accumbens	Non-specific (linked to depression, but also seen in schizophrenia and stimulant withdrawal)	Willner, 2005[9]
Morris Water maze or radial arm maze	Learn to find the way to a hidden target	Ability to use external spatial cues	Rodents, humans	Hippocampus	Needs complex procedures, depends on the level of motivation	Andersen & Pouzet, 2004[10]
Attentional set-shift	To cope with a modified learned rule	Behavior flexibility and response perseverance	Rodents, monkeys, humans	Prefrontal cortex	Needs complex conditioning procedures, depends on the level of motivation	Brooks et al., 2012[11]
Delayed non-matched to sample	Keeping a cue transitorily in memory until solving the task	Working memory storage capacity	Rodents, monkeys, humans	Prefrontal cortex	Major theoretical and methodological differences between lower animal and human testing methods	Lipska et al., 2002[12]
Grooming	Measures the amount of grooming over a period of time	Compulsive behavior	Rodent	Basal ganglia	Major theoretical and methodological differences between lower animal and human behavior	Welch et al., 2007[13]
Sleeping time	Measures the amount of sleep and its phases during a period of time	Alterations of the circadian cycle	Any species	Hypothalamus, reticular formation	Nonspecific (any uncomfortable situation may cause it), perhaps related to mania	Roybal et al., 2007[14]

assumption that a failure in brain development is involved in psychiatric diseases, using lesions (neonatal hippocampal lesion), prenatal exposure to toxins (methylazoxymethanol [MAM]), or environmental constraints (social isolation model) to elicit alterations in endophenotypes of interest.[15] Examples of such approaches are listed in Table 2.

The great challenge: reconstructing mental illness in models

Another challenge is the construction of models to understand how genetic alterations interact with environmental factors over time to result in the syndromic phenotype. Clear epidemiological information is a prerequisite for construction of such models, which have been on a quest for a genetic determinism for most psychiatric diseases. Despite indisputable achievements, discoveries in this field have been disappointing.[31] We suggest that this could be due to a mistake in the a priori assumption of such studies. They postulate, often implicitly, the occurrence of rare mutations with a weak expression of their corresponding phenotype, except in some individuals in which an unfortunate environmental feature acts as a trigger. The opposite assumption was not considered – namely, that psychiatric disorders are sustained by a very frequent

Table 2 Examples of approaches used to explore endophenotypes as dependent variables in models of psychiatric disorders

Hypothesis	Period of action	Type of action	Otherwise	Most recent relevant review
Excessive dopamine release in the mesocorticolimbic system	Adult	Pharmacological → Enhancing dopamine (D2) neurotransmission	Also tested with chronic administration	Lodge & Grace, 2008[16]
Reduced glutamatergic activity	Adult	Pharmacological → NMDA antagonists (ketamine, PCP, *MK801*)	Also tested with neonatal ketamine administration	Javitt et al., 2012[17]
Serotonergic system malfunction	Adult	Pharmacological → Psychedelic drugs (LSD)	Models the hallucinatory aspect of psychosis	Moreno et al., 2013[18]
Brain connectivity abnormalities	Neonatal (PN7)	Lesion → of the ventral hippocampus (NVHL model)	Models the delayed onset of schizophrenia	Tseng et al., 2009[19]
Epigenetic control of development	Prenatal (GD17)	Toxin → MAM	MAM is a strong methylating agent (possible role of DNA methylation)	Peleg-Raibstein et al., 2012[20]
Shaping of brain development by the environment	Weaning to adulthood	Social isolation	Could be mediated by oxidative stress	Fabricius et al., 2011[21]
Mother-pup interaction shaping brain development	Weaning to adulthood	Neonatal isolation (PN9)	Potential contribution of the brain-neurovegetative system interplay	De la Fuente et al., 2009[22]
Genetic determinism of schizophrenia	Genetic	Knockout of *DISC1* (disrupted gene in schizophrenia)	Rare human mutation enhancing the incidence of some diseases	Jaaro-Peled; 2009[23]
Neuronal migration, altered synaptogenesis	Genetic	Reelin-deficient mouse	Reelin gene found reduced in patients with schizophrenia	Laviola et al., 2009[24]
Modified dopamine neurotransmission	Genetic	Dopamine transporter knockout	Also produces a cholinergic deficit	Weiss et al., 2007[25]
Metabotropic glutamate receptor alteration	Genetic	mGluR5 knockout	Belongs to the models pointing to altered glutamatergic system	Wierońska et al., 2012[26]
Dysfunctional neurotransmission	Genetic	Sandy ''sdy'' mouse (knockout of dysbindin-1)	Affects dopaminergic, GABAergic, and glutamatergic transmission	Talbot, 2009[27]
Reduced growth factor production	Every age	BDNF overexpression by stress	Found altered in some disorders	Fumagalli et al., 2012[28]
Viral infection/brain inflammation	Prenatal (PN18)	Infection	Possible role of hyperthermia	Winter et al., 2008[29]
Brain inflammation	Prenatal (or early postnatal)	Immune stimulation by LPS injection	Immune-inflammatory parameters altered in several mental disorders	Elovitz et al., 2011[30]
Mild chronic stress leads to depression	Adult	Application of mild electric shocks chronically	Decreases sucrose preference or engagement in sexual behavior (anhedonia?)	Willner, 2005[9]
Circadian rhythms and their related genes are involved in mania	Genetic	Study of mice with polymorphisms in *CLOCK* gene	Affects dopamine and produces decreased sleep, hypophagia, hyperlocomotion, and risk-taking behavior	Roybal et al., 2007[14]

BDNF = brain-derived neurotrophic factor; LPS = lipopolysaccharide; mGluR5 = metabotropic glutamate receptor 5; MAM = methylazoxymethanol acetate; NMDA = N-methyl-D-aspartate; NVHL = neonatal ventral hippocampal lesion; PCP = phencyclidine.

modification of the genotype, but to which the majority of subjects would be resilient. Some specific failure in this resilience would allow the disease to occur. Such an assumption could even explain why the same genotype contributes to depression in some subjects and schizophrenia in others, as observed in a family in the case of the famous *DISC1* mutation.[32] This general assumption could be of importance for the mathematical basis of future epidemiological investigations and for fundamental investigations, the latter having then to consider the mechanisms of resilience rather than the causes of vulnerability of the brain to its environment.

Perspectives

A better understanding of the subcellular mechanisms that enhance or allow brain resistance to environmental influence – i.e., more basic research into the mechanisms of epigenesis – is required to reconcile these different approaches to genetic-environment interaction. A recent study in rats showed that maternal separation modifies genome expression.[33] This is a crucial gate to the interplay between genotype and social environment. In addition, we need a global thesis compatible with the diverse range of diseases that share similar behavioral and biological traits. Friston's ''disconnection hypothesis'' may serve as a link between the diversity of causes and biological and behavioral manifestations.[34,35] Briefly, it proposes that abnormal functional integration among different brain regions is a feature of several psychiatric disorders. This ''disconnectivity'' would be linked to altered N-methyl-D-aspartate (NMDA) receptor-mediated synaptic plasticity (or even wiring of fibers during brain development) and/or altered regulation of these receptors by neuromodulatory transmitters such as dopamine, serotonin, and acetylcholine. There is a diversity of possibilities for neuronal connections to become particular, which would account for the diversity of their clinical or biological outcomes. Rather than considering more models of depression or schizophrenia, we suggest that an experimental inventory of the possible causes of minor developmental failures be taken and that the biological and behavioral consequences of these developmental failures in the adult animal be explored systematically, with no a priori endponts for this research. Only later on will we be able to decide if the corresponding observations will enlighten our understanding of any given psychiatric disease.

Conclusions

Animal models of psychiatric disorders remain a challenging but highly relevant issue. Progress has been made by the deconstruction of mental syndromes into endophenotypes. The great challenge remains to reconstruct them by understanding how the interplay between genes and environment results, over time, in the full syndrome. In this regard, a promising approach could be the search for possible causes of minor developmental failures and the assessment of their biological and behavioral consequences in the adult animal.

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