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Review

Developing better and more valid animal models of brain disorders

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HIGHLIGHTS

- Valid animal models are crucial to understand the pathobiology of complex brain disorders.
- Cross-species validation of animal models is critical for developing valid experimental models.
- Population (external) validity is key for animal experimental models of brain disorders.
- Optimal animal models must also target the interplay between multiple disordered domains.

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ABSTRACT

Valid sensitive animal models are crucial for understanding the pathobiology of complex human disorders, such as anxiety, autism, depression and schizophrenia, which all have the 'spectrum' nature. Discussing new important strategic directions of research in this field, here we focus i) on cross-species validation of animal models, ii) ensuring their population (external) validity, and iii) the need to target the interplay between multiple disordered domains. We note that optimal animal models of brain disorders should target evolutionary conserved 'core' traits/domains and specifically mimic the clinically relevant inter-relationships between these domains.

Contents

1. Introduction

Human brain disorders are complex multifaceted diseases with growing societal impact. Animal models are a useful tool to understand the pathobiology of human disorders and discover novel efficient therapeutic targets [1–3]. Recently, the existing challenges with constructing 'better' animal models have been discussed, noting the lack of objective behavioral and translational biomarkers, and the importance of models' construct, face and predictive validity [1–3] (Table 1). Other useful methodological approaches suggested recently [4] include extending the test duration, testing laboratory vs. wild-derived strains, and creation of large phenotypical databases to evaluate the validity of endpoints and experimental models.

We agree that in order to achieve a better validity, "there is no alternative but to return to the design table and investigate the behavior in detail to come up with new and better measures" [4].

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Table 1
A summary of main (traditional) and additional types of validity of animal models of brain disorders.

Validity type	Definition
Face	Sensitivity of the proposed model to treatments affecting disease in humans [17]
Predictive	Ability of the proposed model to recapitulate behavioral and other symptoms in humans [17]
Construct	Relevance of the proposed model to disease etiology (mechanisms) in humans [17]
Evolutionary	Ability of the proposed model to target disordered domains in a similar manner across various species
Population (external)	Ability of the proposed model to reflect natural variance in phenotypes observed in general population
Inter-relational	Ability of the proposed model to target the interplay between various disordered domains

But what else can be done for improving animal modeling of brain disorders? Here we outline three important strategies to address this problem—cross-species validation of animal models, improving population validity of the models, and targeting the interplay between a system of multiple disordered domains. Specifically, we argue that optimal animal models of brain disorders should target evolutionary conserved 'core' traits/domains, reflect their natural phenotypic variances within the population, and mimic the clinically relevant inter-relationships between the implicated disordered domains.

2. Cross-species validation of animal models

In line with Dobzhansky's famous notion that "nothing in biology makes sense except in the light of evolution", we recognize that expanding the range of model organisms is an important goal in biomedical research [5]. Given the role of evolutionarily conserved pathogenetic pathways and traits in translational neuroscience [6], we posit that animal models of brain disorders must be thoroughly evaluated in terms of their *evolutionary (cross-species) validity*. Specifically, an animal model will have high validity if it targets evolutionarily conserved behavioral and physiological phenotypes in a similar manner across multiple species (Table 2). For example, mouse freezing and center avoidance in the open field test parallel anxiety-like behavior in humans, primates, birds and fish. Likewise, anhedonic-like responses, traditionally associated with clinical depression, have also been reported in various species, including primates, rodents and birds. In addition to behavioral similarity, these phenotypes also show shared neurophysiology and neurochemistry across various species. Collectively, this indicates that models utilizing novelty-evoked freezing/avoidance or anhedonic-like responses are not only translationally relevant to human disorders, but represent more general, evolutionarily conserved phenomena that are central to pathogenetic mechanisms in question.

Therefore, future efforts are necessary to develop animal models of brain disorders that target several various domains (and their underlying pathological mechanisms) in a similar manner across various species. Briefly, the model that targets the specific domain or trait in a similar manner in a wider range of model organisms will have a higher evolutionary validity, compared to a model that is limited to fewer, evolutionarily close taxa. While this effort may require marked expansion of the available toolbox of model organisms, it will eventually pay off by enabling a better focus on core, evolutionarily conserved (and therefore more fundamental and translationally relevant) aspects of brain pathology. Furthermore, evolutionary validity criterion can be applied in a 'reverse' manner, e.g., enabling the investigators to better select potential endpoints in newly developed models, with behaviors known to be conserved across species becoming the first (and, likely, optimal) choice during the model development.

3. Improving population (external) validity of animal models

The use of behavioral models in various organisms, such as rats, mice or zebrafish, is of interest to a wide range of biomedical investigators [5]. However, there is some concern regarding the use of animal (and clinical) experimental populations that can make it difficult to draw general conclusions from such studies [7]. One approach is to use genetically homogenous inbred strains of animals, to control genetic environment and minimize phenotypic 'variance noise' (due to different genetic composition of the subjects) that can mask important (but often subtle) changes or cause false positives. Another approach is to use a wild-type 'outbred' population to represent a more heterogeneous cohort, as it would be best suited to draw general conclusions about the model's translatability into human disorders (based on the fact that human population is highly outbred, and it is impossible to 'fully control' their genetic environment). Conceptually, this approach is based on population validity (sometimes referred to as external validity), which reflects the model's ability to represent natural variance in phenotypes observed in general population (Table 1), and is becoming widely recognized in translational neuroscience research [2,3]. In various experimental models, population validity can be assessed through the examination of whether sub-populations of subjects (selected based on their differing levels of a specific behavior A) will also display robust differences in other behavioral, physiological or genomic responses. The idea of population validity is not only based on desired similarity of animal models to a 'real-life' human population, but is also in line with the importance of studying individual variances in resilience and susceptibility as a tool to study mechanisms of brain disorders, their risk factors, and mechanisms of adaptation [8].

4. Targeting the interplay between disordered domains

In addition to evolutionary and population validity, we also recognize that human neuropsychiatric disorders have a complex nature with multiple overlapping domains [6,9]. For example, experimental autism models are characterized by social deficits, behavioral perseverations and cognitive/speech deficits (Table 2). However, these domains do not exist separately within autism, but are pathologically interlinked, and this link itself forms the core of the specific pathology [9]. For example, these three domains can co-occur in an unrelated manner, e.g., in an individual with cognitive deficits and high anxiety (manifesting itself as social phobia and obsessive–compulsive disorder, OCD). Albeit seemingly very similar clinically, the exact nature of brain pathogenesis will be different in these two cases. Therefore, the ability of an animal model to mimic both the disordered phenotypes and the inter-relations between them (which we termed as *inter-relational validity*, Table 1) becomes an important consideration when developing experimental models of brain disorders. Recent mouse evidence strongly supports this notion, leading to new genetic models of brain disorders that simultaneously target several interplaying domains within a specific pathology (Table 2). Addressing the emerging translational challenges in neuroscience research, the 'domain interplay' approaches [9,10] examine brain disorders as spectra of *overlapping* and *interplaying* domains, with pathophysiological links between individual phenotypes themselves representing new, 'higher-order' phenotypes of the disorder. In addition to traditional phenotypes, these novel 'derivative' phenotypes may themselves be under an independent genetic control,