Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Casting a wider fish net on animal models in neuropsychiatric research

Zachary J. Hall [a,1], Alex R. De Serrano [b,1], F. Helen Rodd [b,*], Vincent Tropepe [a,**]

[a] Department of Cell & Systems Biology, University of Toronto, Canada
[b] Department of Ecology & Evolutionary Biology, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 18 February 2014
Received in revised form 28 March 2014
Accepted 1 April 2014
Available online xxxx

Keywords:
Behavior
Brain
Guppy
Zebrafish
Neurodevelopment

ABSTRACT

Neuropsychiatric disorders, such as schizophrenia, are associated with abnormal brain development. In this review, we discuss how studying dimensional components of these disorders, or endophenotypes, in a wider range of animal models will deepen our understanding of how interactions between biological and environmental factors alter the trajectory of neurodevelopment leading to aberrant behavior. In particular, we discuss some of the advantages of incorporating studies of brain and behavior using a range of teleost fish species into current neuropsychiatric research. From the perspective of comparative neurobiology, teleosts share a fundamental pattern of neurodevelopment and functional brain organization with other vertebrates, including humans. These shared features provide a basis for experimentally probing the mechanisms of disease-associated brain abnormalities. Moreover, incorporating information about how behaviors have been shaped by evolution will allow us to better understand the relevance of behavioral variation to determine their physiological underpinnings. We believe that exploiting the conservation in brain development across vertebrate species, and the rich diversity of fish behavior in lab and natural populations will lead to significant new insights and a holistic understanding of the neurobiological systems implicated in neuropsychiatric disorders.

Contents

1. Introduction

Neuropsychiatric disorders are characterized by life-long cognitive and behavioral impairments with severe effects on quality of life. A substantial proportion of adults with these disorders can begin exhibiting symptoms while they are relatively young, indicating that a better understanding of the origins of neuropsychiatric illness requires a focus on mechanisms of brain and behavioral development (Money and Stanwood, 2013). This is especially critical because symptoms of disease often manifest long after underlying causal processes have initiated. Neuropsychiatric disorders are often associated with genetic and environmental perturbations during critical periods in brain development (Jaffee and Price, 2007). Thus, the challenge is to understand how interactions between genetic, epigenetic and environmental factors alter the trajectory of neurodevelopment to produce the aberrant structural and biochemical changes in the brain that are characteristic of disease. To improve therapeutic outcomes, we need to learn how to redirect maladaptive developmental trajectories toward a more typical

Abbreviations: GABAergic, Gamma-amino buytaric acid producing neurons; RNA, ribonucleic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

* Correspondence to: H. Rodd, Department of Ecology & Evolutionary Biology, University of Toronto, 25 Harbord Street, Toronto, ON M5S 3G5, Canada. Tel.: +1 416 946 5035.
** Correspondence to: V. Tropepe, Department of Cell & Systems Biology, University of Toronto, 25 Harbord Street, Toronto, ON M5S 3G5, Canada. Tel.: +1 416 946 0338.
E-mail addresses: helen.rodd@utoronto.ca (F.H. Rodd), v.tropepe@utoronto.ca (V. Tropepe).

[1] Equal contribution.

http://dx.doi.org/10.1016/j.pnpbp.2014.04.003

path. Animal models that enable us to easily manipulate genes and the environment could teach us to detect when structural and biochemical changes occur in the brain during development and to determine how they might be corrected. For decades, studies on the causes and treatment of neuropsychiatric disorders have relied mostly on a few, intensively studied, rodent lab species. Therapeutic interventions discovered using these animal models have not always been easily transferred to humans. For example, whereas learning deficits in one genetic mouse model of neurofibromatosis type 1 were rescued with administration of statins, participants in a subsequent human clinical trial using the same therapy showed no significant improvement on any learning measures employed (Castrén et al., 2012; Krab et al., 2008). Despite the impressive progress towards developing animal (especially rodent) models, it is clear that these models do not capture the full complexity of human mental illness.

Limitations in the cross-species transferability in neuropsychiatric interventions stem from: (1) a historic focus on an attempt to recreate complete neuropsychiatric disorders, as they are identified in humans, in lab models; and (2) a disproportionate understanding of how dysfunctional neurobiological substrates produce neuropsychiatric symptoms in only a few model species. In this review, we discuss how a paradigm shift from trying to recreate full neuropsychiatric disorders in a single species to studying dimensional components of these disorders, or endophenotypes, will be extremely productive and allow the use of additional species for research. We specifically discuss some of the advantages of incorporating studies of brain and behavioral development using various fish species into current neuropsychiatric research. Furthermore, we address the suitability of fish as potential lab models from both a comparative neurodevelopmental and neuroethological perspective.

2. Shifting focus to endophenotypes and comparative studies

Recreating the constellation of genetic (*e.g.*, heritable polymorphisms or *de novo* mutations) and environmental (*e.g.*, social interactions, nutrition) factors contributing to neuropsychiatric disorders in lab animals to produce *bona fide* disease models has been challenging. Instead of modeling all aspects of a disorder, focus has shifted toward using animals to model endophenotypes, which are heritable traits with clear, quantifiable, and neurobiological connections to a disorder that has been identified in humans (Bearden and Freimer, 2006; Gottesman and Gould, 2003). Endophenotypes are often considered intermediate neurobiological phenotypes that mediate genetic and environmental effects to produce behavioral and cognitive symptoms in neuropsychiatric disorders (Reus and Freimer, 1997). Unlike many current neuropsychiatric diagnostic criteria, which are criticized for relying on qualitative, discrete symptoms to classify disease and failing to capture variation in the expression of disease among individuals (Hyman, 2010), endophenotypes are often quantifiable and continuous. Accordingly, the National Institute of Mental Health has moved toward the incorporation of endophenotypic data in neuropsychiatric diagnosis by establishing the Research Domain Criteria Matrix framework. This matrix summarizes endophenotypes on all levels of mechanism from genes to behavior for mental health disorders. Among endophenotypes, alterations in brain structure, gene expression, and neurotransmitter signaling are now easily investigated across vertebrate species because of significant conservation in the cellular mechanisms of brain development. For example, endophenotypes of schizophrenia include impaired dopaminergic and GABAergic signaling (reviewed in Souza and Tropepe, 2011). On the other hand, behavioral and cognitive endophenotypes are more challenging to investigate because they rely heavily on behavioral paradigms not adapted for testing non-traditional lab species. For example, negative mood, a cognitive endophenotype of depression, is often sampled in rodents using forced swim tests (Homberg, 2013), which pose clear challenges with cross-species comparison to other taxa such as fish.

The recent shift in emphasis to modeling endophenotypes for neuropsychiatric research has three major benefits. First, endophenotypes provide a biological description of symptoms that can be accurately quantified in non-human animals, such as GABAergic neuronal population size and connectivity, or elevated dopamine receptor expression. Second, using endophenotypes avoids potential problems with anthropomorphic paradigm design and interpretation of animal behavior when models are treated as *bona fide* recreations of human disorders. For example, Homberg (2013) describes the controversial interpretation of depressive immobility in rats placed in an inescapable stressful situation, the Porsolt swim test. In this test, a rat is placed in a pool of water from which it is impossible to escape and the time to which the rat ceases to try to escape and begins treading water is measured. Historically, treading water in this test is interpreted as negative mood or helplessness, although, as Homberg (2013) explains, this behavior may actually reflect an adaptive, presumably energetically favorable, response to chronic stress that indicates how the animal copes with the challenge. Third, a focus on neurobiologically defined endophenotypes affords us the opportunity to expand the repertoire of animal models to other species in which these endophenotypes can be easily observed and manipulated. Specifically, we suggest that a productive approach to studying endophenotypes in animal models is to first describe neural systems and the associated set of normal behaviors they support. These brain–behavior relationships are often originally established using functional neuroscience to correlate neuronal activity with production of a behavior and confirmed by establishing a causal brain–behavior relationship by manipulating neuronal signaling in this pathway and testing for subsequent effects on the behavior of interest. Second, we can test how these brain–behavior patterns compare across species, like the work that has been conducted on the conserved social decision-making circuit, a neural circuit in the basal forebrain and midbrain that appears to mediate social interaction behavior in vertebrates (O'Connell and Hofmann, 2011). Third, we can compare how alterations in conserved brain–behavior relationships compare to endophenotypes associated with cognitive and behavioral impairment. Finally, we stress the importance of validating behavioral tests for each species before using them to make behavioral inferences, as natural history and ecological differences between species can affect the usefulness of said tests. Validation can be thought of as ensuring that the behavioral assay actually represents the theoretical definition of that behavior (Cozby, 1997). Empirical tests of behavioral consistency will help determine how well a test appears to measure the behavioral variable in question. For example, this process has been used to validate the open field test as an assay for exploratory behavior in guppies (Burns, 2008). A similar approach has been applied to larval zebrafish where assessment of individual behavioral variation within a population allowed for a separation of the different types of responders to examine baseline movement and how this movement changed as a result of alterations in neuromodulator signaling (Shamchuk and Tierney, 2012). This approach allows us to take advantage of the burgeoning field of neuroethology, which identifies the neural substrates supporting the production of naturally occurring animal behavior, including individual variation. Here we argue that ongoing neurobiological, genetic, and ethological work has set the stage for the increased use of fish in neuropsychiatric model organism research. By incorporating endophenotypes, new animal models, and comparative studies into neuropsychiatric research, we believe that we can achieve new insight and holistic understanding of the neurobiological systems implicated in neuropsychiatric disorders.

3. Using fish to understand the neurobiological substrates of behavior

Current neuropsychiatric models are almost entirely limited to the use of pharmacologically- and genetically-manipulated rodents. The use of rodent animal models of disease is often justified because of a

Please cite this article as: Hall ZJ, et al, Casting a wider fish net on animal models in neuropsychiatric research, Prog Neuro-Psychopharmacol Biol Psychiatry (2014), http://dx.doi.org/10.1016/j.pnpbp.2014.04.003