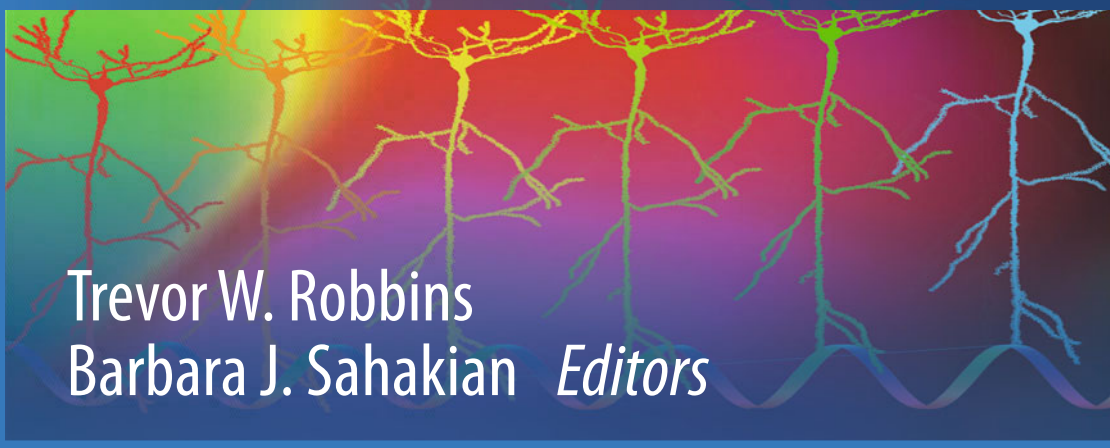
Current Topics in Behavioral Neurosciences 28



Trevor W. Robbins
Barbara J. Sahakian *Editors*

Translational Neuropsychopharmacology

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Current Topics in Behavioral Neurosciences

Volume 28

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Current Topics in Behavioral Neurosciences provides critical and comprehensive discussions of the most significant areas of behavioral neuroscience research, written by leading international authorities. Each volume offers an informative and contemporary account of its subject, making it an unrivalled reference source. Titles in this series are available in both print and electronic formats.

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This volume is dedicated to Athina Markou's enormous contribution to translational neuropsychopharmacology

Preface

Mental health disorders currently exert an enormous socioeconomic burden, greater than those of other medical conditions arising from cardiovascular disease or cancer, and yet there have been very few therapeutic advances in recent years in the form of novel effective drug treatments in psychiatry. Indeed, the results of Phase 3 trials have been so disappointing and unsuccessful that many companies have withdrawn from neuroscience research related to psychiatry, as it has been thought to be somehow 'too difficult'. Various causes for that difficulty have been raised including regulatory stringency (as well as perhaps rigidity), the nosological heterogeneity of psychiatric disorders and the unavailability of predictive animal models. The first of these problems could perhaps eventually be addressed by the demonstration of a more successful drug discovery strategy. The heterogeneity of psychiatric disorders could perhaps be addressed by employing transdiagnostically more accurate and precise neurobehavioural measurements according to a 'Research Domain Criteria' type approach of the form recently advanced by the U. S. National Institute of Mental Health—but this development will not concern us directly here. The third problem, of animal models, has been considered to be replaced by superior predictive tests based on suitable 'biomarkers', but this strategy, although useful is unlikely by itself to replace the ultimate assays for psychiatric symptoms which are likely mainly to be behavioural or cognitive in nature

In the case of animal models, the defence has been offered (by Professor Mark Geyer, San Diego) that companies frequently are unable to predict the outcome of Phase 2 trials from (proof of concept and human dose-response) Phase 2 trials, let alone from the animal models alone. This insight raises the issue of whether there has been sufficiently effective 'translation' of the animal models even to human studies, and whether much more attention has to be paid to this particular 'translational gap', which could arise for example from a failure to ask similar behavioural or cognitive questions across the species—due to the use for example of clinical scales depending on subjective responses or impressions, rather than on objectively measured behavioural or cognitive signs. An alternative approach

would validate animal models by 'back-translation', i.e. by feeding back the results of human studies with compounds to arbitrate amongst the various animal models and test paradigms in order to optimize them and encourage an iterative, 'bidirectional' translational process. This volume surveys some of the best developed examples of how investigators have tried to achieve this goal. It also addresses peripherally the second problem of translation, namely relating such cross-species bidirectional studies to clinical utilization.

Chapter "Translational Mouse Models of Autism: Advancing Toward Pharmacological Therapeutics" by Kazdoba et al. well exemplifies the cross-species approach to modelling a particular complex human disorder with behavioural, cognitive and social dimensions, autism, using rodent studies. In contrast, chapter "Translatable and Back-Translatable Measurement of Impulsivity and Compulsivity: Convergent and Divergent Processes" (Voon & Dalley) though also employing rodents, takes the dimensional approach to modelling psychiatric symptoms that may extend transdiagnostically, for example to attention deficit/hyperactivity disorder to addiction, and thence to eating disorders and obsessive-compulsive disorder. Chapter "Translational Models of Gambling-Related Decision Making" (Winstanley & Clark) continues this analysis specifically by examining these and additional dimensions based on explorations of the reward system and decision-making mechanisms that characterize risk-taking and compulsive gambling behaviour. Other forms of addiction are considered in chapter "Translational Research on Nicotine Dependence" (Falcone et al., nicotine dependence) and chapter "The Need for Treatment Responsive Translational Biomarkers in Alcoholism Research" (alcoholism) Heilig et al). The latter takes a biomarker approach echoed elsewhere in the volume (chapters "Animal Models of Deficient Sensorimotor Gating in Schizophrenia: Are They Still Relevant?" and "Relating Translational Neuroimaging and Amperometric Endpoints: Utility for Neuropsychiatric Drug Discovery") as a possible solution to frustrated attempts to "bridge the valley of death" of translational activity for the pharmacological treatment of alcoholism. Falcone et al. in contrast describe several optimistic approaches to treating the different facets of nicotine dependence, using a classical 'model' approach. Chapter "On the Road to Translation for PTSD Treatment: Theoretical and Practical Considerations of the Use of Human Models of Conditioned Fear for Drug Development" (Risbrough et al.) addresses post-traumatic stress disorder (PTSD) whereas chapter "Translational Approaches Targeting Reconsolidation" (Kroes et al.) introduces the general concept of memory reconsolidation as a route to remediation of conditions such as PTSD (and also addiction). Chapters "Translational Assessment of Reward and Motivational Deficits in Psychiatric Disorders" (Der-Avakian et al.) and "Affective Biases in Humans and Animals" (Robinson & Roiser) take complementary approaches to the special problems posed by modelling human affective disorders−whereas chapter "Translational Assessment of Reward and Motivational Deficits in Psychiatric Disorders" considers reward and effort-based approaches to measuring, e.g. anhedonia, chapter "Affective Biases in Humans and Animals" analyses affective biases, negative as well as positive, that predispose towards depression and its symptomatic

heterogeneity. Chapters "Locomotor Profiling from Rodents to the Clinic and Back Again" and "Animal Models of Deficient Sensorimotor Gating in Schizophrenia: Are They Still Relevant?" deal with approaches to modelling the different forms of psychosis in bipolar and schizophrenia disorders. Chapter "Locomotor Profiling from Rodents to the Clinic and Back Again" (Young & Geyer) uses sophisticated quantitative measures of the pattern of locomotor activity in patients with bipolar disorder and rodents; quite striking parallels are found. Chapter "Animal Models of Deficient Sensorimotor Gating in Schizophrenia: Are They Still Relevant?" (Swerdlow & Light) re-evaluates the utility of the pre-pulse inhibition paradigm for schizophrenia, arriving at some new perspectives on the search for new therapeutic breakthroughs, with a memorable and perhaps radical conclusion, "For animal models to remain relevant in the search for schizophrenia therapeutics, they will need to focus less on what is valid, and focus more on what is useful". Chapter "Attention and the Cholinergic System: Relevance to Schizophrenia" (Lustig and Sarter) well illustrates how basic investigation of the functioning of an important chemical neurotransmitter system in experimental animals, namely that using acetylcholine in neurons originating in the basal forebrain, can lead to new insights into how this system may operate in healthy humans and how it may go wrong in disorders such as schizophrenia, with attendant therapeutic indications. Another approach to measuring attention is highlighted in the elegant translation in chapter "Attentional Set-Shifting Across Species" by Brown and Tait of the primate CANTAB intra-dimensional/extra-dimensional attentional set-shifting paradigm to rodent (rat and mouse) models. Their paradigm has been much used in industry as well as in academia to measure 'cognitive flexibility' and fronto-executive function and a substantial neuropsychopharmacological literature has resulted. Nevertheless, industry is now often taking an approach more akin to biomarkers for predicting future drug discovery that depends, for example, on electrophysiological and brain imaging measures. Chapter "Relating Translational Neuroimaging and Amperometric Endpoints: Utility for Neuropsychiatric Drug Discovery" by Li et al. from an industrial setting shows how it is now feasible to compare human psychopharmacological functional imaging paradigms with those in rodents by using the amperometry technique in rats, providing essentially another measure of the BOLD response in functional settings, including vigilant attention and reward-related behaviour—being very useful for Phase 2 type studies by pharma. Chapter "Cognitive Translation Using the Rodent Touchscreen Testing Approach" (Hvosfelt-Eide et al.) introduces an innovative new method of testing rodents using touch-sensitive screens to assess attention, learning and memory in a computerized tests—several exciting examples of direct animal–human translation are described, including in mice and humans with common genetic polymorphisms. This methodology sprang out of the original invention of touch-screen-sensitive cognitive tests in the CANTAB battery, which is the subject of chapter "The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research". Using the same type of tests in humans and animals is surely the key to achieving translation across the animal–human boundary that is so important for integration of

pre-clinical and clinical (i.e. experimental medicine) studies. Chapter "The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research" (Barnett et al.) illustrates the bidirectional translational approach taken by the invention of the CANTAB battery—focusing on the evolution of a visuospatial Paired Associates Learning Test which is highly sensitive to detection of early Alzheimer's disease in patients with Mild Cognitive Impairment. This chapter not only illustrates the prospects for 'back-translation' to animal models using such a battery, but also bridges a second translational 'gap', by having the tests adopted in an I-Pad format by GP clinics for screening memory dysfunction. Finally, chapter "Experimental Medicine in Psychiatry New Approaches in Schizophrenia, Depression and Cognition" (Dawson) shows how experimental medicine studies may provide an interface between Phase 1 and 2 trials to bridge the gap between animal and human studies.

We would like to thank all of the contributors to this volume, which we hope will have some impact in enabling scientists coming either from academia or industry, or alternatively, from pre-clinical or clinical backgrounds, perhaps to find a more common language, methodology and even motivation, for carrying out translational research. Additionally, we thank the Editors of the Current Topics in Behavioral Neuroscience series, as well as the Susan Dathé and the staff of Springer Verlag, for their nurturing patience in making this volume possible.

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Contents

Translational Mouse Models of Autism: Advancing Toward Pharmacological Therapeutics

Tatiana M. Kazdoba, Prescott T. Leach, Mu Yang, Jill L. Silverman, Marjorie Solomon and Jacqueline N. Crawley

Abstract Animal models provide preclinical tools to investigate the causal role of genetic mutations and environmental factors in the etiology of autism spectrum disorder (ASD). Knockout and humanized knock-in mice, and more recently knockout rats, have been generated for many of the de novo single gene mutations and copy number variants (CNVs) detected in ASD and comorbid neurodevelopmental disorders. Mouse models incorporating genetic and environmental manipulations have been employed for preclinical testing of hypothesis-driven pharmacological targets, to begin to develop treatments for the diagnostic and associated symptoms of autism. In this review, we summarize rodent behavioral assays relevant to the core features of autism, preclinical and clinical evaluations of pharmacological interventions, and strategies to improve the translational value of rodent models of autism.

Keywords Autism · Mice · Rats · Genes · Mutant models · Social behavior · Sociability · Repetitive behavior · Cognition · Ultrasonic vocalization · Pharmacological treatment · Mouse · Preclinical · Translational · Clinical trials · Face validity · Construct validity · Predictive validity

Contents

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1 Introduction

Autism spectrum disorder (ASD) includes common, impairing neurodevelopmental disorders that are present from early childhood and occur in approximately 1 % of the population (Kim et al. 2011; Elsabbagh et al. 2012). To receive an ASD diagnosis, one must exhibit symptoms from two core domains: (1) social interaction and social communication; and (2) restricted repetitive patterns of behaviors, interests, and activities. (American Psychiatric Association 2013). Associated symptoms, appearing in varying percentages of individuals, include intellectual disability, executive dysfunction, anxiety, seizures, attention deficits and hyperactivity, hyper- and hyporeactivity to sensory stimuli, and sleep disruption. The current standard of care for children is early intensive behavioral intervention (Rogers et al. 2012; Lord and Jones 2013). Early intensive behavioral intervention is highly effective in teaching young children to overcome their social challenges, although it does not work for all, and its benefits wane with the appearance of age-related challenges in middle childhood and adolescence. Further, these behavior therapies are expensive and time-intensive, and not uniformly widely available. There is an unmet need for medical therapeutics that can be given in combination with a behavioral intervention or alone. No approved medical treatments exist for reducing or preventing the diagnostic symptoms of autism. Efficacious medications that effectively treat ASD symptoms, and specifically target social deficits, are currently under investigation.

The decision to use the term ASD in DSM-5 reflects the current thinking about the heterogeneous causes and clinical presentations of autism. A large number of de novo single gene mutations and copy number variants (CNVs) are associated with autism, each in a small number of individuals (Parikshak et al. 2013; Coe et al. 2014; Pinto et al. 2014). Environmental risk factors have been implicated, including parental age (Kong et al. 2012) and atypical maternal autoantibodies (Braunschweig et al. 2013). Analogous to "cancers," there may be multiple "autisms," to be defined by clustered genetic mutations with common mechanisms and treated with different classes of therapeutics. No definitive biomarkers have yet been identified across all diagnosed cases. Intensive searches are underway to define abnormalities in neurophysiology, neuroanatomy, brain chemistry, immune markers, and other potential biological abnormalities that may stratify individuals with autism, and offer outcome measures for future clinical trials (Ecker et al. 2013).

Rodent models offer preclinical tools to understand the role of genetic mutations and environmental factors in producing the diagnostic and associated symptoms of autism. Knockout (KO) and humanized knock-in mice have been generated for many of the mutations and CNVs detected in ASD and comorbid neurodevelopmental disorders such as fragile X syndrome and tuberous sclerosis (Silverman et al. 2010b; Ey et al. 2011; Baudouin et al. 2012; Zoghbi and Bear 2012; Gross et al. 2015). Several of these genetic mouse models are in use for the preclinical testing of pharmacological targets to treat the core symptoms of autism (Spooren et al. 2012; Silverman and Crawley 2014; Vorstman et al. 2014; Gross et al. 2015).

One fundamental conundrum is defining mouse behavioral assays with high relevance to the diagnostic symptoms of autism, which is a uniquely human disorder (Crawley 2004). Modeling ASD in rodents is challenging in that the clinical phenotype is heterogeneous and encompasses a wide range of behaviors. Researchers focused on developing animal models based on ASD-related behaviors benefit greatly from participating in clinical observations to obtain a comprehensive understanding of the clinical phenotypes found in individuals with ASD. We have been fortunate to observe diagnostic interviews of children with autism at the University of California Davis MIND Institute. Knowledge gained through these sessions and from lectures and conversations with many generous colleagues working with children, adolescents, and adults with autism guided our thinking in the development of analogous behavioral assays to evaluate mouse models of autism. This chapter presents state-of-the-art assays for mouse social and repetitive behaviors and reviews the preclinical progress in evaluating hypothesis-driven pharmacological interventions, employing these behavioral assays in selected mouse models of autism.

2 Animal Models to Understand the Causes of Autism

The causes of autism are under intense investigation. Evidence supporting a large number of risk genes and CNVs at chromosomal loci is strong. Twin and family studies suggest that the genetic heritability of ASD is very high, ranging from 50 to 90 % (Ritvo et al. 1985; Smalley et al. 1988; Hallmayer et al. 2011; Miles 2011; Nordenbaek et al. 2014; Sandin et al. 2014). Genetic causes, primarily de novo mutations, have been identified in approximately 20–30 % of ASD cases, with no identified gene mutation in the majority of ASD cases (Miles 2011; Devlin and Scherer 2012; Murdoch and State 2013). Of the known genetic abnormalities associated with ASD, at least 5 % are caused by single gene mutations (Lim et al. 2013; De Rubeis et al. 2014; Iossifov et al. 2014), and at least 10 % are due to CNVs that cause structural variation, including duplications, deletions, inversions, and translocations (Marshall et al. 2008; Rosenfeld et al. 2010; Matsunami et al. 2013; Poultney et al. 2013). A remarkable preponderance of genetic mutations in ASD code for proteins mediating synaptic functions, such as those coding for the synaptic protein families SHANK (Durand et al. 2007), CNTNAP (Alarcon et al.