

# 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 Indeed, the results of Phase 3 trials have been so disappointing and unsuccessful that many companies have withdrawn from neuroscience research related to psychiatry, as it has been thought to be somehow ‘too difficult’.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.

Cambridge  
November 2015

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Translational Neuropsychopharmacology

Robbins, T.W.; Sahakian, B.J. (Eds.)

2016, XII, 498 p. 124 illus., 92 illus. in color., Hardcover

ISBN: 978-3-319-33911-5