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Commentary

# Innovative solutions to novel drug development in mental health

T.R. Insel[a,1], V. Voon[b,c,1], J.S. Nye[d], V.J. Brown[e], B.M. Altevogt[f], E.T. Bullmore[g], G.M. Goodwin[h], R.J. Howard[i], D.J. Kupfer[j], G. Malloch[k], H.M. Marston[l], D.J. Nutt[m], T.W. Robbins[c,n], S.M. Stahl[b,o], M.D. Tricklebank[p], J.H. Williams[q], B.J. Sahakian[b,c,*,1]

[a] National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA
[b] Department of Psychiatry, University of Cambridge, Cambridge, UK
[c] MRC/Wellcome Trust Behavioral and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
[d] Neuroscience, Janssen Pharmaceutical of Johnson and Johnson, Titusville, NJ, USA
[e] School of Psychology and Neuroscience, St Andrews University, St Andrews, UK
[f] Institute of Medicine, Forum on Neuroscience and Nervous System Disorders, Washington, DC, USA
[g] Glaxo Smith Kline, Clinical Unit, Addenbrookes Hospital, Cambridge, UK
[h] Department of Psychiatry, University of Oxford, Oxford, UK
[i] Royal College of Psychiatrists and Institute of Psychiatry, Kings College London, London, UK
[j] University of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburg, PA, USA
[k] Medical Research Council, UK
[l] TPP Global Development, Edinburgh, UK
[m] Centre for Pharmacology and Therapeutics, Division of Experimental Medicine, Imperial College London, London, UK
[n] Department of Psychology, University of Cambridge, Cambridge, UK
[o] Department of Psychiatry, University of California, San Diego, USA
[p] Eli Lilly and Co Ltd, Windlesham, UK
[q] Wellcome Trust, UK

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ABSTRACT

There are many new advances in neuroscience and mental health which should lead to a greater understanding of the neurobiological dysfunction in neuropsychiatric disorders and new developments for early, effective treatments. To do this, a biomarker approach combining genetic, neuroimaging, cognitive and other biological measures is needed. The aim of this article is to highlight novel approaches for pharmacological and non-pharmacological treatment development. This article suggests approaches that can be taken in the future including novel mechanisms with preliminary clinical validation to provide a toolbox for mechanistic studies and also examples of translation and back-translation. The review also emphasizes the need for clinician-scientists to be trained in a novel way in order to equip them with the conceptual and experimental techniques required, and emphasizes the need for private-public partnership and pre-competitive knowledge exchange. This should lead the way for important new holistic treatment developments to improve cognition, functional outcome and well-being of people with neuropsychiatric disorders.



The last decade has witnessed exciting and important advances in the neuroscience of mental health including the mapping of neural circuitry and neurochemical mechanisms, identification of multiple genetic loci and the application of novel technologies to both the pathophysiology and treatment of mental disorders. Despite these advances, major unmet needs remain. Mental illness remains the leading cause of morbidity and mortality (Bloom et al., 2011; Collins et al., 2011; Insel, 2009). Psychiatric conditions account for five of the top ten causes of disability and premature death and mental health conditions are the leading cause of Disability Adjusted Life Years accounting globally for 37% of healthy life years lost from Non-Communicable Diseases. The global cost for disorders of mental health in 2010 was $2.5 trillion and projected to markedly increase to $6.5 trillion in 2030, making mental illness the most costly form of chronic disease worldwide (Bloom et al., 2011). Furthermore, a considerable proportion of people with mental health problems remain untreated. For example, in the USA 67% and in Europe 74% of people with mental illness are untreated. (Thornicroft, 2007) Yet, in spite of these urgent unmet needs, mental health is experiencing a crisis in the development

* Corresponding author at: Department of Psychiatry and MRC/Wellcome Trust Behavioural and Clinical Neurosciences Institute, Box 189, Level E4, Addenbrookes Hospital, Cambridge, CB2 0QQ, UK. Tel.: +44 1223 768009.
*E-mail addresses:* bjs1001@cam.ac.uk, bjs-sec@medschl.cam.ac.uk (B.J. Sahakian).
[1] These authors contributed equally to this work.

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of new treatments, especially drug treatments. In the last 40 years, very few therapeutics with novel mechanisms have progressed to phase III clinical trials or regulatory approval. Major pharmaceutical companies are even shifting drug discovery efforts away from psychiatric toward non-psychiatric disorders with identified biological targets (Cressey, 2010; Miller, 2010). This issue of private sector drug development is one major symptom reflecting deeper underlying infrastructural issues in mental health research. The Royal Society recently convened an International Scientific Seminar to find innovative solutions for novel drug development. The meeting concluded that to address these issues, we require a paradigm shift in how we: diagnose and categorize psychiatric disorders, view and approach mental health research, encourage collaborative partnership models between academia and drug companies, train the next generation of clinicians, maintain the pre-clinical knowledge base and influence the public perception of mental illness. The following seeks to address these fundamental problems and to propose a way forward for the next two decades.

## 1. Many psychiatric disorders are neurodevelopmental in origin

Psychiatric disorders are brain disorders of complex and variable genetic risk interacting with neural circuitry and experience. Mental disorders disproportionately affect the young with 75% of illnesses having onset before the age of 24 (Kessler et al., 2005). The identification of multiple genetic loci for complex disorders exploded in the decade following the sequencing of the first human genome, with 2850 disease genes identified for Mendelian-based disorders and 1100 loci identified for 165 common multigenic diseases as of February, 2011 (Lander, 2011). Accordingly, in the most heritable neuropsychiatric disorders (autism, schizophrenia, bipolar disorder) at least a dozen risk alleles have been reported from genome wide association studies, including many common variants replicated recently in a global effort with over 100,000 subjects across 65 research institutions (Fig. 1) (Ripke et al., 2011; Sklar et al., 2011). Supporting the concept of mental disorders as neurodevelopmental, several of these apparent risk loci are key factors in neurodevelopmental pathways. In addition to the genomic evidence, longitudinal imaging studies have demonstrated altered patterns of development in patients with mental disorders. For instance, children with attention deficit hyperactivity disorder show a profound and consistent delay in cortical maturation (Shaw et al., 2007). These kinds of findings have led to a reconceptualization of mental disorders as brain disorders resulting from the aberrant development of specific circuits. This reconceptualization is exemplified in a new model of major depression which proposes different nodes for the underlying circuits, with alterations in neural pathways for emotion, cognition, interoception, and self-awareness (Drevets et al., 1997; Ressler and Mayberg, 2007). These pathways not only suggest a new stratification for depression, they may provide differential targets for medications, cognitive behavioral therapy, and deep brain stimulation. (Drevets and Furey, 2010; Holtzheimer and Mayberg, 2011; Zarate et al., 2006) Initiatives such as The Human Connectome Project (www.humanconnectomeproject.org) and the 1000 Connectomes Project (www.fcon_1000.projects.nitrc.org) which are mapping the variation in whole brain structural and functional network organization through large scale data sharing schemes should yield a consensus wiring diagram of the human brain and a range of individual variation, analogous to the maps of common and uncommon variation in the human genome.

### 1.1. Challenges in drug development

Despite these major advances in knowledge, progress in the search for novel therapeutic compounds has been difficult. Several inter-related factors account for this failure. Thus far, genetics has not uncovered druggable targets for mental disorders. The many variants identified have conspicuously not revealed targets related to monoamines, suggesting that genetics may take us beyond the cluster of current drugs, but we will need to bridge the gap between genetic findings and targets. An additional challenge is that the disease state remains based on phenomenological rather than biological categories, with limited understanding of pathophysiology. Additionally, there is a need for breakthrough clinical insights. The development of an antihistaminergic compound into chlorpromazine as an antipsychotic and imipramine as an antidepressant in the 1950s was a major novel development that revolutionized treatment in psychiatry. While we are likely to dismiss these discoveries in mental health as the result of serendipity and careful observation rather than anchored in established rational mechanistic processes, there is no reason to assume that careful clinical insights will not yield important therapeutic innovations in the future. Nevertheless, without a clear understanding of the biological basis of a disorder it will certainly be more difficult to find a rational approach to novel treatments. An example of hypothesis-driven drug development was that of the cholinesterase inhibitors in treating cognitive symptoms in dementias. This development was based on a pathological hypothesis derived from neuropathology and clinical analysis with utilization of existing pharmacological tools to validate the target. The result is a class of compounds particularly useful in improving attention and concentration, in patients with mild to moderate Alzheimer's disease (Eagger et al., 1991) but clearly more effective treatments are required particularly for episodic memory symptoms and neuroprotection.

A constellation of factors including the absence of molecular targets for drug discovery, the increasing cost and average duration of treatment discovery, and increasing placebo response rate and failure rates in clinical trials has led us to this crisis in drug development. (Nutt and Goodwin, 2011) Due to these challenges, a wealth of compounds interacting with promising targets have been developed by drug companies but lack convincing evidence of efficacy and are generally not available for widespread research by academic investigators. At the same time that we are facing a profound unmet need for new treatments and unprecedented scientific progress, research and development in industry is moving elsewhere, risking a lost generation for new treatment development.

### 1.2. Novel approaches for drug development

How can we address these fundamental issues? Our goals and perspective of mental health must change. Understanding molecular mechanisms will allow the identification of novel therapeutic targets including that of circuitry, genomics and epigenomics. Genetic findings in psychiatry, especially highly penetrant genetic lesions, need to advance to define new molecular targets. Unlike other fields where tissue biopsies or tumor removal has routinely been used to study pathophysiology and create cellular models of disease for testing new therapeutics, in psychiatric disorders brain tissue is rarely available during life. Functional and structural imaging, electrophysiology, and blood and cerebrospinal fluid-based measurements might yield glimpses into underlying pathological processes, especially when applied longitudinally during the years of risk and prodromal stages. Recently, the advent of skin-derived stem cells, also known as induced pluripotent cells (iPSc), that can be converted into neurons and glia in vitro promises to unveil pathogenetic mechanisms. (Tobe et al., 2011) Not only will iPScs create a "disease in a dish", these individualized cultures can serve as substrates for high throughput screening and testing novel therapeutics. Indeed, early results using iPSc's in genetically determined neurological disorders such as Rett's syndrome, Parkinson's disease