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Advances in multidisciplinary and cross-species approaches to examine the neurobiology of psychiatric disorders

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Abstract

Current approaches to dissect the molecular neurobiology of complex neuropsychiatric disorders such as schizophrenia and major depression have been rightly criticized for failing to provide benefits to patients. Improving the translational potential of our efforts will require the development and refinement of better disease models that consider a wide variety of contributing factors, such as genetic variation, gene-by-environment interactions, endophenotype or intermediate phenotype assessment, cross species analysis, sex differences, and developmental stages. During a targeted expert meeting of the European College of

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Neuropsychopharmacology (ECNP) in Istanbul, we addressed the opportunities and pitfalls of current translational animal models of psychiatric disorders and agreed on a series of core guidelines and recommendations that we believe will help guiding further research in this area.

1. Introduction

Disease entities that are currently categorized under the auspices of "psychiatry" have suffered numerous obstacles in both the understanding of their pathophysiology and in advances in diagnosis and treatment. It is only within the last few decades have we begun to truly appreciate how these disorders are the end products of subtle neurodevelopmental alterations and/or unique interactions between genetic diatheses and environmental adversity. In fact, their *subtlety* is what distinguishes this class of diseases from other chronic illnesses such as acquired immunodeficiency syndrome (AIDS) or cardiovascular disease. Patients with neuropsychiatric disorders have no gross anatomical alterations of the brain on autopsy, lack differentiating serum biomarkers or highly penetrant genetic predispositions, and can have symptoms that are variable across time (such as in the case of bipolar disorder). And yet, patients affected with these disorders have very obvious phenotypes: the social and language deficits of autistic patients, the hallucinations and delusions of chronic schizophrenic patients, the debilitating compulsions of patients with obsessive–compulsive disorder, and prolonged episodes of melancholia and anorexia in depressed patients are well-recognized by both clinicians and members of the lay public. These and other neuropsychiatric syndromes cause significant disability. A 1998 World Health Organization (WHO) report (Lopez and Murray, 1998) produced a "top ten" list of chronic disabling conditions, of which five are official diagnoses of the DSM IV (Diagnostic and Statistical Manual of Mental Disorders-IV). Rather than focusing on a specific type of psychopathology, this manuscript serves to highlight recent trends and advances in this field (summarized in Box 1), with an emphasis on improving and unifying efforts to translate these advances from the bench to the bedside.

2. Genetic risk factors

There is no doubt that psychiatric disorders have a high degree of heritability, with robust evidence from several decades of twin, family and adoption studies. These demonstrate heritability in excess of 80% for schizophrenia (Cardno and Gottesman, 2000), autism (Rosenberg et al., 2009) and bipolar disorder (McGuffin et al., 2003), and more moderate heritability (40–60%) for other psychiatric disorders such as depression and anorexia nervosa (Bulik et al., 2000). Despite this high heritability, identifying genetic risk variants has proven difficult, as has been the case for other complex disorders, such as type 2 diabetes and obesity.

Nevertheless, new technologies such as microarrays for genotyping and comparative genomic hybridization have been successful in identifying the first systematically discovered, genomic and genetic risk factors for disorders such as schizophrenia and autism, opening up new avenues in our understanding of pathophysiology (Rujescu and Collier, 2009). In schizophrenia and bipolar disorder, multiple low-risk variants, in genes such as neurogranin, TCF4, ZNF804A, ANK3 and CACNA1C, as well as the MHC locus, have been successfully identified, many of which show cross-disorder association (Williams et al., 2010). In human height, study of almost 200,000 subjects has identified at least associated 180 loci explaining at least 10% of genetic variants (Lango et al., 2010). These fall into biological pathways related to skeletal growth, indicating that GWAS can identify the underlying pathophysiology of complex disorders.

In addition to common variants, rare, moderate risk variants have also been identified for psychiatric disorders, such as copy number variants (CNVs) in schizophrenia, such as those at chromosome 1q21.1, 15q11.2, 15q13.3 and neurexin 1 (St Clair, 2009) and rare or uncommon, non-synonymous protein coding changes, such as those found in SHANK3 (autism) (Gauthier et al., 2010) and ABCA13 (schizophrenia) (Knight et al., 2009). Disease associated CNVs, as well as both rare and common, low risk variants point to a disease pathway involving neurodevelopment, and particularly synaptic function.

In addition to the 3% of the heritability of schizophrenia thus far accounted for by common variants, CNVs are thought to account for up to 5% of heritability, but the contribution from rare point mutations or non-linear genetic effects is as yet unknown. Thus much of the molecular genetic basis of inheritance remains unexplained, the so called dark matter (Maher, 2008). This is likely to reflect the low odds ratio (average genotype relative 1.25) of common susceptibility variants, and the stringent level of significance required for genome-wide association studies, leading to lack of statistical power, and the contribution of other genetic factors which cannot easily be detected by current approaches. Missing heritability is likely to be composed of additional common variants that have already been detected, rare copy number variants (Stefansson et al., 2009) or rare point mutations, such as non-synonymous single nucleotide mutations in exons. Exome and whole genome sequencing tools are predicted to lead to the discovery of further high or moderate risk mutations (Ng et al., 2009). In addition non-linear effects must be considered, such as gene–gene interactions (epistasis) (Moore and Williams, 2009), epigenetic factors (Rutten and Mill, 2009), and gene environment interaction (van Os et al., 2008).

Copy number variants (CNVs) (Stefansson et al., 2008; Vassos et al., 2010) and non-synonymous protein coding mutations are promising avenues for the development of mouse models through replicating such humanized gene mutations or engineering gene specific or locus deletions and duplications. For example, deletions in the Neurexin 1 gene are associated with autism (Kim et al., 2008) and schizophrenia (Rujescu et al., 2009) and mice deficient for this gene show increased repetitive grooming behavior indicating an abnormality with face validity to one of the major