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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

symptom domains relevant to ASD (Etherton et al., 2009). Likewise deletion of the α7 neural nicotinic acid receptor, CHRNA7, which give rise to neuropsychiatric phenotypes including schizophrenia in humans, produces a cognitive deficit in mice (Dempster et al., 2006). The advantage of modeling these moderate risk variants is that their biological basis is at least partly understood, in that we know that hemizygosity or overexpression of a gene leads to corresponding changes of gene expression in both mouse and man. Point mutations which affect coding or regulatory regions of genes can also be tested for effects on protein function or expression in vitro or in humanized transgenic mice.

Common, low effect size variants derived from genome-wide association studies (GWAS) (Stefansson et al., 2009) are also good candidates but could be considered less promising, for two main reasons. Firstly, because of their small effect size (typical OR 1.25) (Pawitan et al., 2009) it may be less likely they will show a phenotypic effect in mice. However evidence from the serotonin transporter 5-HTTLPR polymorphism, as well as of COMT Val158Met and BDNF Val66Met humanized mice shows that subtle common variants can have strong phenotypes plausibly related to those in humans (Montag et al., 2010). Secondly, most of common, low risk SNP variations are found in the non-coding regions of the chromosome, sequences of DNA that probably either modulate other genes or are proxy associations for SNPs that do. At present, the nature of this effect is unknown for the majority of associations — do they modulate protein levels, alter temporal or spatial expression, or change the ratios of protein isoforms? Without this information it will be difficult to design valid models for this class of variants, although genetic validity can still be explored.

Thus, despite their apparent small effect size in human genetic association, the study of mice harboring low risk variant genes may still be valuable for the understanding of the biological function of these genes, especially where spatially or temporally restricted expression can be used. GWAS will also be valuable in identifying disease-associated biological pathways (Eleftherohorinou et al., 2009), which can be manipulated at different levels as biological models of neuropychiatric disease. All of these models can use behavioral endophenotypes (discussed below), measured through, for example, cognitive or social tasks (Kas et al., 2009). The creation of mouse models of rare human genetic variants of moderate effect size for specific disease-relevant intermediate phenotypes and/or endophenotypes therefore appear to be a promising avenue for translational studies, especially those which can develop new potential therapeutic agents.

3. Focusing on an endophenotype rather than the complete syndrome

As current genetic studies advance, a full complement of validated animal models will be necessary to pinpoint the relevance of individual single nucleotide polymorphisms (SNPs) and/or CNV's and, subsequently, to define interactions among susceptibility genes. The functions of these genes, when examined through animal models, have often resulted in mild phenotypes, leading to the question: are approaches commonly used in behavioral neuroscience research adequate for understanding the clinical relevance of findings from psychiatric genetics? Our view is that it is necessary that we look beyond behavioral based models to molecular, circuit-based, and ex vivo approaches, to support the development of novel therapeutic approaches for psychiatric disorders.

In clinical attempts to understand psychiatric diseases we have traditionally focused upon symptomatology, rather than pathophysiology. This also holds true for many of our animal models in that they are commonly symptom-based. In contrast, pathophysiology-based models (which are fewer in number, given our poor understanding of pathophysiology) may or may not recapitulate disease symptoms. Thus, current animal models are well suited for developing drugs aimed at symptom amelioration, rather than directly targeting the underlying pathophysiology of psychiatric diseases. One approach that aims to target disease pathophysiology relies upon the use of neuropsychiatric endophenotypes. Endophenotypes tend to make etiological research more manageable by focusing on quantifiable components in genes-to-behaviors pathways, distinct from psychiatric symptoms. The concept was first applied to psychopathology in 1972 by Gottesman and colleagues (Gottesman and Gould, 2003; Gottesman and Shields, 1972). Clinically, endophenotypes may be neurophysiological, biochemical, endocrine, neuroanatomical, cognitive, or neuropsychological. They represent theoretically simpler biological processes that may be intermediate and causal to symptoms and, importantly, as a basic measure of neurobiological structure or function, lend themselves to being directly translated to animal models. Endophenotypes exist and function between behavior and its genetic basis, thus offering a more direct building block useful in deciphering mechanisms of disease (Gould and Gottesman, 2006).

One such example of an endophenotype that straightforwardly lends to translation is hypercortisolemia. While a variety of stressors produce acute rises in serum glucocorticoids, the persistent elevations in serum cortisol observed in certain forms of major depression has been difficult to be fully recapitulated in laboratory rodents. In spite of this fact, the neurobiological consequences of prolonged hypercortisolemia remain an active area of research. Mice that have been exposed to prolonged elevations in corticosterone (administered through their drinking water) develop deficits along indices of anhedonia and fear learning that are persistent and reversible by tricyclic antidepressants (Gourley et al., 2008, 2009). Moreover, these behavioral changes correlate well with decrements in neurotrophic and glutamatergic signaling in the forebrain regions and are reversed by direct infusions of BDNF (brain-derived neurotrophic factor) (Gourley et al., 2008). Thus, rather than focusing on the entire syndrome of depression, such an endophenotype approach aims to dissect a more specific aspect of altered physiology, lends to more simplified and realistic animal models and most importantly, allows for a more fluid translation between clinical data and laboratory investigation (de Mooij-van Malsen et al., 2008). Future major advancements in biological modeling of psychiatric disease will likely be derived extensively from endophenotypes, where acknowledgement and development of valid endophenotypes are increasing (Gottesman and Gould, 2003). The

slow development of endophenotype-based models for diseases such as depression, bipolar disorder, and suicidal behavior has hindered medications development and represents an important area for future research focus (Einat and Manji, 2006; Kovacsics et al., 2009; Nestler et al., 2002).

4. From genome-wide association studies to animal models: the potential offered by integrative approaches

The pathophysiology of neuropsychiatric disorders is likely due to dysregulation of complex biological pathways involving multiple, interacting gene products. Therefore integrative approaches linking the genetic make-up with intermediate phenotypes or endophenotypes (from gene to protein expression, neuroanatomical and neurophysiological data, and ultimately behavioral phenotypes) are needed to identify highly discriminative molecular determinants from the wide number of candidates. A number of translational approaches in this direction are being developed. The challenges arising from the analysis of the functional consequences of genetic variability in the GWAS era are providing an impetus in phenomics, i.e. the systematic study of multiple phenotypes, across multiple biological scales and species, on a genomewide scale. Due to the complexity of neuropsychiatric disorders, there is an increasing need to consider phenotype definitions beyond classical diagnostic categories and neuropsychiatric syndromes, in addition to phenotypes crossing multiple levels of expression, from proteome to syndrome (Bilder et al., 2009a). This concept is central to the Consortium for Neuropsychiatry Phenomics, aimed at developing cognitive ontologies based on behavioral and neuroimaging studies aimed at facilitating the identification of genetic determinants of cognition and cognitive disorders (Bilder et al., 2009b).

To fully capture the potential of phenomics strategies, a particular emphasis should be given to phenotypes that can be relevant for translational investigations. Focusing on molecular "neurophenomics", gene and pathway-centric approaches to the identification of disease markers from analysis of genetic data and expression profiles have been described for schizophrenia (Kurian et al., 2011) and mood disorders (Le Niculescu et al., 2009a). The method is based on the Bayesian integration of multiple datasets from human and animal model studies to identify converging evidence for given genes/pathways (Le Niculescu et al., 2009b). This approach lends evidence to the complexity of interdependence and overlaps at molecular level of major psychiatric disorders, such as the observed similarities between bipolar disorder and schizophrenia (Le Niculescu et al., 2007). Converging evidence for the association of particular gene in multiple phenotypes related to a specific psychiatric disorder, or to a neurophysiological trait, is a probably a better start than a simple, even though strong, association from a case–control GWAS. The recent development of GWAS of quantitative expression traits in human samples could be a real help in navigating the wealth of information arising from high-throughput genetics when searching for functionally relevant variants.

In the last five years, an increasing literature has been developed on the impact of SNPs and CNVs on gene expression at genome-wide level in human cell lines (Nica et al., 2010; Stranger et al., 2005, 2007a, 2007b; Ge et al., 2009), documenting the large impact of genotypic differences on the transcriptional machinery at a cellular level. More recently, genome-wide association mapping of gene expression in peripheral tissues (Goring et al., 2007; Emilsson et al., 2008; Antoniades et al., 2009) and the brain (Myers et al., 2007) have been investigated. Kim and Webster (2011) have extended this approach to the genome-wide analysis of cytoarchitectural abnormalities in the prefrontal cortex of psychiatric disorders (Kim and Webster, 2011). By combining GWAS of expression and neuroanatomical parameters, they were able to identify two novel candidate genes associated to both gene expression traits and cytoarchitectural abnormalities, as well as an association with the number of perineuronal oligodendrocytes for a previously identified bipolar disorder susceptibility gene (*PPP2R2C* which encodes a subunit of protein phosphatase 2A). The study is an elegant example of an integrative approach to the identification of molecular determinants involved in the neuropathology of schizophrenia and bipolar disorder.

5. Translational paradigms in psychiatry

Further increasing our knowledge of relevant genotype–phenotype relationships for psychiatric disorders is currently largely hampered by the inability to pin-point and to assess the core features of these heterogeneous disorders. While psychiatric disorders display disturbances in certain behavioral domains, such as cognitive deficits, motor changes or abnormalities in sociability, the question remains how to assess these characteristics in a patient population and how to study their relevance to etiology. Furthermore, to systematically study these genotype–phenotype relationships in a controlled genetic and environmental background, parallel comparative paradigms in animals are highly needed (Kas et al., 2007, 2009). Recently, several novel initiatives have been put forward to address these issues of translational research for psychiatric disorders.

One example is the development of reverse translational paradigms, whereby classical behavioral paradigms for rodents, such as the open field (OF) test, have been adapted in a comparable way for human subjects (Perry et al., 2009). In this pioneering study, humans were exposed to a novel room with objects, and patients with bipolar disorder and schizophrenia displayed different exploratory strategies than normal controls. In addition to these differences in exploratory behavior, direct comparisons between humans and animals can be made with measurements of autonomic activation (Vinkers et al., 2010c). As a read-out parameter of autonomic nervous system activation, core body temperature is a very convenient measure as it robustly increases upon any stressor (stress-induced hyperthermia: SIH) and appears dependent upon stressor intensity (Vinkers et al., 2008). Moreover, rats display individual differences in response to novel cage stress resulting from genetic and environmental factors (Vinkers et al., 2008). There is evidence in humans that autonomic stress responses correlate with perceived stress levels, probably modulated by processes in the amygdala (Carrasco and Van de Kar, 2003). GABAA-ergic and serotonergic mechanisms in the brain play

an important role in the modulation of the SIH (Vinkers et al., 2010a, 2010b) and rodent and human studies into the underlying brain mechanisms indicate a high translational comparability (Ulrich-Lai and Herman, 2009). This makes the SIH paradigm an attractive translational paradigm.

In addition, mouse genetic mapping studies have been applied to identify genetic loci for behavioral strategies that are likely evolutionary conserved across species, such as avoidance and approach behavior (Kas et al., 2008). By making use of mouse genetic reference populations, novel genetic loci for these behaviors can be identified. Integration of the genomic information of these mouse loci with known linkage regions for psychiatric disorders may subsequently reveal homologous genes. In this way, a recent study found homology between a quantitative trait locus (QTL) for mouse avoidance behavior and an often identified linkage region for bipolar disorders (Avramopoulos et al., 2004; McInnis et al., 2003; Zandi et al., 2007). By integrating genetic data from the mouse and from a large human GWAS on this mood disorder, novel candidate genes with potential translational value for this complex mood disorder were discovered (de Mooij-van Malsen et al., 2009).

As described above, the genetic mapping of automated home cage behaviors offers new opportunities to study dissected behavioral components (e.g., sheltering preference and motor activity levels) for ethologically and evolutionary oriented behavioral strategies and that may have translational value to mood disorders. Longitudinal measurements of behavioral components provide a way to dissociate novelty-induced behavioral responses (when mice are placed in the home cage for the first time) versus adapted behavioral responses (after being housed in the home cage for multiple days). These aspects have also become evident in short-lasting behavioral tests, such as the open field exploration test. For example, the often assessed open field test show a very different behavioral outcome with highly organized exploration pattern when mice are given a deliberate choice of voluntary actions to explore the open field from a home cage environment (Fonio et al., 2009). Furthermore, home cage behaviors can be studied as a function of circadian rhythms and without human interference, a confounding factor for behavioral outcome (for review, see (Kas and van Ree, 2004)). These relatively long-lasting complex experiments provide many parameters that need to be systematically investigated and offer an important challenge for behavioral neuroscientist to implement a wide variety of behavioral components, such as components of social defeat or within the domain of learning and memory. Integrating behavioral home cage measures with simultaneously recorded autonomic and/or neural activity recordings further enhances translational power of objective measures and allows to do dynamical non-linear rather than classical linear statistical measures (Stiedl and Meyer, 2003). In view of the complexity of endophenotypes or intermediate phenotypes in psychiatric disorders, the field has to move forward and develop novel ways to longitudinally study dissected behavioral components of complex behavioral strategies that can be combined with simultaneous recordings of physiological measures.

Finally, the GWAS approach also offers a large pool of novel candidate genes for psychiatric disorders. Functional studies in mice that are mutant for these particular genes in parallel with human studies with individuals with known deletions in these candidate genes (Luykx et al., 2010), offer new roads to further optimize our understanding of the relationships between these genotypes and core features of psychiatric disorders. Another novel possibility to approach the pathophysiology of neurodevelopmental disorders is to model them in cultured neurons. In this regard, embryonic and neural stem cells can be differentiated into a neuronal phenotype and these stem cells are amendable to genetic manipulation (Gage, 2000). Importantly, abnormal neuronal differentiation was recently reported in neural stem cells derived from the brain of human Fragile X embryo as well as from a mouse model of the Fragile X syndrome (Castren et al., 2005). The advent of induced pluripotent stem (iPS) cell technology has produced an explosion of interest in modeling neuronal disorders in cultured neurons, since this technology potentially allows for the examination of differentiated neurons directly derived from fibroblasts of the patient with a diagnosed disorder (Yamanaka, 2007; Chamberlain et al., 2008). Although the application of iPS technology is still young, there is a significant promise that differentiated neurons from patient-derived iPS cells may become an important tool in the characterization of the neurobiological background of neuropsychiatric disorders (Kim, 2010). Thus, new translation paradigms are needed and on their way, but intensive interaction between clinical, genetic, and fundamental neuroscience researchers is necessary to optimize the implementation of this translational need for these complex disorders.

6. Gene-by-environment interactions in psychiatric disorders

Research on the role of genes in the etiology of psychiatric disorders has been complicated by a mysterious discrepancy between high heritability estimates and a scarcity of replicable gene-disorder associations. Although this "missing" heritability has often been euphemized as the "dark matter" of gene-trait association or aggravated as the "looming crisis in human genetics" (Maher, 2008), more refined statistical and pathway-focused analyses of GWAS and CNV screening approaches now begin to reveal this apparently "hidden" heritability (Gibson, 2010; Yang et al., 2010). Another reason for this incongruity is that at least some specific gene effects are conditional on environmental factors comprising the "exposome", i.e. *gene-by-environment interaction* (G×E) is present (Caspi and Moffitt, 2006). Although converging epidemiological evidence links exposure to stressful life events with increased risk for psychiatric disorders, there is significant individual variability in vulnerability to environmental factors, and the environmentally moderated penetrance of genetic (or epigenetic) variation is thought to play a major role in determining who will either develop disease or will remain resilient to it (Gillespie et al., 2009; Krishnan and Nestler, 2008). Based on numerous reports there is general consensus – although there are also a considerable number of replication failures – that the short, low-expressing variant of the repeat length polymorphism in the human serotonin (5-HT) transporter gene (*5-HTT, SLC6A4*), commonly referred to as the *5-HTT*-linked polymorphic region (5-HTTLPR), is associated with

anxiety-related traits and increased risk for depression in interaction with psychosocial adversity across the lifespan (for comprehensive reviews see (Homberg and Lesch, 2011; Lesch et al., 1996; Uher and McGuffin, 2010)). Modest effect sizes typical of complex traits and disease endophenotypes, polygenic patterns of inheritance, epistatic and epigenetic interactions, and heterogeneity across studies lead to inconsistent success in replication and considerably confounded attempts to reach agreement regarding the role of 5-HTT in the pathophysiology of these diseases. Nevertheless, the impact of 5-HTT on complex traits in humans, with as well as in supportive evidence from studies in non-human primates and genetically modified mice, has become a model par excellence in cognitive and psychiatric neurosciences (Canli and Lesch, 2007).

In the rhesus macaque, there is allelic variation of 5-HTT function based on a repeat length variation structurally and functionally orthologous to the 5-HTTLPR in humans. The low expressing short 5-HTTLPR allele interacts with adverse early rearing conditions (peer rearing) to result in more distress, less activity, stronger neuroendocrine responses to stress, higher consumption of alcohol and lower 5-HT turnover in the brain (Barr et al., 2003; Bennett et al., 2002; Champoux et al., 2002; Canli and Lesch, 2007). During peer-rearing, monkeys homozygous for the long 5-HTTLPR develop more socially acceptable playful behaviors but short/long heterozygotes tend to become aggressive, suggesting that the long/long homozygous status confers a potential for adaptation for adverse environment.

Although the mouse does not carry a polymorphism that is orthologous to the human and macaque 5-HTTLPR, several studies have used 5-HTT-deficient mice as a model of allelic variation in 5-HTT function. Null mutant 5-HTT−/− mice show an altered ability to cope with stress, and increased anxiety- and depression-like behaviors (Bengel et al., 1998; Murphy and Lesch, 2008). Several studies used heterozygous 5-HTT+/− mice (having a 50% gene dose dependent reduction of 5-HTT expression, thus representing a model for individuals with the short 5-HTTLPR variant) and found that, although these "humanized" mice do not show behavioral deficits at baseline, they developed increased anxiety and depression-like behavior in adulthood when exposed to prenatal stressors, to early life adverse experiences including poor maternal care, or to adult psychosocial stress (Bartolomucci et al., 2010; Carola et al., 2008; Heiming et al., 2009; Jansen et al., 2010; Lewejohann et al., 2010). The neural and molecular mechanisms by which environmental adversity in early life increases disease risk in adulthood is not known, but is likely to include epigenetic programming of gene expression. Moreover, the integration of G×E-driven differential gene expression into biological pathways underlying (epi)genetic vulnerability and resilience to depression and dissection of specificity and pleiotropy for comorbid disorders is still elusive (Wellman et al., 2007). To explore molecular mechanisms of these G×E animal models array-based genome-wide expression, methylation, and histone modification profiles are currently being analysed (Tsankova et al., 2006). Epigenetic markers are dynamic and reversible and may also provide powerful targets for intervention strategies. Therefore, more insight into the exact role of epigenetic regulation in the process of neurodevelopmental programming contributes to the establishment of early diagnosis and the design of innovative treatments targeting mechanisms of resilience.

Thus, bidirectional translation (humans to preclinical models and back) using non-human primate and mouse models has become an indispensable tool for studying the biological function and endophenotypic expression of specific gene variations in interaction with vulnerability to adversity across the lifespan leading to multiple unfavorable outcomes resembling psychiatric disorders. Identifying the molecular mechanisms underlying epigenetic programming by adverse environment in animal models amenable to genetic manipulation or with similar genetic variation in conjunction with an improved characterization of disease endophenotypes is likely to help our understanding of the individual differences in resilience to stress and psychiatric disorders.

7. Cross-species analysis and computational models

The power of animal models in psychiatric research lies in the unique possibility they offer to identify causal molecular mechanisms under controlled environmental and genetic conditions. A small number of model organisms have dominated psychiatric research in the last years, with the laboratory mouse and rat attaining dominant roles in behavioral, pharmacological and genetic studies. However, psychiatric researchers should be strongly encouraged to consider using a wide variety of animal species in their work, selecting species in an opportunistic fashion to address the research question (Insel, 2007). Several major advantages of such a cross-species approach deserve to be highlighted.

First, simple organisms provide rapid and cost effective screening platforms for assessing gene function. It is widely recognized that genetic screens in fruit flies (*Drosophila melanogaster*) have provided most of the functional annotations of the genes routinely studied today in psychiatric genetics. The zebra fish (*Danio rerio*) offers outstanding live imaging of cellular dynamics in the undisturbed organism and, for example, has provide unprecedented insight into the role of microglia in brain development and injury (Peri and Nusslein-Volhard, 2008), a rapidly expanding field critical for understanding both developmental programming and brain repair. The stereotyped brain circuits of the roundworm (*Caenorhabditis elegans*), on the other hand, allow for direct relationships to be uncovered between gene expression within defined cells and phenotypes, for example, that for the first time offer mechanisms for understanding the partial penetrance of genetic mutations, a phenomenon central to psychiatric genetics (Raj et al., 2010). Second, niche species can offer unique opportunities to understand specialized phenotypes that are not evident in common model organisms. Voles, songbirds, and naked mole rats, for example, are just some of the species that have offered breakthroughs in our molecular understanding of attachment behavior (Insel, 2007), neurogenesis (Nottebohm and Liu, 2010), and somatosensory cortex remodeling (Catania and Remple, 2002), respectively. The well-documented and dramatic changes seen in some adult primates during changes in social position (Knott and Cheryl, 1999), for example, ought to receive more attention from

physiologists and molecular biologists given their close kinship to humans. Third, the enormous drop in costs for sequencing now makes virtually any organism genetically tractable and researchers are no longer restricted to well-characterized species. Whole-genome sequencing coupled to phenotype-based association studies will become a feasible route to uncover novel gene-phenotype associations in most organisms (Stratton, 2008) and a wealth of new psychiatric candidate genes deriving from such studies in wild or semi-wild animal populations will become available in the near future.

A renewed research focus on diversity, both at the species and individual levels, could help accelerate the current move in the psychiatric research field away from simple deterministic assumptions about disease risk and origin to a more holistic view of mental illness as pathological deviations or alternative strategies of adaptive brain mechanisms (Troisi, 2005). Recent work has done much to highlight individual differences, even in genetically identical populations (Krishnan and Nestler, 2008; Wilkinson et al., 2009) and a better understanding of the environmental and stochastic events underlying such diversity will reveal information about the genetic and epigenetic mechanisms underlying variability in predisposition. Of course, mice will continue to assume a dominant position as a convenient and powerful tool for studying the molecular mechanisms of psychiatric phenotypes. The availability of Cre-conditional knockout alleles (EUCOMM, (Friedel et al., 2007)) and expression atlases (Allen Brain Atlas, (Lein et al., 2007), EUREXPRESS http://www.eurexpress.org/ee/) covering all known mouse genes will accelerate our ability to rapidly assess gene function in the mammalian context. The study of mice engineered to carry selected human disease-associated mutations such as SNPs, CNVs and missense mutations (so called "humanized" mice) is rapidly becoming a routine tool of translational research with the potential to redefine and realign disease phenotypes across species.

8. When gender matters: The need to consider sex differences in our understanding of neuropsychiatric disorders

A rapidly increasing literature documents a number of sexual dimorphisms in brain anatomy, chemistry and function. The striking number of these differences indicates that the assumption that sex influences are negligible in most areas of biology requires revision (Zucker and Beery, 2010; Cahill, 2006). Moreover, many neuro-psychiatric disorders show sex differences in their occurrence, frequency and/or nature. The obvious impact of sex differences should require to examine sex influences in both basic and clinical researches with the ultimate aim to understand the pathophysiology of these and other disorders and to develop effective therapeutic strategies. There is, however, a great discrepancy between our knowledge about the existence of sex differences and ongoing research activities, as exemplified by the current state of research in major depressive disorder (MDD). MDD ranks among the top causes of worldwide disease burden and disability, with a lifetime risk of 7% to 12% in men and 20% to 25% in women (Kessler et al., 1993, 2005b). In addition, there is increasing evidence of sex differences in clinical features of depression and preliminary evidence for the prevalence of subtypes in females versus males (Smith et al., 2008; Dekker et al., 2007; Halbreich and Kahn, 2007).

Although epidemiological studies clearly demonstrate that women are more vulnerable than men to stress-related psychopathologies, preclinical research modeling MDD is still mainly conducted on male animals. The rationales for the predominant investigation of males in research programs on stress and stress-related psychopathologies are obvious. First, it is easier and cheaper to use only males because it is not necessary to check for the stage of the ovarian cycle. Second, there is a large discrepancy in the possibility to induce stress in males and females, particularly within stress-related models. Today, it is broadly accepted that life stress plays a crucial role in affective disorders (Hammen, 2005; Kessler, 1997) but this role is significantly influenced by mediators (e.g., cognitive style (Monroe et al., 2007)) and moderators (e.g., genetic predisposition (Caspi et al., 2003; Risch et al., 2009)). In humans, the most common stressors that may induce MDD are of psychological or social nature (Kessler, 1997). In male animals, chronic social defeat stress has been a valuable tool to induce depressive-like behavior (Fuchs and Flugge, 2002; Rygula et al., 2008; Becker et al., 2008); however, social defeat is not suitable to induce sustained stress in female animals (Haller et al., 1999; Palanza, 2001). However, other social paradigms have been developed and validated in females. In rats, the social instability stress paradigm, which consists of alternating periods of crowding and social isolation, has been shown to evoke stress responses (Haller et al., 1999; Herzog et al., 2009). Sex-specific modulations of the mechanisms that lead to stress responses have been described for various CNS circuits (Cahill, 2006). In addition, sex differences or effects of gonadal hormones have been reported for anatomic and functional characteristics of several neurotransmitter and neuromodulatory systems such as the gamma-aminobutyric acid, dopaminergic, noradrenergic and serotonergic systems. Interestingly, until now, the influence of gonadal hormones on the characteristics of the response to stress has been only partially elucidated. Nevertheless, they seem to modify the efficacy of glucocorticoids in the brain either by acting directly as transcription factors or by acting transsynaptically (Patchev and Almeida, 1998).

The clear sex differences in neurobiological substrates of the stress response and the pronounced differences in the reaction of the HPA axis to various challenges (Palanza, 2001; Kudielka and Kirschbaum, 2005) suggest the need for more research on stress effects in females. Only a very small number of studies utilized female animals in preclinical research on the psychopharmacology of depression. This is somehow problematic since important differences in the bioavailability of drugs between women and men have been described. Factors such as drug absorption and metabolism, percentage of body fat, renal clearance, and a variety of other physiological mechanisms have been reported to be gender specific (Weissman and Olfson, 1995). In addition to sex differences regarding mood disorder-related hormonal background (Peeters et al., 2003) and stress reactivity (Aloisi et al., 1998; Lipa and Kavaliers, 1990), recent studies revealed that selected gene alleles are associated with psychiatric disorders in either sex. A tandem repeat in the MAOA gene was associated with MDD in men but not women

whereas other alleles were more associated with MDD in women (Fan et al., 2010). Another study reported that the met(158) allele of the COMT gene was associated with OCD in men but not in women (Pooley et al., 2007). Polymorphisms in *CACNA1C*, which codes for the pore forming alpha-1C subunit of the $Ca_v1.2$L-type calcium channel, have been associated with a bipolar disorder diagnosis in GWA studies (Ferreira et al., 2008). Recent evidence has indicated that some of these SNPs show a significantly stronger association in females than in males, and that only female mice haploinsufficient for *Cacna1c* show many behavioral differences from wild type animals (Dao et al., 2010). However, one has to state that these reported gene×sex interactions describe either candidate genes inconsistently associated with the psychiatric phenotype or in the case of *CACNA1C* a translation model of uncertain validity. Thus, the urgent need to use female individuals in preclinical psychopharmacological research programs is not met yet.

9. The impact of age: contributions from development, adolescence and senescence

Without clear molecular pathological starting points for investigation, the classical tactic to dissect the biology of neuropsychiatric syndromes has been to apply psychosocial/physical and/or chemical perturbations to one group of adult male rodents, with an age- and sex-matched group serving as a control (Krishnan and Nestler, 2008). This reductionistic methodology is highly valuable to a field where multifactorial clinical syndromes are the rule and not the exception. Unfortunately, such an overwhelming preference for utilizing adult rodents has limited our appreciation of how understanding age-related changes in emotional/cognitive processing can further improve our knowledge of psychiatric diseases that cause morbidity across the entire age spectrum (Kessler et al., 2005a). Focusing on different age periods provides useful paradigms for studying various aspects of behavioral neuroscience. For instance, the early postnatal and developmental stages are critical periods for numerous endpoints including establishing parental bonds, learning social behavior and refining synaptic connections (Schmidt, 2010). This field has received a tremendous amount of attention through studies of "early-life stress", where prenatal stress (applied to the pregnant mother) or early postnatal stressors are demonstrated to have clear and measurable impacts on adult emotionality. While the vast majority of studies have focused on the detrimental role of such early perturbations, under certain conditions they can promote resilience during adulthood (Lyons et al., 2009; Macri et al., 2009) and elucidating the mechanisms of this type of stress *inoculation* has obvious therapeutic relevance (Feder et al., 2009). Epigenetic mechanisms play a prominent role in the establishment of such long-term neuroplastic adaptations, such that environmental stimuli alter epigenetic markings on specific genes causing stable changes in their levels and patterns of expression (Weaver et al., 2004; Tsankova et al., 2007; Murgatroyd et al., 2009).

Similarly, adolescence can be thought of as a stage of exquisite sensitivity to chemical stimuli that are either external (abused substances and psychoactive medications) or internal (puberty-related hormonal fluctuations) (Spear, 2000; Vidal et al., 2007). While it has been challenging to precisely define the duration of the adolescent period for non-primate species, understanding the unique neurobiology of this stage has significant clinical relevance (Hawkins, 2009). Similarly, more efforts are necessary to examine psychiatric endophenotypes in aged animal models. This has implications to not only the field of geriatric mental health, but also offers a window into the neuropsychiatric impacts of neoplastic, cerebrovascular and inflammatory diseases that potently alter the neurochemical milieu of limbic substrates in elderly populations. Several key molecular hypotheses have been invoked to explain a heightened vulnerability to mental illness during this period, including reduced cognitive reserve (Nithianantharajah and Hannan, 2009), a drop in gonadal hormones (Frye and Walf, 2009) as well as a natural decline in adult hippocampal neurogenesis (Couillard-Despres et al., 2009; Simon et al., 2005; Gould et al., 1999). In this way, by expanding the scope of our studies beyond male adults, we can begin to recognize important molecular and cellular themes that play key roles in psychiatric disease.

10. Discussion/conclusion

We suggest that genotype–phenotype associations should be prioritized when aiming to generate *translationally* relevant animal models for the functional testing of neurobiological mechanisms underlying psychiatric disorders. In addition to intermediate phenotypes or endophenotypes, such as behavioral endpoints or gene expression profiles, the molecular and cellular markers of psychiatric disorders can also be studied in human stem cells differentiated into neurons. For genetic approaches, gene knock-out technology and genetic reference populations provide complementary research strategies in mice to identify and functional test biological substrates relevant to psychiatric disorders. They have added value for systematic studies to the influence of gene by environment interactions, sex differences, and time dependent changes in central nervous system development and/or sensitivity. New challenges are on the road to design proper phenotyping methods for clinically relevant intermediate phenotypes or endophenotypes across species.

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Conflict of interest

The authors declare no conflict of interest.

Box 1 Recommendations for further research.

Following the lectures and discussions during the Target Expert Meeting, we agreed on a set of guidelines/statements that we think might help guide further research in this area and are particularly promising or worthy of mention.

- Animal models should be focused on clearly defined intermediate phenotypes and/or endophenotypes rather than on anthropomorphized psychiatric symptoms or complex syndromes. Endophenotypes are trait phenotypes with a strong genetic basis, whereas intermediate phenotypes may not be strongly influenced by genetics, but nonetheless are still associated with disease and useful because they shed light on to a variety of environmental mediators of molecular neuroplasticity.
- We encourage a cross-species approach, so that each level of analysis is examined using an appropriate disease model. For example, studies in Drosophila have laid significant ground work for the study of neuronal networks, and similarly, zebra fish species have been crucial for studies of neurodevelopment. Applying these non-mammalian animal models towards studies of psychiatric disorders will also require an endophenotype approach, e.g., studying simple quantifiable endpoints such as sleep–wake cycles, feeding behavior, etc. While these species show a weak overlap in neuroanatomy with humans, their advantages lie in the ease of genetic manipulation, pharmacological manipulations and high throughput studies.
- Molecular and cellular biological markers of psychiatric disorders can now be studied in human stem cells differentiated into neurons. In particular, applying the induced pluripotent stem cell technology to these disorders will be critical, since it allows the examination of differentiated neurons directly derived from the patient with a diagnosed disorder.
- Given good quantitative data in certain fields of neuroscience, computational modeling is gaining traction and should be encouraged. This will require integration between biologists, mathematicians and computer scientists.
- The role of bidirectional translational efforts cannot be overemphasized, and will require continued cooperation between psychiatrists and basic scientists. This translation occurs across levels, including the identification of genetic variants and the recapitulation into mouse/animal models, the continued application of advanced molecular and imaging techniques to study post-mortem samples, as well as the continued development and evolution of basic models of disease inspired by clinical endophenotypes.
- The creation of mouse models of rare human genetic variants of relatively high effect size for specific disease-relevant intermediate phenotypes and/or endophenotypes may be a promising avenue to conduct translational studies. New whole genome sequencing tools are predicted to lead to the discovery of such mutations. Common, low effect size variants coming out of genome-wide association studies (GWAs) are also good candidates but were considered less promising; because it is less likely they will show a phenotypic effect in mice. However, GWAs studies may be valuable in identifying biological pathways which can be manipulated rather than individual genes.
- Integrative analysis of endophenotypes and/or intermediate phenotypes (e.g., anatomical, physiological, molecular, and behavioral) is recommended, since it will contribute to the definition of phenotypic specificity in relation to, for example, genetic variations. This integrated analysis should go hand-in-hand with psychiatric assessment of these phenotypes.
- Age has also received too little attention, and is a powerful variable to better understand anatomical, physiological, and molecular risk factors for mental illness. Understanding brain changes associated with early postnatal development, adolescence and old age allows for an appreciation of the varied types of neuroplasticity that form substrates for neuropsychiatric illnesses. Furthermore, there will be certain time windows during which relevant epigenetic mechanism may alter normal brain development and functioning (e.g., via gene-by-environment interactions).

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