Modern Psychiatry: From Genes to Therapies

(Nils Brose and Florian Holsboer)

Definition of Research

The end of the 20th century has witnessed the 'coming of age' of psychiatry. After a history of scientific obscurity, during which an almost complete lack of functional insights into mental illnesses caused psychiatry to drift towards psychoanalysis and community or social psychiatry, the field has changed fundamentally. Epidemiological findings, twin studies, studies on the genetics of mental disorders, novel techniques in neuroimaging and neurophysiology, and advances in pharmacology, biochemistry, and neuroendocrinology have moved the neurobiological basis of mental illnesses into the focus of psychiatric research. Based on the notion that mental illnesses are disorders of brain circuitries, modern psychiatry explores the genetic, cellular, and neural network perturbations that cause mental illness. It investigates biomarkers - or endophenotypes - of mental disorders, which are the consequence of genetic predisposition and environmental factors and can thus be employed for diagnosis or targeted for therapies. The ultimate aims are the generation of reliable diagnoses that are based upon objectifiable data and the development of systematic evidence-based differential therapies for mental disorders. Such therapies are of eminent importance, as the WHO predicts that 25% of all years spent by the population in a diseased state will soon be caused by mental disorders.

Status of the Field

Genetics has been one of the key driving forces in psychiatric research. Based on the now decade-old recognition that many - if not all - psychiatric illnesses have a major genetic contribution, the field was initially dominated by a huge number of association studies, which indicates associations between individual genetic variants and diagnostic categories. The corresponding studies were more or less exclusively based on the hypothesis that the disorders under investigation are multigenic in nature and that multiple common genetic variants with small effects lead to a

common disease phenotype. Unfortunately, the vast majority of these studies could never be replicated. This is due to the circumstance that the patient cohorts studied were usually much too small and too heterogeneous with regard to the underlying pathology, which made the reliable identification of small-effect genetic variations essentially impossible.

In recognition of these difficulties with psychiatric genetics studies, scientists in the field developed two alternative strategies. On the one hand, large consortia assembled to conduct genome-wide genetic analyses on very large patient cohorts. In the field of schizophrenia, for example, this has led to the identification of genetic variants with small-effects that are very likely important (Owen et al., Curr. Opin. Genet. Dev. 19, 266-270, 2009). On the other hand, systematic searches for individually rare genetic variants in groups of related patients have yielded important insights into genetic causes of psychiatric disorders that may have large effects or even be solely responsible for the corresponding disorder. In the case of autism, for example, successful studies of this type involved analyses of copy number variations or resequencing of candidate genes and identified mutations in genes encoding components of glutamatergic synapses in the brain that may lead to monogenic heritable forms of autism (e.g. Bourgeron, Curr. Opin. Neurobiol. 19, 231-234, 2009). Both approaches, i.e. genome-wide searches for small-effect variants and analyses of rare large-effect variants, will profit from the ongoing development of next-generation sequencing methods and the ability to ultimately study and compare whole genome sequences of many affected patients.

It is important to note, however, that these two strategies have not been successful in psychiatric disorders with large environmental influences, such as mood and anxiety disorders. Here, a number of candidate-driven approaches indicate the power of gene-environment interaction analyses for these disorders (e.g. Binder et al., JAMA 299, 1291-1305, 2008), with the effects of specific genetic variants only becoming apparent in combination with exposure to certain environmental stressors. Genome-wide gene-environment interaction studies are needed in the field, but currently available samples are either too small or not sufficiently well characterized for these types of analyses.

Even when successful in reliably identifying genetic variants with a potentially causal role in a given psychiatric disorder, it is usually not obvious what the functional consequences of the corresponding genetic variation might be. Exceptions are rare cases in which single loss-of-function mutations are implicated, such as mutations in the *NLGN3* and *NLGN4X* genes, which encode synaptic adhesion proteins whose mutation causes autism and other related mental disorders (e.g. Sudhof, Nature 455, 903-911, 2008).

In most other cases, however, the identification of genetic variants is a mere starting point, and genetic data must be complemented by epigenetic analyses, analyses of gene expression profiles (i.e. transcriptomics and proteomics studies), analyses of the metabolic profile of patients (i.e. metabolomics studies), and functional studies (e.g. by functional MRI, PET, or EEG). In principle, such studies would be ideally suited to yield important information on disease biomarkers or endophenotypes (as reviewed by Holsboer, Nat. Rev. Neurosci. 9, 638-646, 2008), but they have been less frequent and much less comprehensive than genetic studies so far. Nevertheless, transcriptomics and proteomics studies on mental disorders, which can in principle be conducted with whole transcriptomes or proteomes, have already yielded interesting findings.

In summary, the neurobiological research in area of psychiatry has so far mainly relied on genetic studies. These have yielded important information on putative disease genes and, in some cases, even formed a solid basis for the development of informative animal models of psychiatric diseases (e.g. Jamain et al., Proc. Natl. Acad. Sci. U.S.A. 105, 1710-1715, 2008). The complementation of genetic studies by systematic transcriptomics, proteomics, metabolomics, and functional studies is still somewhat in its infancy but has the great potential to lead to the identification of disease biomarkers.

International Activities

Studies on the genetic and functional basis of psychiatric disorders are in the focus of more or less every respectable biomedically oriented scientific institution in the world.

This is clearly owed to the ever-increasing importance that such disorders have, particularly in societies with an ageing population where dementias rise at a staggering rate. Consequently, several huge international consortia have assembled to study the genetics and biological basis of psychiatric diseases. Examples are the Autism Genome Project (2007) or the International Schizophrenia Consortium (2009).

Research Opportunities and Needs

Diagnosis

Historically, patient cohorts used for psychiatric genetics and comparable studies have been rather poorly characterized and extremely heterogeneous with regard to their clinical characteristics and the differences in underlying causal mechanisms. Patients with identical clinical features can have separate pathologies and diseased identical twins can present with different clinical phenotypes. This is a major confounding factor that cannot be entirely circumvented by using very large cohorts. What is clearly needed is a phenotype-based exploration of genetic disease factors, based on the assumption that valuable information about relevant genetic disease mechanisms can be obtained much more reliably if studies are performed on very detailed clinical datasets and quantifiable biological readouts of a given disorder, rather than the endpoint diagnosis in comparison to healthy controls. This requires a large, concerted, and standardised effort at the clinical level and implementation of objective biomarkers. The ultimate aim would be the establishment of patient databases that allow the association of genetic, transcriptomic, proteomic, metabolomic, or functional information with clinical readouts and phenotypes of the given disease. Only with this degree of clinical detail will it be possible to establish diagnostic attributions that are related to the underlying pathology, that allow to prognosticate the course of disease, and that can support the decision making process for differential therapy.

Genes

Genetics will remain a key driving force in biological psychiatry. The development of novel high-throughput sequencing technologies will continue to revolutionize psychiatric genetics and ultimately allow for whole genome sequencing of all relevant patients at an affordable cost. To make corresponding studies logistically feasible, continuous investments into novel instrumentation are necessary. In addition, the huge datasets resulting form such analyses will require massive bioinformatics support for data handling, data processing, sequence comparisons, and modeling.

Environment and Epigenetics

Determining neurobiological sequelae of genomic variations that are linked to psychiatric conditions is not a far-fetched goal. However, it requires knowledge about the mechanisms by which environmental factors interact with genes and their variants, and how epigenetic modifications are triggered to adapt to changing demands. Moreover, it is important to understand how epigenetic modifications are imprinted and how such processes can be prevented or reversed. Of particular interest in this regard is an understanding of the sensitive periods of epigenetic programming and of the mechanisms by which external factors determine vulnerability or resilience towards gene-environment interactions. Here animal experiments that mimic adversities in different periods of life will be indispensable. In fact, the epigenetic mechanism by which an adverse experience in early life, e.g. maternal separation of mouse pups, results in lifelong behavioral traits bearing resemblance with depression has recently been revealed (Murgatroyd et al., Nat. Neurosci., in press, 2009).

Such studies will have to be complemented by human studies, interrogating how for example early childhood experiences may interact with disease susceptibility or resilience. Along this road, determinants paving the way to vulnerability as opposed to resilience need to be identified across the health-span. The vulnerability or resilience of a given individual towards potentially noxious environmental influences may markedly depend on genetic variants conferring risk as opposed to protective

factors. Therefore, identification of robust risk factors at different phases of these disease trajectories need to be identified in order to allow intervention at a pre-symptomatic stage, i.e. before overt psychopathology emerges.

Biomarkers/Endophenotypes

The diagnostic analyses of patients will have to include systematic searches for reliable biomarkers, bio-signatures, or endophenotypes, which will be of eminent importance not only for diagnosis and therapy in general but also for the identification of disase-onset before symptoms become overt and for the analysis of disease progression, remission, and relapse. Biomarkers are most likely to be discovered by transcriptomics, proteomics, metabolomics, and endocrinological studies on patients as well as from functional MRI, PET, and EEG analyses. Many of the technologies needed for this purpose are still very elaborate and thus problematic in the context of large patient cohorts, but novel technological developments will circumvent these problems.

Due to rather inadequate technologies (e.g. DNA microarrays) the use of transcriptomics in psychiatry has struggled with issues of reproducibility. The new-generation sequencing technologies will overcome problems of reproducibility and signal intensity. With this technology also candidate genome areas will be identified that are potentially modified by epigenetic processes. As is the case with genomics, transcriptomic studies require extensive bioinformatic support and continuous investments into novel instrumentation.

Proteins are the key players in physiology and pathophysiology, but the comprehensive analysis and identification of protein biomarkers of psychiatric disorders has been a daunting task. New developments in protein detection and analysis (e.g. antibody chips), in comparative proteomics, and in mass spectrometry techniques and instrumentation are likely to resolve many of the current protein analysis problems that are associated with the analysis of very large samples numbers, provided that corresponding bioinformatic support is available.

A patient's metabolic profile represents a phenotype that reflects the interplay of ongoing gene-environment interactions. The 'metabotype' of an individual can thus be a key indicator of the normal physiologcial state, of a possible pathophysiological perturbation, or of a response to a given drug, its clinical efficacy, and its possible adverse effects. The 'metabolome' of an individual is extremely complex and heterogeneous with regard to its molecular composition. Systematic metabolomic studies will thus require a complex and highly diversified bioanalytical instrumentation along with strong bioinformatics support.

NMR based neuroimaging provides important information on brain structure and function. The possibility to examine the brain with NMR imaging and to interpret the results in terms of morphological and functional characteristics has revolutionized clinical neurosciences, including neurosurgery, psychiatry, and neurology. For example, meta-analyses showed that volume changes are apparent in the hippocampi and amygdalae of patients with depression, and refined analyses of NMR imaging scans indicate that a combination of certain morphological changes in various brain areas can be used as predictors of clinical drug-treatment responses. With the aid of novel neuroimaging technologies (e.g. diffusion tensor imaging) brain connectivity in patients and controls can be analysed, which will lead to insights into the brain dysfunctions that underlie a given psychiatric disorder. However, in order to be useful in the identification of disease endophenotypes, NMR imaging will have to be made available to large numbers of patients, which will remain logistically problematic in the foreseeable future unless major investments into instrumentation and trained staff are made.

Since the eighties of last century, neuroendocrinology has played an important role in psychiatry, which was initially based on the discovery that neuropeptides have direct effects on brain function with corresponding behavioral consequences. This led to the notion of the 'window-to-the-brain', i.e. the hypothesis that refined analytical and functional neuroendocrinologic studies would yield essential insights into altered brain function based on changes in peripheral hormone levels. Research in psychiatric neuroendocrinology has been and continues to be very important. It has led to the first non-monoamine-based drugs in psychiatry, which have the striking potential to be used in a much more specific - or personalised - manner than for

example conventional 'broad-spectrum' antidepressants. In addition, neuroendocrinological readouts, such as stress hormone levels in patients with depression, have important clinical prognostic value. Clearly, neuroendocrinology will remain an important source for better treatments of subgroups of psychiatry patients. However, its value with regard to the development of novel diagnostic and therapeutic strategies is critically dependent on the continued development and application of novel proteomics and metabolomics approaches in psychiatry.

Essentially all patients with psychiatric disorders suffer from disturbed sleep, which can be shown by polysomnographic EEG analysis of electrical brain activity during sleep. Patients with depression, for example, spend less time in deep non-REM sleep but more time in REM sleep, which is characterized rapid eye movements, associated with dreaming, and possibly important for memory consolidation. The potential of sleep EEG analyses in psychiatry mainly lies in the bidirectional translation of clinical questions into the animal sleep laboratory, from which hypotheses emerge that can be tested in the human sleep laboratory. This approach has already yielded important insights into the effects of antidepressants targeting certain neuropeptide signalling processes and the role that these peptide play in depression. Thus, sleep EEG analyses have already yielded information on biomarker candidates, and refined tools to measure sleep-associated electric brain activity will likely provide an important basis for specific personalised medicine.

Models

Most animal models of psychiatric diseases that have been used in the past suffered from a lack of construct validity. With the advent of informative genetic studies and the identification of monogenic heritable forms of psychiatric disorders, this situation has changed. Particularly in cases where defined mutations with known effects (e.g. loss of function) are the basis of the given disorders, genetic models have gained importance as they provide very good construct validity. With regard to psychiatric disorders, which all involve behavioural deficits, mouse models have so far been most useful, and some of them have proven to provide very good face validity, i.e. the symptoms in the genetic models mimic symptoms in the patients.

With psychiatric genetics constantly progressing, the development of genetic mouse models for psychiatric diseases will further gain importance. Such models will have to include more complex (e.g. inducible or brain region specific) genetic variants, and will have to be tested in conjunction with experimental 'environmental' factors such as stress, infection, drug exposure, or physical trauma. In addition, animal models defined by certain 'environmentally' induced (e.g. stress) behavioural deficits will be helpful.

Given that many behavioural traits that characterise psychiatric disorders cannot be mimicked in mice, it will be necessary to develop more useful genetic models. In this regard, even the use of primates as models will have to be considered.

Pharmacotherapy

A key research goal of the search for biomarkers or endophenotypes in psychiatric disorders is the discovery of perturbed signalling pathways that can be targeted by drugs. To base the search for therapeutically relevant drugs on biomarkers rather than on psychopathological features has the advantage that subgroups of patients, which likely respond similarly to certain pharmacological treatments, can be differentiated. The major tasks in this respect will be to identify different pathological mechanisms that result in the same psychopathological phenotype, to identify biomarkers that are useful to differentiate patient sub-samples, and finally to develop drugs that specifically target these pathological mechanisms.

If public research shies away from employing chemical genomics the stagnation in psychopharmacology will persist. Instead, a setup is required that gives scientists direct access to small-molecule libraries and high-throughput analysis resources in order to enable them to screen their targets under ideal conditions (e.g. in the Lead Discovery Centre of the Max Planck Society in Dortmund, Germany, or in the corresponding NIMH initiative and that of the Broad Institute at the MIT in Cambridge, USA).

Expected Outcome and Benefit

By capitalising on the research opportunities and satisfying the needs outlined above, we will be able to

- elucidate the genetic basis of mental disease,
- identify changes in brain function (biomarkers, endophenotypes) that characterise the prodromic phase of mental disease,
- identify in detail the changes in brain function (biomarkers, endophenotypes) that cause mental disease symptoms,
- identify functional perturbations (biomarkers, endophenotypes) that can be targeted by drugs, and
- identify drugs that specifically affect endophenotypic changes (e.g. perturbations of individual signalling pathways in the brain).

This, in turn, will allow us to ultimately

- develop new diagnostic strategies in order to determine the trajectories by which mental illnesses develop, and to detect mental diseases before the clinical condition becomes manifest, and
- develop evidence-based new (and ideally personalised) treatments for psychiatric disorders.

Given that psychiatric disorders are extremely prevalent, the type of research described here is not only relevant in the context of basic science but also of eminent importance for society.

References

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