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Psychiatry as a Clinical Neuroscience Discipline

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Abstract

One of the fundamental insights emerging from contemporary neuroscience is that mental illnesses are brain disorders. In contrast to classic neurological illnesses that involve discrete brain lesions, mental disorders need to be addressed as disorders of distributed brain systems with symptoms forged by developmental and social experiences. While genomics will be important for revealing risk, and cellular neuroscience should provide targets for novel treatments for these disorders, it is most likely that the tools of systems neuroscience will yield the biomarkers needed to revolutionize psychiatric diagnosis and treatment. This essay considers the discoveries that will be necessary over the next two decades to translate the promise of modern neuroscience into strategies for prevention and cures of mental disorders. To deliver on this spectacular new potential, clinical neuroscience must be integrated into the discipline of psychiatry, thereby transforming current psychiatric training, tools, and practices.

Genomics and neuroscience represent two areas of science fundamental to understanding the brain, and thus, fundamental to psychiatry. By any measure, they have undergone revolutionary changes in the past twenty years. Yet methods of diagnosis and treatment for patients with mental disorders have remained relatively unchanged. Meanwhile, during this period the public health burden of mental disorders has grown alarmingly. Mental disorders are now among the largest sources of medical disability not only in North America but worldwide¹ and, like AIDS and cancer, they are problems that are both urgent and deadly.²

In this essay we argue that psychiatry's impact on public health will require that mental disorders be understood and treated as brain disorders. In the past, mental disorders were defined by the absence of an "organic" lesion. Mental disorders became neurological disorders at the moment a lesion was found. With the advent of functional neuroimaging, we can now visualize patterns of regional brain activity associated with both normal and pathological mental experience. This approach has allowed clinicians to identify abnormal activity in brain circuits in the absence of an identifiable structural lesion in mental disorders from schizophrenia to obsessive-compulsive disorder. If mental disorders are brain disorders, then it follows logically that the basic sciences of psychiatry must include neuroscience and genomics, and that the training of psychiatrists in the future needs to be profoundly different from what it has been in the past. As with other brain disorders, such as Alzheimer's and Parkinson's, one of the routes to identifying brain pathology, in cells or in systems, may be genetics. In mental disorders, we have many useful somatic treatments, but few molecular, cellular, or system targets for developing new therapies. Here we will begin by describing the importance of genetics and epigenetics for identifying pathophysiology before addressing the role of abnormal brain function in mental disorders. Throughout this essay we suggest opportunities for the discipline of psychiatry to change. We also recognize that psychiatry presents to the rest of medicine a unique blend of interpersonal skills and behavioral expertise that will be increasingly needed in this era of care dominated by technology. The challenge

will be to incorporate neuroscience without losing the discipline's sophisticated understanding of behavior and emotion.³

Mental Disorders as Complex Genetic Disorders

Mental disorders are considered genetically complex disorders, similar to hypertension, diabetes, and cancer. This means they are not the result of a single causative mutation as in cystic fibrosis or Huntington's disease. Although we may yet discover rare cases of mental disorders resulting from a mutation of large effect, current evidence suggests that several common genetic variations contribute to risk.⁴ Scores of genes will likely be involved in risk for schizophrenia, autism, bipolar disorder, and even the vulnerability to addiction, but, as we have seen in hypertension and certain types of cancer, their function may aggregate around key intracellular pathways. In the past few months, the map of human haplotypes has been added to the map of the human genome (<http://www.hapmap.org>). This new map provides a guide to individual variation, a critical tool for identifying the vulnerability genes for genetically complex disorders. Our ability to define the risk architecture of the major psychiatric disorders appears now limited only by our ability to identify the phenotypes and endophenotypes of the illnesses, our access to DNA from enough patients and their relatives, and our skill in detecting critical gene-environment interactions.

It is also important to recognize the limitations of genetics for complex illnesses, such as schizophrenia. For instance, it is unlikely that genetics research will yield a diagnostic test for most of the psychiatric disorders, in the sense that we have genetic tests for cystic fibrosis or Huntington's disease. Defining the genetics-based risk architecture of major psychiatric illnesses may also not lead directly to a treatment. More than 20 years following identification of the genes for single gene disorders such as Huntington's, we have yet to be able to use this knowledge to develop novel treatments. If genetics does not give us a diagnostic test or a new treatment even for Mendelian disorders, why bother to identify the various genes for these complex genetic disorders? Genetic variations associated with disease provide a gateway into pathophysiology, revealing new targets for treatment. Genomics should also yield an approach to understanding risk and thus optimize strategies for preventive interventions.

Gene-Environment Interaction

Twin studies and genetic epidemiological research indicate that the environment, in both a social and physical sense, interacts with genetic vulnerability to exert a powerful influence on the development of mental disorders. Psychiatry has spent much of the last century investigating the infantile roots of adult psychopathology. The current era allows us to extend this investigation to molecular mechanisms, asking how environmental factors during critical intervals of development exert long-term effects on gene expression. Exploring the mechanisms of gene-environment interactions for depression is not substantially different from understanding how environmental toxins contribute to cancer or how diet influences cardiovascular disease. The difference is that for mental disorders the trigger may be psychosocial experiences, the exposure may only have an impact at specific stages of development, and the effects may be limited to a narrow range of cells in the brain.

The recent work by Ian Weaver and his colleagues⁵ in infant rats may prove an instructive paradigm. Infants receiving the most maternal licking and grooming were subsequently less stress-responsive in adulthood. This long-term effect may be mediated by an enduring increase in hippocampal glucocorticoid receptors, which serve as a brake on the brain's stress response system. How could maternal licking and grooming increase hippocampal glucocorticoid receptors? Weaver and colleagues demonstrated that in the first six days of life, high levels of maternal licking and grooming were associated with a decrease in methylation of a key segment of the promoter region of the glucocorticoid receptor. Methylation is a common mechanism in

the genome that leads to silencing of specific genes (in each cell, only about 15% of the genome is active; the remainder is silenced by methylation and other mechanisms). The proposed mechanism by which nurture affects nature is straightforward: maternal care reduces methylation, loss of methylation increases expression of the receptor, and with more receptors in the hippocampus there is less reaction to stress. Note that there is no change in gene sequence; the changes are only in gene expression. Hence, these kinds of effects are called “epigenetic.” Epigenetic mechanisms, such as methylation, can have enduring effects on gene expression, providing a potential pathway by which early experience can have lasting effects on behavior. In this case, the effects are localized to a single region of the genome (glucocorticoid receptor promoter), a single cell type (within hippocampus), and a discrete developmental window (first 6 post-natal days). The challenge now will be to demonstrate similar mechanisms in humans.

Genomics in psychiatry will need to grapple not only with classical genetics, but also with developmental changes in methylation and other mechanisms conferring long-term effects on gene expression. Although measuring exposure to a traumatic human experience appears more complex than measuring exposure to carcinogens or a high cholesterol diet, the more vexing problem is the range of individual responses. Can we understand how stressful circumstances destroy hope and opportunity in one individual and “build character” in others? Can we measure genetic variations that not only confer vulnerability or resilience to risk but increase the likelihood of exposure to risk? Can we develop a quantifiable science of exposure to psychosocial trauma just as we have done for environmental toxins? These are some of the questions that will be addressed by researchers in the genomic era.

New Approaches to Neural Regulation

One of the major insights from the Human Genome Project has been the discovery of the number of human genes: roughly 23,000, with perhaps 50% of these expressed in the brain. As we have noted elsewhere, it is likely that, until very recently, 99% of everything written about the neurochemistry of mental disorders has focused on less than 1% of the genome.⁶ As most genes code for many proteins, the number of proteins in the brain undoubtedly exceeds 100,000. Theories of mental disorders based on a few monoamines, such as serotonin and dopamine, while helpful, will no doubt appear naïve as we begin to explore more of the amines and proteins found in the brain. In that sense, we are in a discovery phase of neurochemistry, often called neurogenomics, trying to understand where and when all of the genes in the brain are expressed.⁷ One such discovery approach, known as the Gene Expression Nervous System Atlas (GENSAT) project, has been developing maps of expression of hundreds of recently discovered genes in the mouse brain.⁸ The maps, available at <http://www.gensat.org>, reveal remarkably discrete patterns, with certain genes expressed only in a small subset of neurons, sometimes at specific times of development.

Neurogenomics will provide maps of RNA in the rodent brain and should alter our understanding of neuroanatomy, but is unlikely to yield a biomarker for any mental disorder. A newer approach, neuroproteomics, attempts to measure all of the available proteins to detect potential biomarkers associated with major mental disorders.⁹ It seems likely that among the vast sea of RNAs or proteins, some will be associated with specific mental disorders, providing either a trait or state marker that will permit a finer grain of diagnosis than has been possible with clinical observation. These may come from cerebrospinal fluid, CNS cells, or peripheral cells grown in culture. Early results in schizophrenia,¹⁰ PTSD,¹¹ and autism¹² are just emerging. In addition, differentiating bipolar from major depressive disorder and identifying the prodrome of schizophrenia are high priorities for research for diagnostic markers.

While we still have a limited number of DNA variations, RNA expression patterns, or protein changes that have been linked to mental disorders, molecular and cellular neuroscience studies

in non-human animals are already pointing to important principles of neural regulation that should prove critical for our ultimate understanding of mental disorders. Two recent examples illustrate this potential. First, the increasing recognition of neurogenesis in the adult brain has led to a novel hypothesis of the pathophysiology and treatment of depression. Clinical imaging studies have reported decreased hippocampal volume in people with major depressive disorder. While it is not clear that depression is associated with reduced neurogenesis, and changes in hippocampal volume have yet to be shown to part of the pathophysiology of depression, animal studies have demonstrated that stress reduces neurogenesis in these regions^{13, 14} and several classes of clinically useful antidepressants increase the rate of neurogenesis in the hippocampus.¹⁵ In one study, a selective blockade of the drug's effect on neurogenesis also reduced the behavioral effect of the antidepressant.¹⁶ The resulting hypothesis, based largely on animal studies, is that chronic stress reduces the rate of neurogenesis in a critical pool of forebrain neurons, leading in genetically vulnerable individuals to a depressive episode. The importance of this hypothesis is that it introduces a long roster of known molecular mechanisms for neurogenesis as novel targets for developing new classes of pharmacological and behavioral treatments.

A second example arises from studies of synaptic plasticity, focusing on the role of excitatory amino acid receptors, the NMDA and AMPA receptors. Learning appears to be associated with a translocation of a cytoplasmic pool of AMPA receptors to the post-synaptic cell membrane.¹⁷ This change leads to a long-term facilitation of neurotransmission in specific dendritic spines. Recently, Rumpel and colleagues¹⁸ have demonstrated that the acquisition of fear is associated with a similar mechanism in the lateral amygdala. That is, when animals learn to associate a neutral stimulus with a shock, the resulting fearful response depends on this cellular change in a small population of cells in the lateral amygdala. It is not clear when pathological fears (phobias, panic disorder) involve an overactivation of this mechanism, but the identification of the mechanisms for the acquisition and extinction of fear responses should provide important clues for the pathophysiology of anxiety disorders. For instance, d-cycloserine, a compound which alters glutamate neurotransmission and facilitates extinction in animal studies, has recently been shown to enhance behavior therapy for phobias.¹⁹ As with neurogenesis, understanding the cellular basis for plasticity promises to introduce a new series of targets for treating disorders such as PTSD, which involve a deficit in extinction.

Revealing Brain Systems as Biomarkers

Ultimately, biomarkers for mental disorders may not be proteins or neurotransmitters, but will emerge from neuroimaging (fMRI, SPECT, etc). Logically, if these are disorders of brain systems, then the visualization of abnormal patterns of brain activity will be the "pathology" of these illnesses. One can imagine studies in which patterns of brain activation following stimulation may be diagnostic, just as a nuclear stress test is now used widely by cardiologists to diagnose coronary artery disease.

Already we are seeing multiple approaches to identifying abnormal functional activity in the brain, from functional MRI to in vivo neurochemistry and studies of brain receptors. One approach uses functional imaging to identify differences in regional activity. For instance, evidence from several different approaches implicates circuitry involving ventral, medial prefrontal cortex (Area 25) with major depressive disorder.²⁰ In addition to structural studies reporting decreased gray matter volume in this region,²¹ PET studies comparing responders and non-responders to SSRIs, treatment with SSRI and cognitive behavior therapy, and even placebo responders with non-responders have all shown that recovery from depression is associated with a decrease in activity in this region.²² This region has nearly the highest serotonergic innervation in the human forebrain as measured by the expression of the serotonin transporter.²³ Individuals with the short allele of the serotonin transporter gene have reduced

expression of the transporter and appear to be at a higher risk for developing depression following stressful life events.²⁴ Recently, this short allele has been shown to be associated with reduced gray matter volume of Area 25 and uncoupling of an anterior cingulate-amygdala circuit necessary for extinction of negative affect, providing a model for linking genetic risk and environmental stress to a specific neural circuit implicated in depression.²⁵ One might imagine that studies of this circuit could be used to predict response to treatment, just as imaging in cardiology or oncology can be used to predict treatment response.

As an alternate approach, imaging of receptors may reveal regional abnormalities that could serve as a biomarker or diagnostic test. While receptor imaging has been useful for studying drug occupancy, there are relatively few applications to date that are promising for patient care. Although there is a recent report of reduced 5HT1a receptor binding in the cingulate cortex of patients with panic disorder,²⁶ and there are remarkable reports of enduring changes in striatal D2 receptors following psychostimulant abuse,²⁷ there are no receptor studies for the diagnosis or treatment of major mental disorders. Unfortunately, we still have relatively few radio-ligands for membrane-bound receptors, and the technique may fail to detect small, localized changes or intra-cellular changes distal to the receptor. In spite of these shortcomings, it seems likely that imaging receptors or cell signaling could allow a quantitative approach to biodiagnosis of mental disorders in the coming decade.

Training in Clinical Neuroscience

The recognition that mental disorders are brain disorders suggests that the psychiatrist of the future will need to be a brain scientist. Indeed, psychiatrists and neurologists may be best considered “clinical neuroscientists,” applying the revolutionary insights from neuroscience to the care of those with brain disorders.²⁸ Studying unconscious processes, motivation, or defenses, while at one time the sole province of psychoanalytic therapies, are now also in the domain of cognitive neuroscience.^{29, 30} Systems neuroscience will be reformulating our notions of complex cognition in the next decade just as it reformulated our understanding of language and perception in the last decade. Future training might begin with two post-graduate years of clinical neuroscience shared by the disciplines we now call neurology and psychiatry, followed by two or three years of specialty training in one of several sub-disciplines (ranging from peripheral neuropathies to public sector and transcultural psychiatry). This model recognizes that the clinical neurosciences have matured sufficiently to resemble internal medicine, with core training required prior to specializing.³¹

Will a deep understanding of the psyche remain a central focus of psychiatry? The need for a sophisticated understanding of interpersonal relationships along with the use of evidence-based, non-pharmacological treatments (from psychoeducation to cognitive behavioral treatments) will be the tools of the effective healer in the future as much as in the past. Just as we recognize the need for rehabilitation following the acute care for any serious injury or medical illness, ideally the psychiatrist will increasingly be part of a team that provides culturally-valid, psychosocial rehabilitation along with medications to help those with mental disorders recover and return to a productive and satisfying life. What will be different is that we will be able to target these treatments to specific aspects of the disease process.

By re-defining the foundation of psychiatry as clinical neuroscience, we also accelerate the integration of psychiatry with the rest of medicine. The separation of psychiatry from other medical specialties has contributed to the stigma of those who treat mental disorders as well as those who suffer from these illnesses. Even beyond stigma, this separation has led to inadequate care. The recent scientific recognition of the key importance of effective treatments of mental illnesses in cardiovascular disease and diabetes^{32, 33} mandates the incorporation of psychiatry into truly integrated and effective treatment teams.

Where Do We Go From Here?

The 1990s were identified as the Decade of the Brain with major new insights into brain circuitry and function. The current decade may be recognized in retrospect as the Decade of Discovery during which many of the major candidate molecules, cells, and circuits for normal and abnormal brain function will be identified for the first time. A goal of the Decade of Discovery must be the description of the basic pathophysiology of each of the major mental disorders (Figure 1). Currently, we treat those with mental disorders episodically, with medications that are focused on symptoms and not on the core pathology. The available treatments are slow, incomplete, and can be handicapped by adverse effects. All pharmacological treatments have been developed either through a new application of a drug developed for other purposes or through a slight modification of an existing compound. In mental disorders, just as in the rest of medicine, pathophysiology should yield diagnosis based on biomarkers and treatments based on rational designs targeting the pathophysiology. For a person with schizophrenia or bipolar illness, one can imagine that a future psychiatrist would use a cognitive task accompanied by functional and structural neuroimaging to diagnose and select a specific treatment, just as a contemporary cardiologist uses a nuclear stress test and echocardiogram to diagnose ischemic heart disease and select the appropriate intervention.

It is critical to realize that clinical neuroscience does not mean designing exotic technologies for a few privileged patients. The ultimate goal is personalized or individualized care for a broad spectrum of people with mental disorders. Recently a better understanding of pathophysiology has led to a strategy for individualizing treatment of cancer.^{34, 35} Currently in psychiatry, specific treatments for any given patient are largely developed empirically. As we learn more about the pathophysiology of mental disorders, treatments should become more specific.

One can now look forward to an “Era of Translation” when we can expect not only diagnosis and treatments but very early detection and prevention. Early detection will require a thorough understanding of risk, based on a comprehensive understanding of genetics and experience. Just as cardiologists increasingly prescribe statins, exercise, and low-carbohydrate diets to prevent ischemic heart disease in high-risk patients, one can imagine preventive interventions to prevent a first break in an adolescent at high risk for schizophrenia.³⁶

While scientists routinely aim for cures for cancer and other serious medical illnesses, psychiatric researchers have been less ambitious, seeking reliable diagnosis or perhaps treatments with fewer adverse effects. Patients with mental disorders deserve more than this. Just as clinical neuroscience seeks prevention and cures for neurologic diseases such as Parkinson’s and Alzheimer’s, attacking mental disorders as brain disorders reminds us that we should expect no less from research and treatment for those with mental diseases.

Conclusion

Sitting at the intersection of an age of discovery in the neurosciences, behavior, and the mysteries of human mental life, psychiatry should emerge once again as among the most compelling and intellectually challenging medical specialties, attracting the best minds to choose this field as a lifelong career. This promise of the future will depend on psychiatry’s (a) incorporation of the insights and tools of modern neuroscience, (b) integration into the mainstream of medicine by focusing on the public health needs of those with mental disorders, and (c) retention among the medical specialties of a unique focus on the contribution of human experience and behavior in health and disease.

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Figure 1. A Vision for Mental Health Research

Pathophysiologic descriptions of mental disorders will permit diagnoses validated by biological measures and treatments aimed at core pathology. Care will become personalized via an understanding of individual risk, allowing for strategic approaches to prevention and treatment. These ambitious goals require application of genomics and proteomics to mental disorders.