

# NEUROBIOLOGY OF MENTAL HEALTH

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Recent years have witnessed a great explosion, not only in understanding the brain, but also in trying to link the brain with what goes on in its higher substrate - that elusive state of activity and existence called the "mind." We have understood for centuries that the brain is the organ of the mind, but the biological mind-brain relationship is only now beginning to be teased out. The question is central to all human scholarship but carries particular significance for the future of mental illnesses and our ability to treat them.

Illness itself is an abnormal state resulting from complex interaction between our genes (which impart predisposition and risk), with the environment to which we are exposed (which introduces injury or insult). In mechanistic terms, mental illness is thus best viewed not as something foreordained but as the stochastic result of dynamic gene-environment interaction taking place in brain tissue from neurogenesis through life. Factors influencing this outcome must include appropriate nurturing and stimulation of the brain during development, maintenance of individual and environmental homeostasis, the physical and societal environment, and also the circumstances of one's life and one's reactions to them. Mental illness could result from a primary event occurring anywhere within this complex interplay.

### COMPLEXITY - THE CHALLENGE OF MENTAL ILLNESS

Fundamental to appreciating the daunting biological challenge posed by mental health and illness is the vast complexity of its scope. At the clinical or bedside level, this complexity manifests in the subtle nature of psychiatric symptoms which, by and large, occupy the fringes of a thought-behavior continuum, lacking sharp distinction from what would be considered normal thinking or behavior. At the neurobiological level, the roots of this complexity lie in the brain being an epigenetic organ par excellence. Because of this, dramatic behavioral differences can emerge from small differences in only a limited number of genes. The human and chimpanzee

genomes, for example, differ by less than 2%, but the corresponding behavioral differences expressed in that narrow genetic gap are staggering.

The complexity of the brain, ultimately, is attributable to the phenomenal dimensions of neuronal interconnections. There are an estimated 1011 neurons in the human cerebral cortex, connected to each other at 613 synapses. The number of interconnections between cortical neurons exceeds the number of galaxies in the known universe. Even if we had deciphered the entire circuitry diagram of the human cerebral cortex, fathoming how the circuit processes data will be beyond - indeed, well beyond - the most powerful supercomputer.

### MOLECULES AND MENTAL ILLNESS

The study of mind draws on brain structure and function - on detailed neuroanatomy including neuronal circuitry and on detailed elucidation of neurochemical functioning - but the study of mental disease demands modified approaches. It begins with epidemiology, the population-based science of measuring burden of disease and its associated and inter-related factors. It is the first step in a reductive approach to mental health, an approach that has been applied with eminent success through the history of science. Part of the difficulty in studying mental health has been that mechanistic reductionism was kept out of this field for decades even as other areas of biology and medicine were yielding to it readily. The arbitrary ideas of Freud and Skinner represented a widespread distraction for students of the mind. In effect, reductionism came to the study of the mind as a scientific reform, and it led to a powerful reappraisal of the symptomatology and phenomenology of psychiatric disease.

As with the study of disease-states of other organs, reductionist approaches to diseases of the mind lead to an examination of the relationship between molecules and mental illness. It is not sufficient to think of individual genes and proteins, but rather in terms of genomics and

proteomics - holistic concepts that fully integrate the dynamic complexity of biological molecules and their interactions in producing the processes of life.

The blueprint for all biological function ultimately lies in the nucleus and mitochondria, and comprises 3 billion nucleotides of DNA. We have learned that this mass of DNA information encodes 30,000 to 40,000 separate genes (significantly less than the 100,000 initially estimated). With the success of the Human Genome Project, the challenge of explaining observed differences between diverse complex phenotypes in terms of genomic diversity has been brought into realistic focus.

The most natural route for linking disease phenotypes with individual genes is provided by familial diseases. Parametric methods can be applied to multiple familial clusters of specific diseases with the purpose of generating logarithmic odds of linkage between pathologic phenotype and gene. In the absence of large clusters in multiple families, one can search for chromosomal abnormalities in sporadic isolated cases of familial aggregates. However, mental disease cannot be studied simply in terms of Mendelian traits because the genomic basis of behavior lies in complex polygenics, which may be seen as a cascade of inter-relationships including gene-gene interactions that may be additive or epistatic, as well as gene-environment interactions. Application of genetic parametric methodologies to familial subgroups of mental diseases shows usually more than one gene underlying the disease condition. The problem is further complicated by the issue of variable penetrance, which causes phenotypes to differ despite identical genetic predisposition.

If the biology of a disease is somewhat understood, it may be possible to identify candidate genes on that basis alone, whose relationship with the disease can be examined through parametric genetics. For example, empirical knowledge about neuropharmacological abnormalities associated with a given psychiatric disease may implicate particular neurotransmitter receptors or transporters in its pathogenesis. Parametric methods make it possible to ask the question if these macromolecules are in some way contributing to the disease. Polymorphisms in candidate genes can be evaluated against familial clustering to search for transmission disequilibrium and determine genetic linkage.

### THE PROMISE OF PROTEOMICS

There is, however, a huge gap between the study of genomics and the clinical expression of disease. The gap is filled by proteomics, the study of proteins and their in

vivo interactions in cellular context. The study of proteomics requires complex methodology that remains underdeveloped, and has therefore been harder to crack. There is no escaping its central role, however, for disease in any form - be it cancer, inflammation, degeneration or other pathology - is ultimately nothing other than abnormal protein-protein interaction. The model has been applied with success to neurological disorders, and should theoretically apply just as well to psychiatric disorders.

The reason proteomics goes well beyond the study of primary protein structure (amino acid sequence predictable from nucleotide sequence), and therefore well beyond genomics, is because once the peptide is formed, proteins undergo potentially extensive modifications, including complex protein-folding (secondary structure) and post-translational modification (tertiary and quaternary structure). Another way of seeing this is to appreciate that while genomes are fixed, proteins are dynamic. Moreover, the multiple steps and modifications following gene translation permit an extra dimension of variety in proteins. Thus from 30,000 genes it is possible to generate from 300,000 to 1 million different kinds of proteins.

### SPECIFIC PSYCHIATRIC DISEASES

With this background, it is worth directing attention to specific examples of mental disease. Manic-depressive disorder (also known as bipolar illness) is a mood disorder in which cyclic fluctuation between depressive and manic or hypomanic moods dominates the clinical picture. A very common disorder with a population frequency of 1%, the disorder approaches a concordance rate of 70% in monozygotic twins. The precise concordance varies according to the diagnostic criteria used, but it is consistently significantly higher than the corresponding figure in dizygotic twins or among first-degree relatives. This observation unequivocally implicates a strong genetic component in the causation of manic-depressive disorder, because clearly the greater one's complement of genes shared with an affected individual, the more likely that one will have the disease.

The list of genes that have thus far been linked to bipolar illness is long. A complex disease in which genetic predisposition is only one of the causative factors is bound to have many different regions of the genome

In parallel with genetic approaches, structural and morphological investigation of the brain is also opening up new avenues of understanding. The most powerful modality is neuroimaging, a field that is enjoying dynamic technological innovations at breakneck speed. Blood flow-

based functional imaging techniques and high-resolution morphometric magnetic resonance imaging (MRI) are starting to reveal abnormalities that had remained undetected with histology and histopathology. According to one study, for example, three-dimensional reconstructed MRI reveals that the hippocampus may be 10% smaller in patients who are depressed. There are numerous other examples of a similar nature in which subtle structural abnormality in brain microanatomy has been linked to mental illness. The absence of a structure-function relationship is what had hitherto represented the greatest hurdle to a mechanistic study of mental disorders. Modern neuroimaging is now bursting with the promise of breaching this gap.

The ability to visualize the human brain during life has transformed the way we look at and study diseases of the brain and mind. The technology is advancing rapidly and breakthroughs of great magnitude can be expected to occur apace in the coming years. Not only can living brain structure be visualized with a level of resolution approaching histological detail, functional aspects of brain function can also be assessed (through spectroscopy and perfusion imaging) and mapped in 3-dimensional space. It is now a real possibility to contemplate the holy grail of psychiatric pathophysiology: identifying bona fide structural correlates of mental diseases in the brain.

The complexity of mental illness strongly suggests that mental diseases are polygenic and/or multi-factorial conditions in which clinical phenotype results from interaction between many, perhaps 50 to 100 or more, genes. Studying polymorphisms in polygenic interactions is challenging enough, but what makes the study of mental diseases particularly daunting is their multi-factorial causation, in which genetic polymorphisms are associated with disease susceptibility rather than symptomatic phenotype. Clinically overt disease would result from an environmental or situational insult to a susceptible mental substrate. For example, even though the evidence is harder to marshal, recent data suggest there may be a susceptibility gene for attention-deficit disorder on chromosome 16.

### **SCHIZOPHRENIA - THE ARCHETYPAL EXAMPLE**

One of the most challenging disease conditions in all of neurobiology is schizophrenia. The archetypal psychosis, it cuts to the core of our very humanness, and we can see elements of it in our daily thoughts and experiences and in belief systems that modern civilized society takes for granted. Literature - scientific as well as non-scientific - abounds with references and treatments of schizophrenia, and the issues it raises in mental health. Indeed, one view

of fiction and novel-writing is as a means to understand and reflect about how we react, believe, and live - our mental health, in other words. The status of schizophrenia as a problem in mental neurobiology is thus pre-eminent.

An interesting point about schizophrenia is that although incidence in both sexes is similar, the disease has earlier onset, greater severity, and weaker response to therapy in males as compared to females. While genetic predisposition in this condition is well recognized, evidence for contribution from non-genetic factors is also strong. The abnormal substrate in schizophrenia is cognition, expressed through loosening of associations and disorganization in thought and speech. Clinically, a distinction is made between the so-called 'positive' symptoms (paranoia, hallucinations, psychotic ideation) and 'negative' symptoms (apathy, flat affect, withdrawal, anhedonia and poverty of speech). Neuroleptic drugs have revolutionized the management of schizophrenia; however, medication improves the positive symptoms of schizophrenia but the negative (also called 'deficit') symptoms are resistant to drug treatment.

Based on neuroleptics being dopamine antagonists, the dopamine hypothesis has emerged as the central theory of schizophrenia neurobiology. In this view, excess dopamine activity in key brain structures including basal ganglia and limbic structures underlies the positive symptomatology of schizophrenia. Temporal variation in symptoms may correlate with episodic changes in this excess neurotransmitter activity. The illness begins with a prodromal phase, giving the impression that brain circuitry is being primed for the abnormal state to follow. It is this recognition that made Kraepelin name the disease dementia praecox. The prodrome is a susceptible period for neuroleptic medication to take effect on positive symptoms. Deficit symptoms, in contrast, are believed to arise from the prefrontal cortex, the seat of executive functioning. They continue throughout life, affecting attention, motivation, initiative, working memory and executive functioning, with anti-psychotic medication making little difference.

Studies have attempted to correlate brain growth and schizophrenia risk. A vulnerable period appears to be the so-called phase 5 of neural development, coinciding with puberty and post-pubertal life, in which a kind of pruning or fine-tuning of synaptic connections takes place, at least part of which may be experience-dependent. This may imply environmental influence in the causation of schizophrenia. Yet the picture is complicated, since genetic factors are also at play, the most straightforward piece of evidence being greater concordance in monozygotic as opposed to dizygotic twins. There is also increased incidence in first-degree relatives. Indeed, as

much as 50% of the risk for schizophrenia may be genetic.

Brain imaging in schizophrenia consistently shows prominent ventricles consistent with tissue loss, along with reduced parenchymal volumes in the frontal and medial temporal lobes. Pathologically, schizophrenia is associated with subtle changes in gray matter. The abnormalities are not diagnostic, but certain brain regions - hippocampus, prefrontal cortex, medio-dorsal nucleus of the thalamus - show preferential atrophy. Functional assessment of synaptic transmission in schizophrenia is difficult, but evidence from PET scanning suggests reduced activation in the prefrontal cortex.

The overall prevalence of schizophrenia in the general population is 1%. Though the genetic predisposition is clear, it is not a Mendelian (single-gene) disorder. The causation therefore is complex and polygenic, requiring both genetic predisposition and environmental interaction. This is emerging to be a common model for other medical disorders as well, such as coronary artery disease and diabetes mellitus. The methodological challenge is significant, because nonparametric techniques are required. The brain is an epigenetic organ and in the causation of complex brain disorders like schizophrenia multiple genes are ultimately involved that modulate risk of disease as well as phenotypic expression, on the background of environmental interaction.

The synaptic hypothesis, which proposes that schizophrenia can be understood in terms of altered synaptic transmission and neuronal connectivity, represents another approach to the problem. A core feature of this hypothesis is disturbance in the cortical inhibitory circuit. Evidence implicates tyrosine hydroxylase-positive cortical interneurons with laminar organization that may produce altered synaptic function at a subset of GABA-ergic receptors. A particular type of such interneuron is the so-called chandelier cell found in the dorsolateral prefrontal cortex which may contribute towards working memory or attention. Pyramidal cell activation may be part of this setup. These disordered elements could be linked to the constant drift of thought and attention that characterizes schizophrenia.

An emerging paradigm of GABA-ergic transmission is that during development, GABA may initially be an excitatory neurotransmitter. As the dendritic arbor develops, glutamate becomes the major excitatory transmitter. In schizophrenic patients, there may be decreased glutamatergic activation because of a defect in GABA transmission, compromising the faculty of attention and alertness, which normally arises from the ability of pyramidal cells in the prefrontal cortex to excite each other.

Other lines of evidence add to the hypothesis of disordered synaptic biology. For example, there is also an important dopaminergic input to the prefrontal cortex; prefrontal dopamine, which may be measured by PET scanning or direct chemical analysis of post-mortem brain tissue, is increased in the brains of schizophrenic patients. Additionally, microarray experiments comparing gene expression between schizophrenic and normal brains indicate that many of the genes involved in the pre-synaptic aspects of neurotransmission are decreased in schizophrenia. The emerging mechanistic picture of the neurobiological basis of schizophrenia is one of synaptic destabilization across multiple neurotransmitter systems in the prefrontal cortex.

Yet another, possibly related, idea has to do with how the brains of schizophrenic patients process sensory information. Evidence suggests there is a good deal of 'noise' in schizophrenic sensory processing, which impairs the ability to gauge serial sensory inputs. The end-result is misinterpretation or misidentification of stimuli. This may be demonstrated in an experimental paradigm using evoked potentials, which will show that the amplitude of successive sensory impulses remains unchanged in schizophrenic patients, as opposed to healthy controls, in whom the amplitude successively drops. The effect may also be detected in the first-degree relatives of patients with schizophrenia.

Interestingly, nicotine usage in schizophrenics is very high. It is known that the gene for abnormal sensory processing in schizophrenia and the gene for the alpha subunit of the nicotinic acetylcholine receptor are closely linked. Immuno-reactivity studies reveal that nicotine binding in hippocampal slices - ordinarily increased in the brains of smokers - is not increased in the brains of schizophrenic patients who smoke. This finding may reflect a relationship between nicotine use and impaired sensory gauging in schizophrenia. It is conceivable that misinterpretation of sensory information leads to the positive symptoms of schizophrenia and that these can sometimes be reversed (or made more tolerable) through the consumption of nicotine.

## CONCLUSION

Many of the neurodegenerative diseases studied by neurologists have profound psychiatric symptoms. It is a tall order, but in principle we can map the marker proteins implicated in these disorders and trace the circuitry of the neurons on which they exert an effect. This provides a potential framework for correlating complex (cognitive) symptoms with neuronal loss and synaptic damage. Selective vulnerability of distinct neuronal populations is

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the pathological hallmark of many neurodegenerative diseases, including the dementias, Huntington's disease, and a range of extrapyramidal disorders. A detailed understanding of the relevant circuitry provides a substrate - in the form of neuronal populations, subpopulations, and interrelated projections - on which to focus for advanced mechanistic analysis of psychiatric disease. Examples include memory loss in frontal lobe dementia, hallucinations in dementia with Parkinson's disease or in Lewy Body dementia, disinhibition in fronto-temporal dementia, depression and suicide in dentato-rubro-pallido-Luysian atrophy (DRPLA), apathy in progressive supranuclear palsy, and delusions in Parkinson's disease, Alzheimer's disease, and REM sleep disorders. These all represent valuable investigative leads where the neuroanatomy is well known and in which protein-protein interactions may be identified and perhaps correlated with symptomatology that would be relevant for psychiatric disease and mental health.

There is a seemingly endless complexity to the human brain, whose normal function exists as a continuum, outside the bounds of which are states of disease. As a complex biological system, the brain incorporates a 'wobble' or 'noise' in its functioning. In mental functioning, the edges of this wobble are what we term 'psychiatric disease' - perhaps partly because it does not fit with our notions of how people (and their minds) should be. The reductive approach to scientific investigation continues to be our best bet as we make our way into the almost cosmological complexity of the human brain and mind.