

BIOTECH Basics

Psychiatric Disorders



What you need to know:

- *The brain is a complex set of neurons, working together to receive and interpret information, control and initiate behavior and actions, and serve as the focal point for intelligent thought.*
- *About 1 in 4 Americans (60 million individuals) is impacted by psychiatric disorders dealing with brain structure and neuron interaction. These include major depressive disorder, schizophrenia and bipolar disorder.*
- *Recent findings are providing new insight on the complex interplay between genetic and environmental signals in the brain that lead to psychiatric disorders.*

If you want to know more

www.nimh.nih.gov

This excellent website was created by the National Institute of Mental Health.

It highlights new findings in science, has a thorough index of various mental health disorders and includes numerous educational resources.

Support groups:

There are a number of support, educational and advocacy groups for psychiatric disorders. See a sampling below.

Mental Health America
www.mentalhealthamerica.net

Depression & Bipolar Support Alliance
www.dbsalliance.org

Brain & Behavior Research Foundation
www.narsad.org

The brain is the most complex component of the human body. This three-pound organ receives and interprets information from our senses, oversees behavior and actions and serves as the focal point for intelligent thought. Variation in brain structure and function, associated with input from the world around us, shapes our behavior and personality.

In this issue of *Biotech Basics* we'll explore current understanding of psychiatric disorders, including recent findings regarding genetic and environmental risks. Historically, much of this process has been poorly understood. As a result, persons with psychiatric disorders have often been marginalized and misunderstood.

Fortunately, research is beginning to pierce through the darkness of mental illness. This work offers new insights about the genetic and environmental influences that shape the essence of who we are and the forces that alter our patterns of thought and action.

Psychiatric Disorders

According to the National Institute of Mental Health, a psychiatric disorder can be defined as a health condition that changes a person's thinking, feelings or behavior (or all three) and causes distress and difficulty in functioning. As with other diseases, psychiatric disorders can vary in severity – some cases are very mild while others cause extreme disability. This class of disorders impacts 60 million Americans - nearly 1 in 4 American adults. An additional 12 million children are also affected by psychiatric illness.

Each mental illness has its own set of clinical symptoms. Several are described

below, with acknowledgements to the NIMH.

Major depressive disorder affects nearly 10 percent of all Americans in a given year. More than twice as many women as men have depression. MDD is more than simply feeling blue or sad. It includes a loss of interest in activities that used to be enjoyed; a change in appetite, weight or major sleep patterns; loss of energy and difficulty concentrating; and a feeling of worthlessness that may be accompanied by recurring thoughts of death or suicide. MDD is diagnosed when five or more of the above symptoms are present nearly every day during a two-week period. Without treatment, symptoms last an average of nine months.

Bipolar disorder impacts nearly 6 million American adults. Symptoms most frequently appear in the second decade of life and generally cycle between three stages: depression; mania - including euphoria, impulsivity, recklessness and a diminished need for sleep; and interspaced periods without depression or mania. Although historically these interspaced times were believed to be symptom-free, we now realize there are subtle yet important clinical signs. These include attention deficits, issues with memory, problems regulating emotion and disturbances in sleep/wake cycles. Some studies suggest that individuals with BD spend 50 percent of their life in the depression or mania stages.

Schizophrenia impacts approximately 1 percent of the U.S. population. Symptoms generally emerge in the teens or 20s. Contrary to the many myths and misperceptions, SZ is not a multiple or split-per-

sonality disorder, and affected individuals do not spend most of their life constantly incoherent or violent. The symptoms of SZ are classified as “positive” (delusions, hallucinations, disorganized speech and movement issues) and “negative” (lack of emotional response or facial expression and inattention to basic self-care needs). Recent studies have also shown significant cognitive symptoms, including deficits in working memory, organized planning, language comprehension and processing responses to emotional and social stimuli.

Psychiatric Disorders and the Brain

Deep within the brain is an area known as the inner brain. This region contains structures involved in hormone regulation, emotion, movement and memory. For this discussion, we’ll focus on the limbic system (figure 1), an evolutionarily ancient part of the brain involved in emotion and human behavior. Two important parts of the limbic system are the amygdala and subgenual cingulate cortex. These structures regulate emotion in three ways:

- interpreting the emotional significance of visual cues
- experiencing the inward emotions triggered by that cue
- expressing that emotion properly

For example, if you see someone smile at you, the limbic system interprets that smile as a friendly gesture, experiences the emotion of happiness at seeing the smile and directs the face to express that

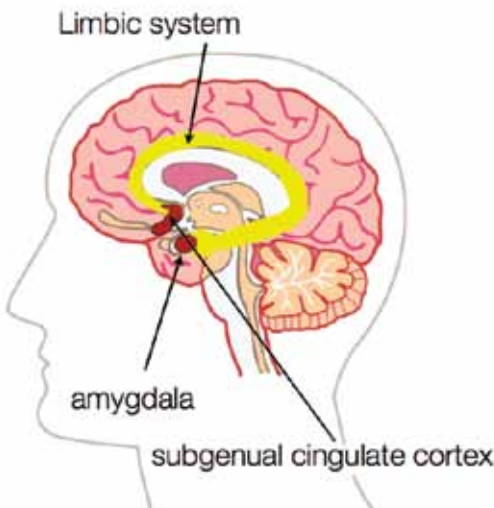


Figure 1: The limbic system of the brain, including the amygdala and subgenual cingulate cortex.

happiness by smiling back. Much of the link between what we see and the emotions that are triggered (including fright, anger and sadness) are controlled by the limbic system.

Scientists have uncovered evidence suggesting that the limbic system is overactive in individuals impacted by schizophrenia, major depressive and bipolar disorders. Visual cues may be improperly interpreted and experienced, potentially explaining the social withdrawal and anxiety experienced by many individuals. For individuals with schizophrenia, this could also explain the lack of expression and relatively flat emotions associated with the negative symptoms.

Genetic Risk Factors

Most psychiatric disorders are influenced by genetic factors although this overall impact varies across disorders. The evidence for genetic influence on major depressive disorder is relatively low. In contrast, family studies find that the risk of developing schizophrenia increases with the degree of relatedness to an individual with schizophrenia. In other words, there is a higher risk if the person has a sibling with schizophrenia than if the affected relative is an uncle or cousin (figure 2).

Until recently, there were few clearly identified risk-increasing genes. Today, genome-wide techniques such as microarray-based genotyping and next generation sequencing have begun to yield key genetic clues. These include:

- **CACNA1C**, a gene that encodes a calcium channel protein. Variants in this gene are linked to altered activity in the amygdala during emotional responses and have been associated with bipolar disease.
- **COMT**, a gene that produces an enzyme that breaks down dopamine in the synaptic space between two neurons. A variant in this gene associated with schizophrenia produces a less active enzyme, resulting in greater activity in certain parts of the brain.

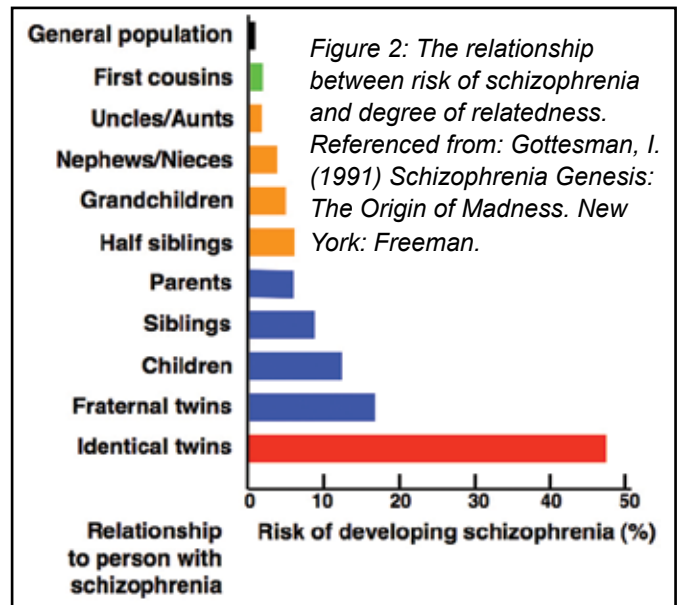


Figure 2: The relationship between risk of schizophrenia and degree of relatedness. Referenced from: Gottesman, I. (1991) *Schizophrenia Genesis: The Origin of Madness*. New York: Freeman.

- **DISC1**, a gene that provides the instructions for a protein involved in neuronal growth and development. Linked to schizophrenia, variation in this gene influences the formation and function of the hippocampus, a critical structure for memory.

Environmental and Societal Risk Factors

A number of environmental factors have been connected to psychiatric disorders. These include stress and alcohol and drug use. In particular, marijuana use appears to be a risk factor for schizophrenia. In addition, evidence is building for the involvement of societal factors in the formation of these disorders. Societal factors include life events (childhood abuse, loss of a parent), emotional stress (experiencing a natural disaster) and relationships (divorce, loss of a spouse) as well as stresses and strains related to culture and socioeconomic position.

Interactions between Genes and Environment

Like most complex diseases, psychiatric disorders are not triggered by change in a single gene or environmental insult. Rather, they develop through a combination of multiple genetic, environmental and societal risk factors, some of which may even occur prenatally or early in childhood. One such combination appears to involve genetic variation in the serotonin pathway, a neurotransmitter that is acted upon by several antidepressants. This particular genetic change occurs in a region of the SLC6A4 gene and alters the amount of serotonin available for

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neuronal signaling, especially in the limbic system. Several studies have found this genetic change is a risk factor for major depressive disorder, but only if the individual also experienced childhood maltreatment (such as physical or sexual abuse). Although this has not been universally found across all studies, it does hint at the existence of genetic influences that predispose for the disorder, but only in the presence of a susceptible environment.

Treatment Options

Many treatment methods for psychiatric disorders, such as antidepressant, anticonvulsant and antipsychotic medications, are aimed at influencing the activity or amount of neurotransmitters in the brain. Serotonin, dopamine and norepinephrine are three commonly targeted neurotransmitters.

Unfortunately, a large number of affected individuals do not respond to these types of medications. In certain cases, electroconvulsive therapy may be administered, but only rarely as a first line of treatment. Counseling, cognitive-behavioral therapy, behavior modification and life skills training may provide additional therapeutic effect.

Research at HudsonAlpha

Large-scale studies of psychiatric disorders at HudsonAlpha are examining genomic variation and the role of epigenetic modifications on the activity and silencing of genes that function in the brain.

- The Myers and Absher labs are studying bipolar, major depression and schizophrenia using next generation sequencing technologies. *Reference: Scott et al. (2009). Genome-wide association and meta-analysis of bipolar*

disorder in individuals of European ancestry. Proc. Natl. Acad. Sci. U.S.A. 106: 7501.

- In Dr. Shawn Levy's lab, targeted sequencing techniques are identifying mutations in genes associated with sporadic schizophrenia. European and Asian ancestry are Neanderthal in origin, yet Africans have no Neanderthal segments. These findings suggest that a low level of interbreeding occurred between Neanderthal and modern day humans, but only with populations that had migrated out of Africa. *Reference: Green, R. et al. A Draft Sequence of the Neanderthal Genome. Science 328, 710 (2010)*

– Dr. Neil Lamb

director of educational outreach
HudsonAlpha Institute for Biotechnology

Partnership for Biotechnology Research spring event

PBR members network and present posters at the Jackson Center



The Partnership for Biotechnology Research 2011 Spring Exhibition was held on March 29 at the Jackson Center. The event featured an afternoon vendor show and student presentation of original research. Above: Nicole Kennedy, Adrienne Johnson and Roya Najafi of Alabama A&M University present their research Biosensor for Rapid Detection of Toxins in Foods and Beverages during poster presentations.

Spring Symposium a success

Investigators, postdoctoral fellows, graduate students, university faculty and other scientists from across the Southeast attended the 2011 HudsonAlpha Symposium on April 6 at the Jackson Center.

The symposium focused on neuroscience and genetics with speakers from Vanderbilt, Emory, UAB, and Auburn universities as well as HudsonAlpha investigators. A representative from the company Illumina, founding sponsor of the symposium, also updated the group on the latest genomic technologies to enable research.

William Talbot, professor of developmental biology at Stanford University, delivered the keynote speech on genetic analysis of nervous system development and function in zebrafish. Dr. Talbot collaborates with HudsonAlpha on U.S. Army-funded projects involving the response of zebrafish to drugs given to Gulf War soldiers.

"We wanted to involve scientists both locally and regionally, because we feel research collaborations are crucial for our success as an institute," said Dr. Chris Gunter, HudsonAlpha director of research affairs. "It was great to hear about work going on in Alabama and neighboring states, and then to trade ideas and plan projects together."