



STUDIES OF BRAIN CELL SIGNALING PATHWAYS HELP IMPROVE TREATMENT OF BIPOLAR DISORDER

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Advances in understanding bipolar disorder (BPD) at the cellular level may help clinicians diagnose this illness earlier, treat it more effectively, and perhaps even slow or stop its progression.

The new findings, emerging over the past 5 to 10 years, shed light on the complex machinery that allows brain cells to adjust to changes occurring within the cell and elsewhere in the body. Learning, memory, mood, and emotion all rely on the brain's ability to "go with the flow." An adaptive process known as cellular plasticity makes such functions possible.

A breakdown in cellular plasticity--faulty regulation of nerve cell signaling pathways known as cellular plasticity cascades--contributes to the "here and now" symptoms of BPD. These often dramatic symptoms may include profound swings in mood, racing thoughts, and frenetic energy. When cell machinery fails to work as it should, the brain may be less resilient and more vulnerable to harm from injuries and infections. Brain cells may fail to thrive, shrink, and die.

The new research provides ample cause for optimism: it shows existing medications can halt and even reverse cell deterioration. They change

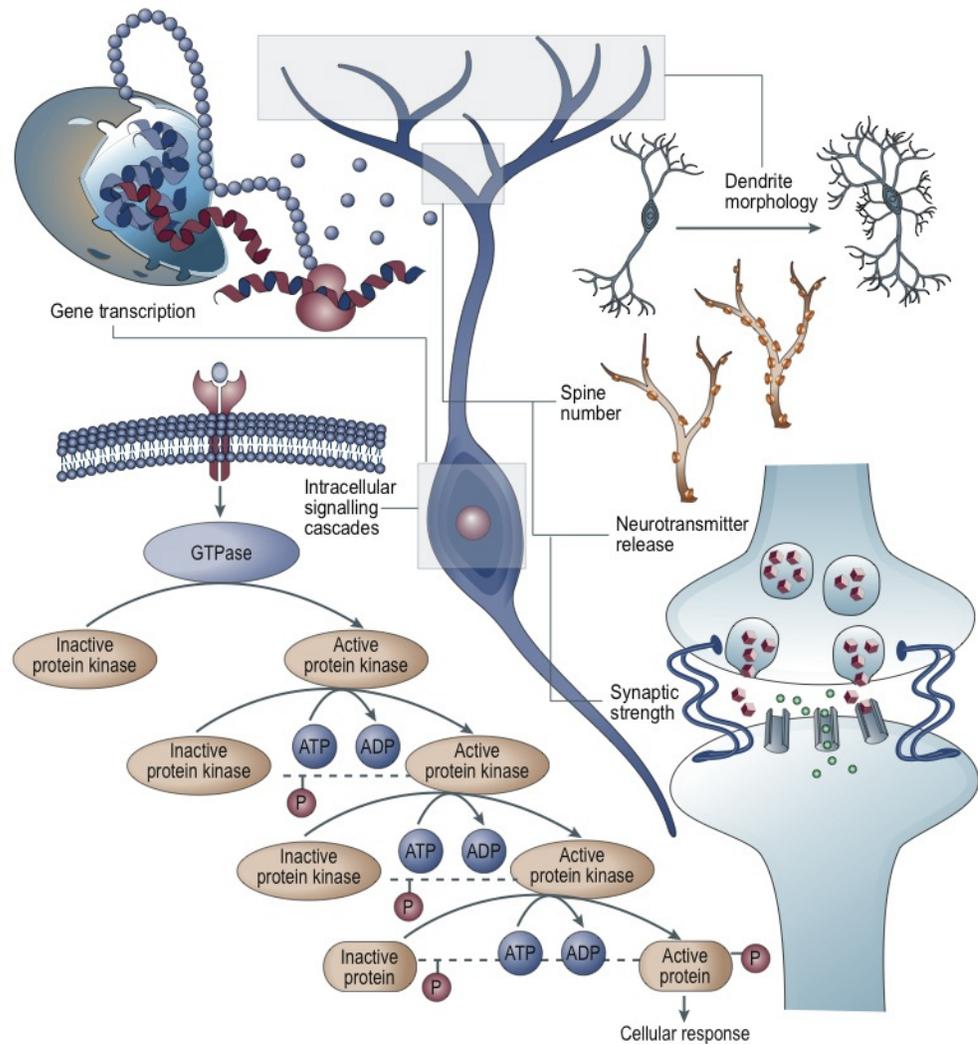


Figure 1
Cellular plasticity cascades

The remarkable adaptability of neuronal circuits is achieved through different biological means including alterations in gene transcription and intracellular signaling cascades. These changes can modify many aspects of how neurons work, and even change their physical characteristics. Reprinted with permission from *Neuropsychopharmacology Reviews*.

not only brain chemistry, but also brain anatomy. Medications now in development that target cellular plasticity may work even better and more rapidly than those available today.

Husseini K. Manji, MD, Director of the Mood and Anxiety Disorders Program at the National Institute of Mental Health (NIMH), and colleagues describe their recent findings on cellular plasticity in BPD in the January 2008 *Neuropsychopharmacology Reviews*, the journal's inaugural annual review issue. Their paper is one of 12 in-depth reports on various aspects of brain plasticity in psychiatric disorders.

The new focus on nerve cell signaling pathways grew out of more than 40 years' effort to identify and quantify brain chemicals such as serotonin and norepinephrine in people with BPD and other mood disorders, and to determine how inherited and environmental factors contribute to the risk of developing these disorders.

"These illnesses can best be conceptualized as genetically-influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters," Manji's group asserts.

BPD likely arises from the complex interaction of multiple genes and environmental factors, the NIMH researchers say. Some genes increase susceptibility to the disorder, while others offer protection against it. BPD is viewed as highly familial.

Unlike some brain diseases, such as Huntington's Disease, no single gene has been implicated in BPD. In a recent whole genome association study, another team of NIMH researchers found that several genes reproducibly influenced a person's risk of developing BPD. Each gene that they identified had only a modest effect, however, suggesting that multiple genes likely are involved in the disorder. All of the highly significant associations implicated cellular signaling cascades.

BPD disrupts the lives and functioning of millions of people worldwide. Although people with BPD and their families may view BPD as an episodic illness, the disorder has a persistent dampening impact on well-being and productivity, Manji notes. Most people with BPD experience relapses. Many struggle with lingering residual symptoms.

Neuroimaging studies show widespread involvement of cortical and subcortical areas of the brain in people with BPD, even in those experiencing their first episode. Follow-up studies of people newly diagnosed with BPD suggest that remodeling occurs in the areas of the brain that are involved in BPD. The brain's working tissue, or gray matter, shows a loss of volume, and abnormalities develop in the insulating white matter. Such changes are associated with deficits in managing emotions, thinking, and other brain functions. These findings underscore the need for earlier diagnosis and more effective treatment of BPD, Manji stresses, to prevent long term disability.

Figure 2
The central role of cellular plasticity cascades

The central role of cellular plasticity cascades explains many of the findings noted in BPD. These cascades regulate multiple neurotransmitter systems, as well as diverse physiological processes. Abnormalities in these cascades thus have the potential to explain not only the multiple neurotransmitter abnormalities seen in BPD, but also the frequent medical comorbidities associated with it. These cascades are targets for our most effective treatments. They control not only "here and now" neurotransmitter function, but also regional brain growth and shrinkage. Reprinted with permission from *Neuropsychopharmacology Reviews*.

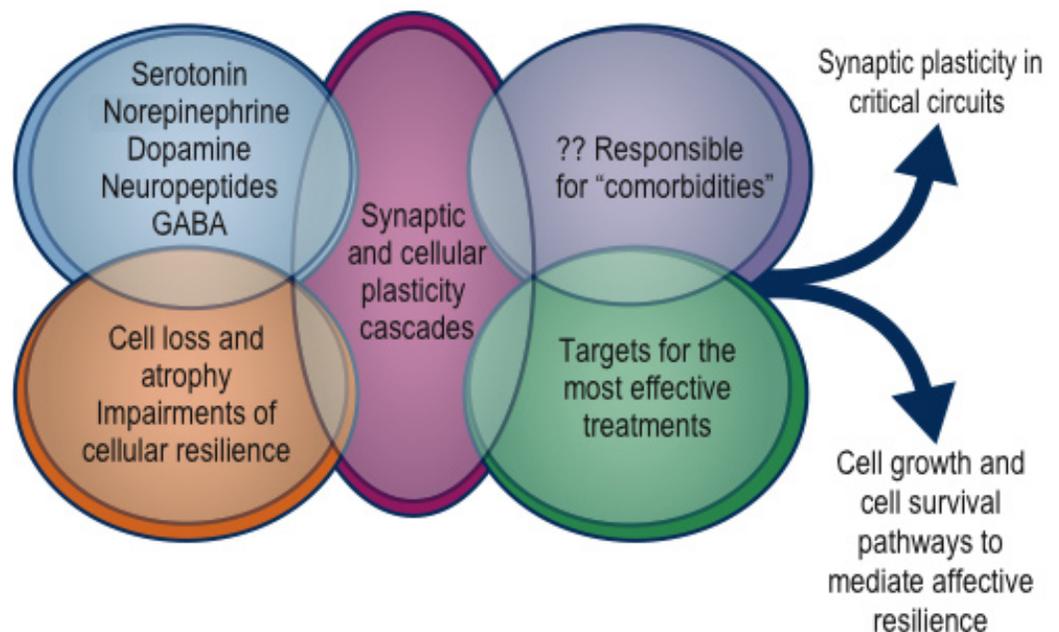
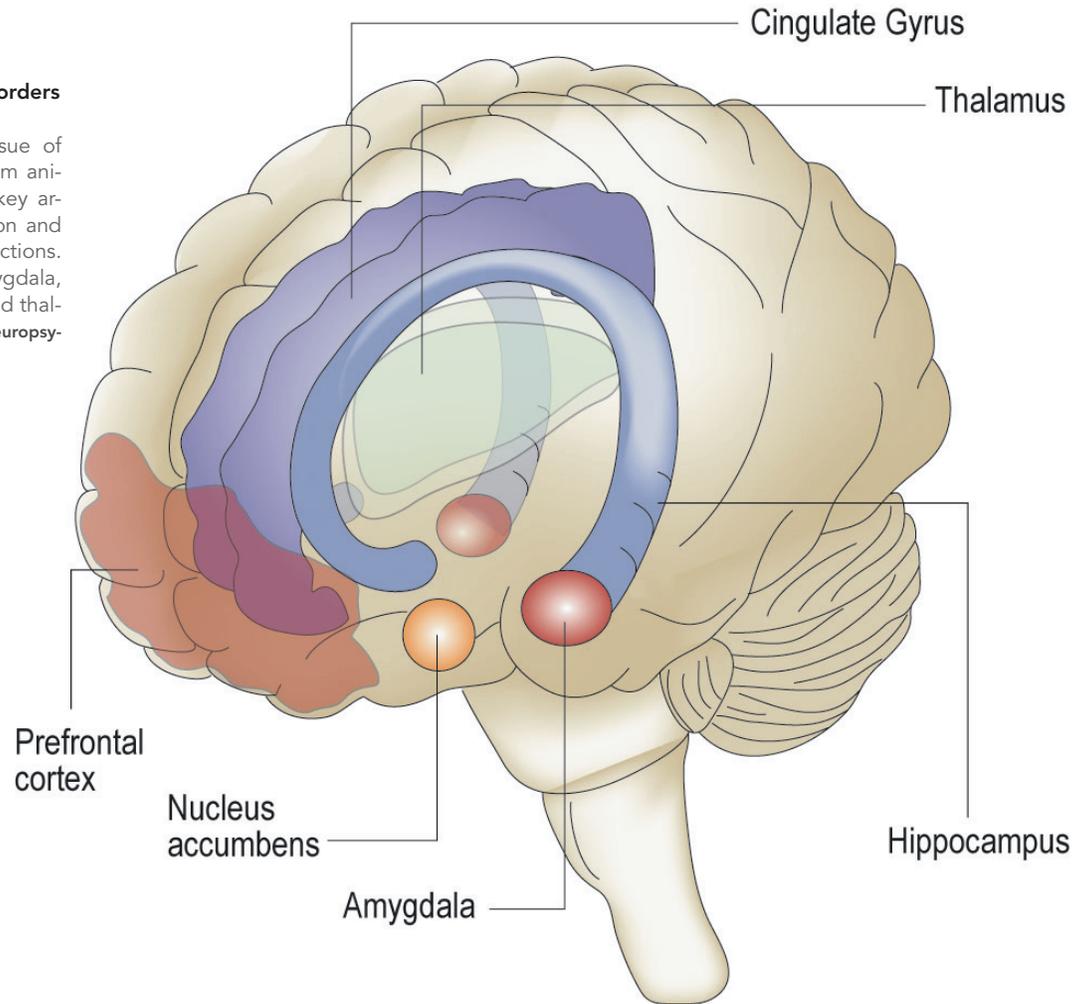


Figure 3

Brain areas implicated in mood disorders

Research on postmortem brain tissue of BPD patients as well as findings from animal studies have revealed several key areas implicated in emotion perception and control, thinking, and other brain functions. These include the hippocampus, amygdala, prefrontal cortex, cingulate gyrus, and thalamus. Reprinted with permission from *Neuropsychopharmacology Reviews*.



BPD has wide-ranging effects beyond the brain; it affects cellular machinery throughout the body. It disrupts not only mood and perception, but also heart activity, blood pressure, hormone release, and the daily sleep/wake cycle. People in the throes of mania often feel a markedly reduced need for sleep. They sometimes skip sleep entirely for a day or two.

People with BPD have higher rates of heart disease, diabetes mellitus, obesity, substance abuse, and thyroid disease than those who do not have it. Damage to cellular machinery may be a shared mechanism in such disorders, Manji suggests, even after factoring out smoking, poor nutrition, insufficient exercise, or other harmful health habits that, by themselves, are more common in people with chronic mental illnesses.

The currently most effective antidepressant medications work inside the cell. While these medications initially increase levels of the neurotransmitters serotonin and/or norepinephrine in the brain, it takes days to weeks before patients benefit from their antidepressant effects.

This time lag suggests the rise in neurotransmitter levels is only an early step in the therapeutic process, Manji notes. The medications likely spark signals that travel along intracellular pathways, triggering a rolling series of biochemical events. When all goes well, this trickle-down process eventually eases BPD symptoms.

Lithium, used for decades to treat BPD, and approved for use as a medication in the United States in 1970, remains the most effective therapy for the disorder. Taken consistently, it helps calm the highs of mania, ease the lows of depression, and stabilize moods. Lithium also reverses some deterioration seen in neuroimaging studies; it increases the volume of gray matter in the brain, for example.

In recent years, scientists have identified and studied several direct targets of lithium in the brain, part of their search for new medications that offer benefits similar to those of lithium, with fewer of this drug's adverse effects that include unwanted weight gain, nausea, and diarrhea.

Lithium blocks an enzyme in the brain called protein kinase C, thought to be over-active in the manic phase of BPD. Curiously, a medication used to treat breast cancer, tamoxifen, has the same effect. Tamoxifen is the only medication currently approved for human use other than lithium that has been indentified so far as having the ability to block protein kinase C.

Carlos Zarate, Jr., M.D., Chief of Experimental Therapeutics in the NIMH's Mood and Anxiety Disorders Program, working with Manji and others, recently assessed the effects of tamoxifen in BPD.

The researchers randomly assigned 16 people with BPD who were experiencing an acute manic episode to receive either tamoxifen or a placebo for 3 weeks. In 5 of the 8 who received tamoxifen, but only one of the 8 who received the placebo, symptoms of mania subsided significantly within 5 days. Those who got better maintained their improvement for the rest of the study.

Tamoxifen per se likely will not join the BPD treatment arsenal, Zarate says. While there is no evidence tamoxifen causes harm when used for only a few weeks, its long-term use may pose an increased risk of endometrial cancer. Other rapidly-acting selective protein kinase C inhibitors, however, may improve treatment of acute episodes of mania in settings such as hospital emergency departments.

The next generation of medications also may be able to ease cognitive difficulties or other debilitating aspects of BPD, along with the core mood symptoms. "Our goal," Zarate says, "is to achieve antidepressant effects in hours rather than in weeks." Medications of the future also may be able to prevent or reverse harm to the cardiovascular or endocrine systems affected by BPD.

Such advances, now on the horizon, would dramatically brighten the outlook for people with BPD and their families.

What Is Bipolar Disorder?

An estimated 5.7 million adults in the United States, or about 2.6 percent of the nation's population aged 18 years and over, experience symptoms associated with bipolar disorder (BPD) in a given year.

The hallmark symptom is an episode of mania--a distinct period of abnormally and persistently elevated, expansive, or irritable mood that lasts at least one week, or a shorter time if severe enough to require hospitalization, according to the current *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (DSM-IV-TR, 2000).

The constellation of symptoms associated with mania may include inflated self-esteem or grandiosity, a decreased need for sleep, excessive talkativeness, and distractibility. Some people experience episodes of similar but less extreme mood changes known as hypomania.

Between episodes of mania or hypomania, and occasionally simultaneously, moods range from normal to profoundly depressed. The average person with BPD spends far more time struggling with depression than caught up in an episode of mania.

Clinicians distinguish two forms of BPD, known simply as BPD I and BPD II. People with BPD I experience the extremes of mania, and those with BPD II, the less severe—and harder to diagnose—mood disturbances of hypomania. People with BPD II sometimes mistakenly are thought to have a recurrent Major Depressive Disorder (MDD). If that occurs, they also may receive incorrect treatment--traditional antidepressants that do not relieve their symptoms and may even prompt rapid cycling between mania or hypomania and depression--rather than the mood stabilizers usually given alone or in combination with antidepressants for BPD.

BPD occurs with equal frequency in men and women. This prevalence contrasts with that of MDD, which affects women about twice as often as it does men. Some women undergo their first episode of BPD soon after childbirth, reporting severe depression, and often thoughts of suicide and of harming their child. The median age of onset for BPD is 25 years. Onset of the disorder prior to age 13 occurs mainly in males.

People experiencing mania sometimes go on spending sprees, gamble, make rash business decisions, or engage in other imprudent behaviors they would not ordinarily contemplate. Though long romanticized because of its well-publicized association with artists, musicians, writers, and other creative people, "overall, BPD is a major cause of disability" Manji says.

"People with BPD often lose their jobs and marriages. Perhaps only 40% of individuals who experience mania function as well two years after the episode as they did before it," he adds. "After several episodes, people often function quite poorly."

Clinicians commonly use a variety of types of talk therapy, as well as family education and support to help prevent relapses, and improve daily functioning and overall quality of life.

Many newly diagnosed adults report having experienced depression and other BPD symptoms earlier in life, and sometimes even in childhood. Growing attention to early diagnosis has focused attention on children with symptoms suggestive of BPD.

NIMH researchers reported in the September 2007 *Archives of General Psychiatry* that the rate of diagnosis of children with BPD has increased 40-fold in the United States in the past decade. But the jury is still out, Manji says, on whether the disorder actually has become more common, was under-diagnosed in the past, or is over-diagnosed today.

"Children with a family history of BPD who display a reduced need for sleep and other symptoms of the disorder need careful evaluation and follow-up," he notes. "Some may benefit from lifestyle interventions, such as education in sleep management strategies. But medications should be reserved only for those with strong evidence of BPD."

For more information:

Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. *Neuropsychopharmacology Reviews*. Advance online publication, October 3, 2007; doi:10.1038/sj.npp.1301575

American College of Neuropsychopharmacology:
<http://www.acnp.org/>

National Institute of Mental Health:
<http://www.nimh.nih.gov/>

NIMH Perspective on Diagnosing and Treating Bipolar Disorder in Children: <http://www.nimh.nih.gov/about/director/updates/2007/nimh-perspective-on-diagnosing-and-treating-bipolar-disorder-in-children.shtml>

NIMH links to bipolar disorder resources: <http://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml>