WALSH RESEARCH INSTITUTE

A Neuroscience Theory of Bipolar Disorder

P7-039

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ABSTRACT

Bipolar Disorder, also known as manic depression, is a unique mental disorder distinguished by alternating periods of excitability (mania) and depression. More than six million Americans are challenged by this disorder which continues to be a leading cause of suicide, unemployment, and loss of human potential. After decades of intensive research, the fundamental causes and mechanisms of this mental disorder have remained poorly understood. In 2013 the authors initiated an investigation of bipolar disorder in an attempt to capitalize on remarkable advances in fundamental brain science achieved in recent years. We concentrated on neuroscience properties and mechanisms of individual brain neurons, glial cells and ion channels. After four years of study we discovered a single mechanism that can explain the chronic cycling between mania and depression that has puzzled researchers for decades. In our model, the initiating event is the loss of the brain's ability to produce robust resting potentials (voltages) due to excessive build-up of potassium ions in extracellular spaces. Hundreds of genes collaborate in the clearance of potassium ions into glial cells and presynaptic neurons which may explain why dominant bipolar-predisposing genes have never been found for this highly-heritable disorder. In our model, the weakened resting potentials initiate the following chain of events: (a) accelerating neuronal hyperactivity (mania) produces a steadily-increasing outward flow of potassium ions that continually lower resting potentials; (b) eventually certain local brain areas become unable to form functional action potentials resulting in widespread neuronal hypoactivity and clinical depression; (c) as time passes, the disabled brain sites recover the ability to form functional action potentials due to reduced potassium neuronal outflow and improved potassium clearance; (d) the brain returns to a manic hyperactive condition because of a continuing inability to develop robust resting voltages; (e) in the absence of effective treatment, the individual can be trapped in a permanent cycle of alternating mania and depression. This presentation will include increasing evidence that bipolar disorder is a channelopathy including large genome studies (GWAS) implicating potassium and calcium ion-channel genes. Potential triggers of bipolar onset including epigenetic insults, impaired neuronal pruning, and emotional trauma will be discussed.

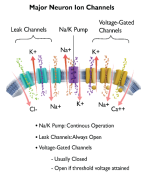
1. Introduction

After decades of research, the underlying mechanisms of BD have remained a mystery. The prevailing unknowns include:

- Fundamental cause of bipolar onset.
- Why does BD persist after onset?
- Why does mania usually worsen after onset?
- What causes the switch to depression?
- What causes the switch back to mania?
- What causes chronic mania/depression cycling?
- Why are there no dominant BD genes?

We have identified a single mechanism that can explain these unknowns. According to our model, the essence of BD involves lost ability to form complete resting potentials (voltages). Hundreds of genes collaborate to enable proper rest potentials after neuron firing. However, severe emotional or physical trauma can permanently impair regulation of numerous genes by an epigenetic mechanism and cause BD. Mass transport changes during mania onset initiate the unique switching between mania and depression in BD that often persists a lifetime.

2. Ion Channels



Resting potentials (voltages) are formed by ion concentration gradients across a neuron's bilayer membrane. Na/K pumps powered by mitochondrial ATP maintain high K^+ and low Na^+ levels within neurons. Various ion channels imbedded in the membrane enable ion flows in and out of the neuron.

Typical Ion Concentrations at Rest (millimoles per liter)

Inside Axon	Outside Axon
K^+ = 400	K^+ = 20
Na^+ = 60	Na^+ = 436
Cl^- = 30	Cl^- = 590

3. Potassium Ions Dominate Resting Potential

Resting potential is dominated by the K^+ ion gradient due to the relatively large population of K^+ leak channels and high outward flow rate (permeability). The number of Na^+, Cl^-, and other leak channels is relatively low and their influence on resting potential is nearly negligible.

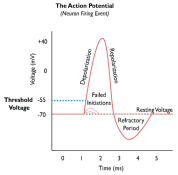
GOLDMAN EQUATION

$$V_m = \frac{RT}{F} \ln\left(\frac{p_K[K^+]_o + p_{Na}[Na^+]_o + p_{Cl}[Cl^-]_i}{p_K[K^+]_i + p_{Na}[Na^+]_i + p_{Cl}[Cl^-]_o}\right)$$

Vm = Membrane resting potential. **R** = Universal gas constant. **T** = Temperature, Kelvin. ***F*** = Faraday's constant (96485 coulombs/mol). **Px** = Permeability of ion x.

4. The Action Potential (Neuron Firing Event)

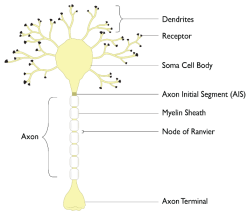
At rest, membrane potentials are about -70 mV and the threshold for firing about -55 mV. Neurotransmitters docking at neuron receptors cause inward ion flows that may either increase distance from threshold (inhibitory) or approach the threshold for firing. The net voltage is continuously summed at the axon initial segment (AIS) that acts as the neuron's control center. If threshold is reached, voltage-gated Na channels open to initiate neuron firing and ejection of NTs into a synapse.

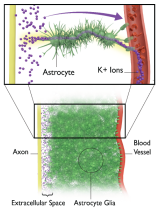


Voltage-gated Na^+ channels at the AIS and nodes of Ranvier suddenly open allowing rapid influx of Na^+ ions for about one millisecond (depolarization). The pulse reaches the axon terminal allowing entry of Ca^{++} ions that cause NTs to be sprayed into the synapse. Repolarization involves closing of Na^+ channels and opening of voltage-gated and calcium-activated K^+ channels.

5. Mass Transport

Each neuron firing causes influx of Na^+ and Ca^{++} ions and a net outflow of K^+ ions. The Na/K pump and other mechanisms can quickly restore interior ion levels. However, removal of K^+ ions from the extracellular space is more complex and requires assistance of astrocyte glial cells. Incomplete K^+ clearance can reduce resting potential and cause the neuronal hyperactivity associated with mania.





6. Potassium Clearance by Glial Cells

Astrocyte glial cells pack around neurons and participate in removal of excess K^+ ions. Glial ion channels efficiently take up K^+ ions and remove them from the scene by spatial buffering and other mechanisms. Brain astrocytes are connected by gap junctions forming a network that enables tiny "rivers" of K^+ ions to flow to blood capillaries for disposal. Glial cells also deliver nutrients to neurons and assist in memory formation, plasticity, and neurotransmission.

7. K^+ Buildup Mechanisms

K^+ ion buildup in the extracellular space can result from either (a) excessive K^+ flow from neurons or (b) impaired K^+ clearance from the extracellular space. Hundreds of genes participate in K^+ regulation and there are a great number of possible causes of reduced resting potentials. Examples include:

- Excessive K^+ outflow from leak channels or voltage-gated channels.
- Prolonged Ca^{++} inflow and activation of K^+ channels.
- Reduced K^+ ion transport into glial cells.
- Impaired axon initial segment (AIS) "summing" of voltage inputs from receptors.
- Altered Na/K pump kinetics.
- Etc.

8. Bipolar Triggers and Epigenetics

Onset typically occurs in late adolescence or early adulthood. Triggers include emotional trauma, physical injury, stress, pregnancy, and oxidative overload. Each of these factors can cause life-long changes in multiple gene expressions. BD fits the major criteria for an epigenetic disorder:

- Cases of sudden onset after relative normalcy.
- Persistence of condition after onset.
- Complexity of disorder since many genes may be affected.
- Heritable illness that violates Mendelian laws of genetics.
- Oxidative overload.

We believe that most cases of BD are epigenetic in nature, but conclusive proof is not yet available. Future research will eventually resolve this issue.

BIPOLAR DISORDER THEORY

A. MANIA ONSET: **Emotional trauma, physical injury, or environmental toxins trigger epigenetic changes in expression of numerous genes causing reduced resting potentials, neuronal hyperactivity, and mania or hypomania.**

B. MANIA WORSENING: **Overactive neurons eject K^+ ions at increased rates into the exterior fluid and resting potentials gradually move closer to threshold causing increased neuronal hyperactivity and worsening mania/hypomania.**

C. DEPRESSION ONSET: **Local brain areas experience severe K^+ buildup and become unable to form functional action potentials, resulting in widespread neuronal hypoactivity and a switch to clinical depression.**

D. RETURN OF MANIA: **Disabled brain sites gradually recover due to reduced K^+ outflow from hypoactive neurons while K^+ clearance mechanisms continue to operate. A return to normality does not occur since the neurons remain unable to form complete resting potentials.**

E. PERSISTENT SWITCHING BETWEEN MANIA AND DEPRESSION: **Without effective treatment, a person can be trapped in chronic cycles of alternating mania/hypomania and depression.**

DISCUSSION

Loss of the brain's ability to form a complete resting potential can explain most of the century-long mysteries shrouding this unique disorder. Recent advances by neuroscientists and epigenetics researchers were central to this observation and the development of our BD Theory. We acknowledge their remarkable achievements.

This study suggests that bipolar mania is the cause of bipolar depression and that new research should focus on prevention and treatment of mania.

Overmethylated persons appear more prone to Bipolar I since their in-utero epigenetic bookmarks cause under-expression of norepinephrine transport proteins and an inborn tendency for anxiety. In contrast, undermethylated persons appear more prone to Bipolar II since they tend to over-express SERT transporters that promote serotonin reuptake and an innate tendency for depression.

BD is one of the most heritable mental disorders, but major bipolar genes have never been found. Since hundreds of genes collaborate in formation of resting potentials, many combinations of altered gene expressions may lead to BD. This may explain absence of high-incidence BD genes and also the great variation in BD symptoms for different individuals. Recent GWAS large-population studies have implicated ANK3, CACNAIC, KCNQ2, KCNQ3, and other ion channel genes in BD and support our new theory. There is increasing evidence that BD is a channelopathy (ion-channel disorder).

For decades psychiatrists have debated whether trauma or altered neurotransmission are central to the development of BD. Epigenetic research indicates that emotional trauma can change neurotransmission which could unify the opposing schools of thought.

SUMMARY

We have identified a single mechanism that explains chronic cycling between mania and depression in BD: The lost ability to form complete resting potentials. A Bipolar Disorder Theory is proposed to describe the mass-transport mechanisms that can cause BD switching. We believe this bipolar theory reveals the true nature of BD and can lead to improved therapies and prevention approaches.