

# Earlier Treatment of Bipolar Disorder: Preventing Illness Progression

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The message of this talk is positive and optimistic.

While Bipolar Disorder is a recurrent potentially deteriorating illness, appropriate treatment intervention at any stage of illness evolution can be effective.

However,

The earlier, the easier the task;

The more delayed, the more difficult.

# What progresses?

(if bipolar disorder is inadequately treated)

1. Episodes Recur Faster & More Autonomously
2. Stressors Accumulate
3. Substance Abuse Occurs
4. Cognitive Dysfunction
5. Disability
6. Medical Comorbidity
7. Loss of Years of Life Expectancy  
(from excess medical mortality)

# THE NEW VIEW OF LONG-TERM TREATMENT IS:

## MOOD STABILIZERS;

Lithium,

Valproate (Depakote),

Carbamazepine (Tegretol, Equetro), and

Lamotrigine (Lamictal), and some

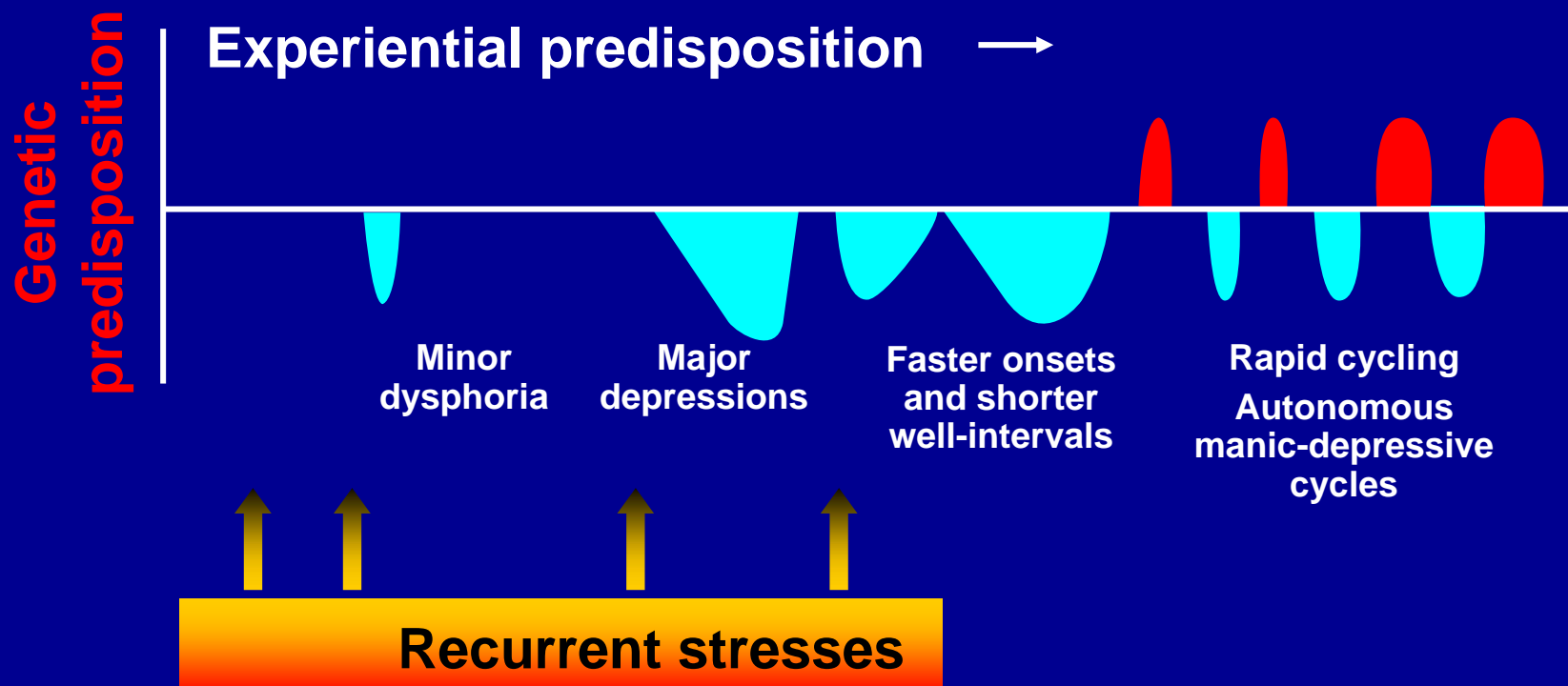
## ATYPICAL ANTIPSYCHOTICS

PREVENT EPISODES,

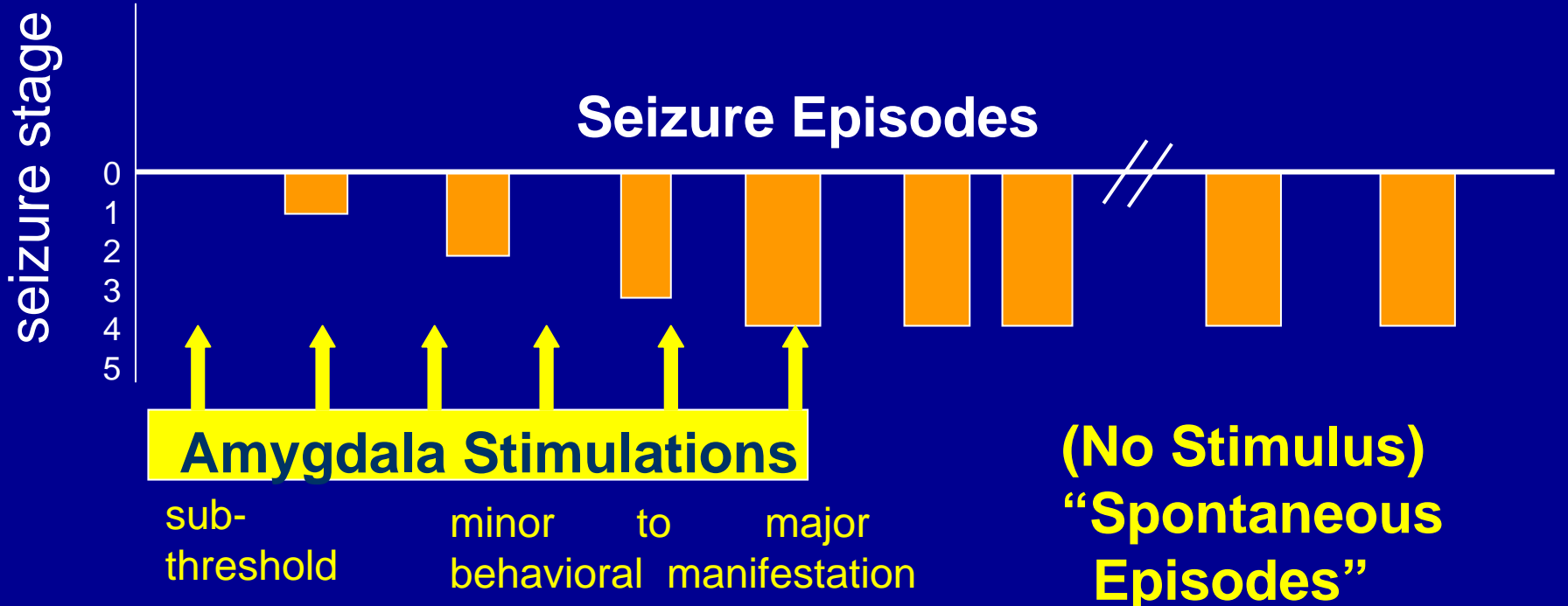
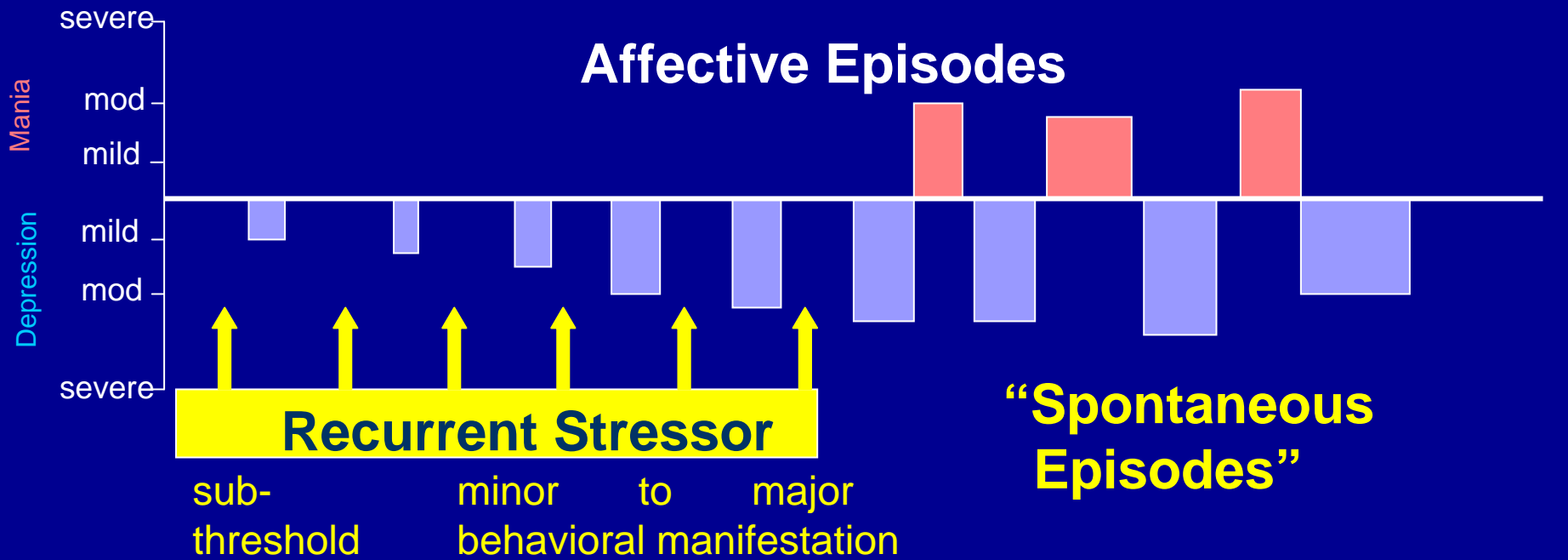
INCREASE NEUROTROPHIC FACTORS, AND

MAY HELP PROTECT THE BRAIN

# Schematic of Stress and Episode Sensitization in Bipolar Illness



# Parallelisms in Kindling of Seizures and Affective Episodes



# Cocaine-Induced Behavioral Sensitization

Progressive **Increases in Hyperactivity and Repetitive (Stereotypic) Behavior** in Response to Repetition of the Same Dose of Drug

Increases in Behavioral Responsivity are **Long Lasting** and

Are **Conditioned** (Context Dependent)

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Cocaine **Mimics Mania** and its progression from **Euphoric** to **Dysphoric Mania** and Paranoid Psychosis

# Accumulating Stress and Episode-Related Vulnerability in Recurrent Affective Illness

Putative Effects on Gene Expression:

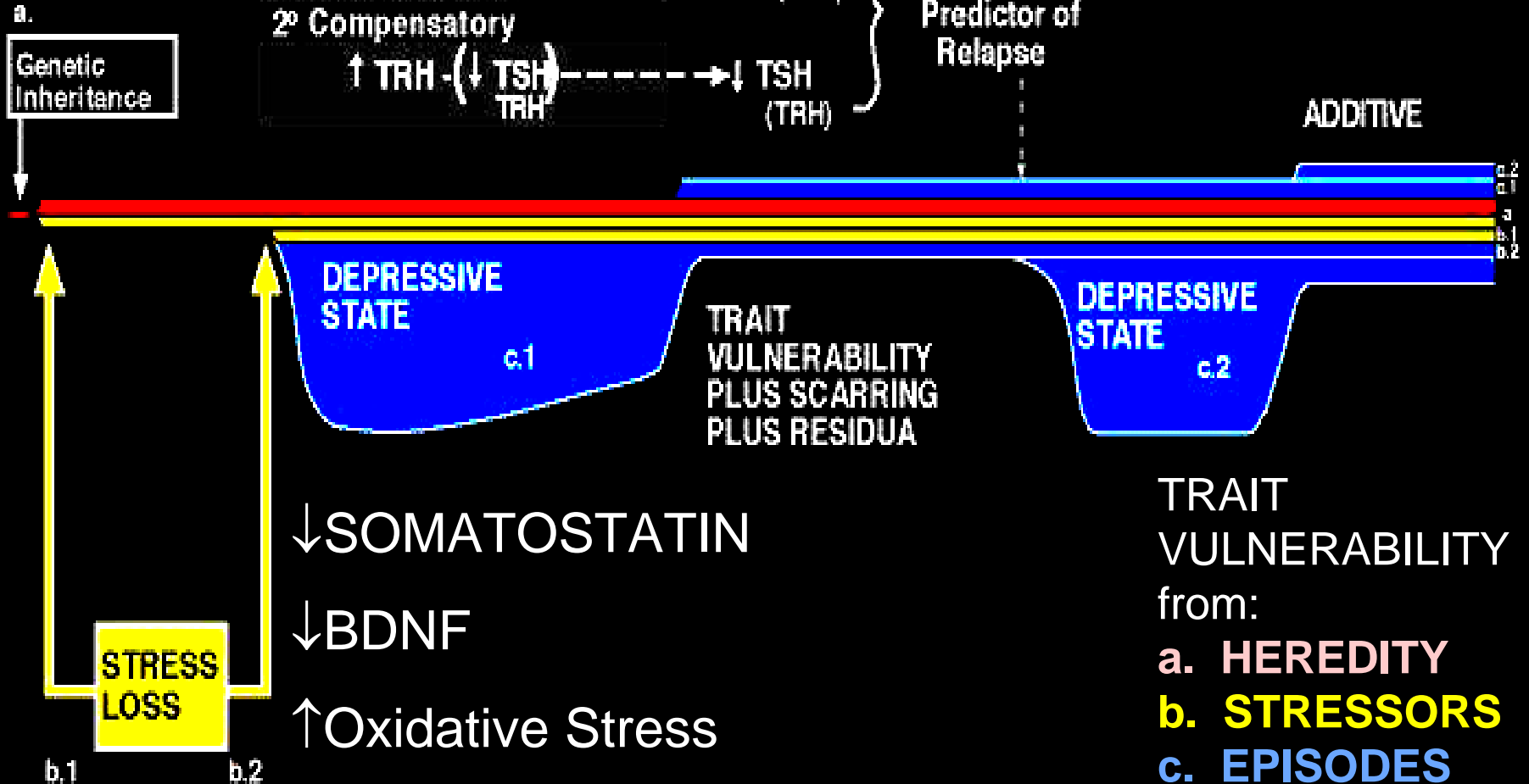
1° Pathological

↑ CRH - (↓ ACTH)  
CRH → ↑ cortisol → ↑ cortisol (DEX)

2° Compensatory

↑ TRH - (↓ TSH)  
TRH → ↓ TSH (TRH)

Failure to Normalize a Predictor of Relapse

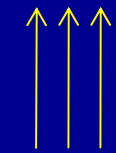


# Brain Derived Neurotrophic Factor (BDNF):

1. Is Secreted by **Neurons**
2. Is Needed for **Synapse** Formation and Synaptic Plasticity
3. Helps in Neuronal **Survival** and Production of New Neurons (**Neurogenesis**)
4. Is Necessary for Long-Term **Memory**

# BDNF is Involved in the ONSET, COURSE, and TREATMENT of Bipolar Disorder

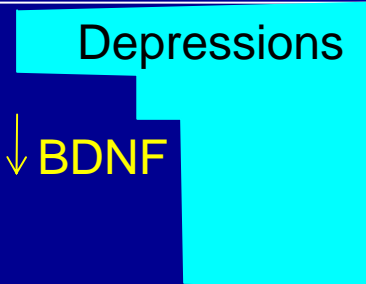
Val 66 val  
Pro BDNF



Early Stressors  
↓ BDNF into Adulthood



Adult Stressors  
↓ BDNF



Depressions

↓ BDNF

Manias

↓ BDNF

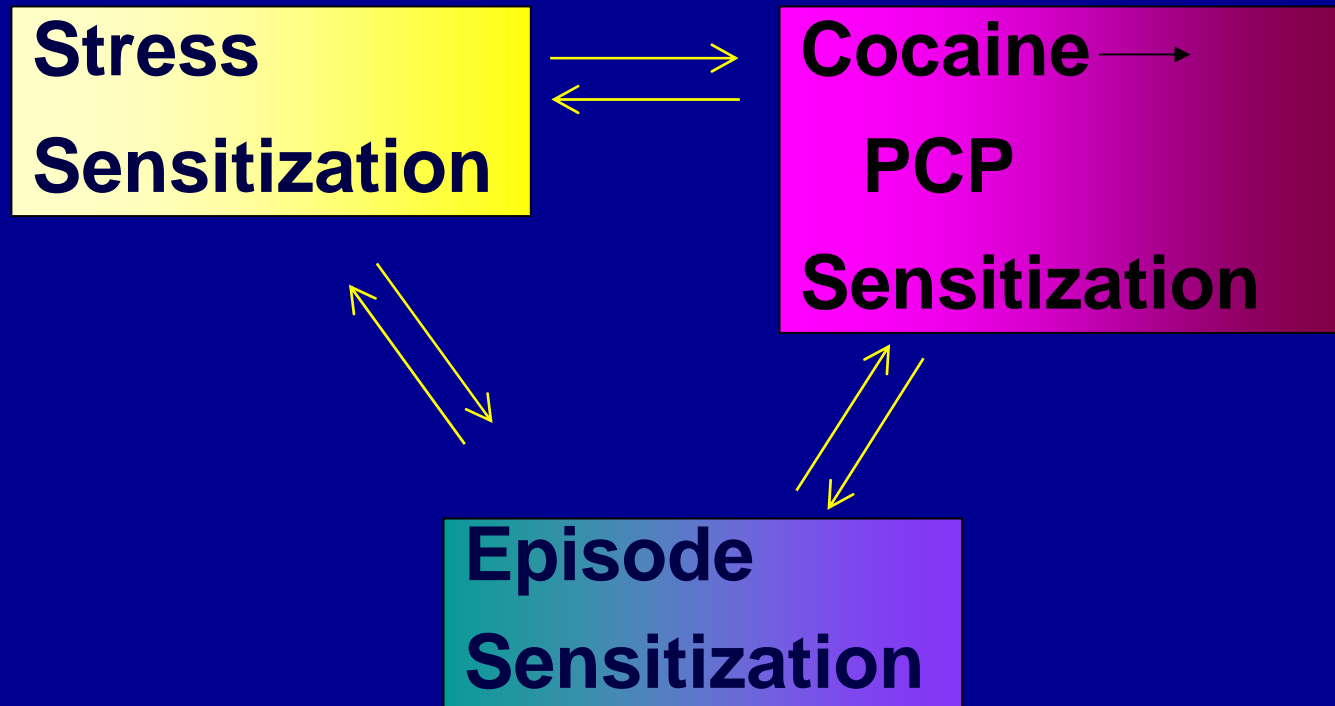
(Depressive and Manic Episodes Decrease BDNF (in Proportion to their severity))

TREATMENTS INCREASE BDNF

(Mood Stabilizers: Li, VPA, CBZ, LTG) and

ANTIDEPRESSANTS and Quetiapine INCREASE BDNF and Prevent Stress-Induced Decreases in BDNF

# CROSS SENSITIZATION AMONG STRESSORS, DRUGS OF ABUSE AND EPISODES



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Repetition of Each Increases Responsivity to Itself  
and the Two Others

# Chronic Cocaine, Defeat Stress, and Clinical Depression Share Common BDNF Mechanisms

	Chronic Cocaine	Defeat Stress	Clinical Depression (Suicide)
Hippocampus: (Memory)	↓↑BDNF	↓BDNF	↓BDNF
VTA/ Nucleus Accumbens (Reward)	↑ BDNF	↑BDNF	↑BDNF

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Could These Mediate Cross Sensitization Among Stressors, Cocaine, Depression?

The N. Accumbens (Ventral Striatum) Likely Mediates Emotion-Based Habit Memory which is Automatic and Unconscious

Defeat Stress and Cocaine Behaviors May be Overlearned Pathological Habits via Excess Cued Glutamate Reactivity

(Kalivas et al.)

If there are **Common Mechanisms**,  
**A Single Treatment** Could Work  
on **Stress**, **Episode**, and **Substance**  
**Sensitization**

# N-Acetylcysteine 500 mg caps, 2 B.I.D.

- Decreases Cocaine, Heroin, and Gambling **Addiction** (Kalivas et al.)
- Decreases **Trichotillomania** (2 months to work) (Grant et al., 2009)
- Improves **Mood** in Bipolar Disorder (3 months to work, M. Berk, 2008)
- **Irritability and Stereotypy** in Autism (L.K. Fung, 2010)

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Via a **reset of the habit memory system?**

# Episodes, Stress, Cocaine

Since each shows increased behavioral responsiveness upon repetition,

There likely is a long-term **memory trace or scar** at the level of:

A. **Psychology** (Memory)

B. **Neurobiology** (BDNF)

C. **Epigenetics** (DNA & Histone Marks & Synaptic mRNA)

(Si, Kandel, et al., 2010;

Gupta et al., 2010)

# EPIGENETICS

## Means Epi (Above) Genetics

- I. New data indicate that environmental events change DNA structure (not gene sequences).
- II. Stressors and Abused Substances put Methyl groups on DNA and Methyl and Acetyl groups on histones (around which DNA is wrapped).
- III. DNA is usually:
  - repressed when DNA is methylated
  - activated when histones are acetylated.
- IV. These epigenetic marks influence how easily genes are turned on or off

- **Environmental Adversity** in the Rat Pup Results in Lifelong **Decreases in BDNF in the Prefrontal Cortex** based on an epigenetic mechanism (i.e. methylation of the DNA promoter for BDNF)
- Treatment with a methylation inhibitor reverses the low brain BDNF

(Roth et. al 2009)

Based on defeat-stress studies in adult animals (Tsankova et al 2007) and preliminary studies in humans (McGowan et al 2009), it is likely that:

**Epigenetic Marks** From  
**Stressors,**  
Episodes, and  
Substances of Abuse

Accumulate at Each Stage of Illness Evolution  
and **Mediate Aspects of Illness Progression**

# Stages of Bipolar Illness Development and Progression

I Vulnerability

II Well Interval

III Prodrome

IV Syndrome Onset

V Recurrence-Progression

VI Treatment Resistance

VII Late Deterioration

## Bad News:

Epigenetic methyl marks from childhood stressors can last a lifetime (and some can even be passed to the next generation.)

(Nestler, 2009; Feinberg, 2009; Roth et al., 2009; Science, 29 Oct 2010)

## Good News:

Substances have been identified that transfer or inhibit:  
Methyl Groups on DNA, and  
Acetyl Groups on histones.

These will likely represent a new generation of psychotropic drugs.

(Some are already approved for cancer treatment; and valproate is a histone de-acetylase Inhibitor)

# Mood Episodes Are Associated With:

- I. Decreases in the Positive Adaptations, such as Peptides (TRH) and Neurotrophins (BDNF)
- II. Increases in the Pathological Processes, such as Peptides (CRH), Inflammatory Cytokines ( $TNF_a$ ) and Oxidative Stress

These Effects Could Account for:

- A. Nonspecific Alterations in Brain
- B. Specific increases in maladaptive learning in the habit memory system

Such episode-related  
decreases in neurotrophins  
and increases in toxic factors  
may account for the findings  
that even in euthymic (well)  
patients with bipolar disorder,  
the severity of cognitive  
dysfunction is related to the  
number of prior mood episodes

Yurgelun-Todd and Sneider, 2006)

# Many Current Drug Treatments Have a Dual Benefit in:

I. Preventing Episodes

II. Protecting Brain Neurons and Glia via:

A. Increases BDNF and Neurogenesis

B. Prevention of Stress-Induced Decreases  
in BDNF

Thus, early recognition and treatment can prevent episode accumulation and may lead to a more benign course of bipolar disorder.

# Childhood Onset Bipolar Disorder:

- I. Is common (22-28% of adults in the U.S. have their first episode prior to age 13)
- II. Has a difficult course prospectively;
  - A. Youngsters are ill 60% of the time
  - B. Most remit, but on average it
  - C. Takes a year to achieve, and
  - D. Relapses are common
- III. Adults with a childhood onset do more poorly than those with adult onset
- IV. The earlier the age of onset, the longer the delay to first treatment
- V. The duration of the treatment delay is independently related to more time and severity of depression in adults

Children with **bipolar disorder** are too often treated only for their **ADHD** with stimulants and antidepressants and not with the recommended mood stabilizers and atypical antipsychotics

# Comorbid **BIPOLAR DISORDER** in a child with **ADHD** is Suggested by:

1. Brief and Extended Periods of **ELATION** (out of context)
2. **DECREASED SLEEP** and Decreased Need for **SLEEP**
3. **SUICIDAL** Ideas and Actions
4. **EXTREME AGGRESSION**
5. **HOMICIDAL** Ideas and Actions
6. **PSYCHOSIS** (Hallucinations and Delusions)
7. **HYPERSEXUALITY** (in absence of sexual abuse)
8. Multiple **Distinct MOOD SWITCHES** per day
9. **JUMPING** Out of **MOVING CAR**

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These symptoms are usually not present in uncomplicated ADHD

**A clear diagnosis** (from a world expert, Barbara Geller, from Washington University at St. Louis) **is not enough.**

In her 8-year follow-up study of **children with bipolar disorder (average age 11) treated in the community, 37% never received any of the treatments recommended by consensus guidelines** (i.e. lithium, a mood stabilizing anticonvulsant, or an atypical antipsychotic)

Those who did receive lithium did the best.

Childhood onset bipolar disorder may be more prevalent and a greater problem in the US than in some European countries.

# Investigators in the Bipolar Collaborative Network (B

## United States

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### UCLA

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- Mark Frye

### UTSW

#### 2. Dallas

- Trisha Suppes

#### 3. Cincinnati

- Paul Keck
- Sue McElroy

### NIMH

#### 4. Bethesda

- Kirk Denicoff
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- Robert Post

## Europe

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### HC Rumke Group

#### 1. Utrecht, Netherlands

- Willem Nolen
- Ralph Kupka

#### 2. Freiburg, Germany

- Jörg Walden

#### 3. Munich, Germany

- Heinz Grunze

# More Vulnerability Factors and a More Adverse Illness Course in US than in the Netherlands and Germany:

## I. Vulnerability:

Genetic: More Parental Bipolar Disorder  
More Both Parents with a Mood Disorder

Environmental: More Stressors in Childhood

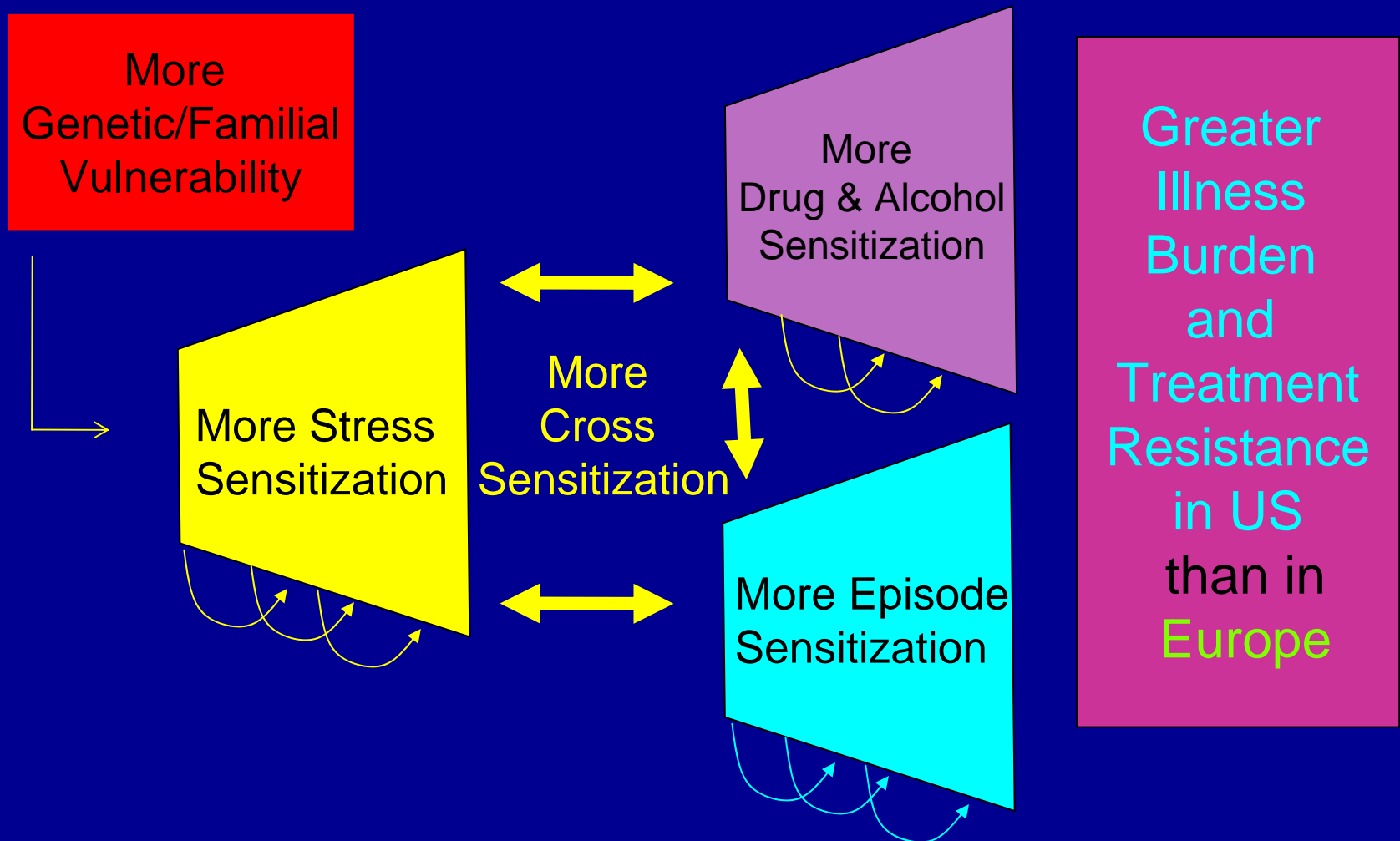
## II. Stressors at Illness Onset and Prior to the Latest Episode

## III. Earlier Age of Illness Onset

## IV. Course: More Episodes, Substance Use, Anxiety Disorder, and Rapid Cycling

## V. Outcome: More Nonresponders to Naturalistic Treatment

# Bipolar Disorder in US Compared to the Netherlands and Germany



Reframing:

Bipolar Disorder is a Potentially  
Progressive Medical Illness of  
Brain and Body  
Requiring Lifelong  
Monitoring and Treatment

# MEDICATIONS CAN HAVE POSITIVE EFFECTS

In Patients with Unipolar Depression:

**ADs Increase Hippocampal Volume  
and Prevent its Decline** (A. Sheline)

In Patients with Bipolar Disorder:

**Lithium: Increases Hippocampal  
Volume & Gray Matter in Cortex, &  
May Decrease Dementia in Old Age**

(G. Moore, N. Bearden, H. Manji, D. Chuang, L. Kessing)

These new views of the illness and treatment should facilitate earlier, more consistent intervention and **help slow or prevent:**

**stress, episode,** and **substance abuse** accumulation and sensitization and their **adverse effects** on behavior, cognition, and brain function.

NAMI is Playing a Critical Role  
in Education, Advocacy,  
Treatment Access, and  
Destigmatization.

This Will Hopefully Help Make  
the Recurrent Mood Disorders  
More Benign Illnesses in the  
Future