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Updates in Bipolar Disorder: Pathophysiology & Treatment Considerations

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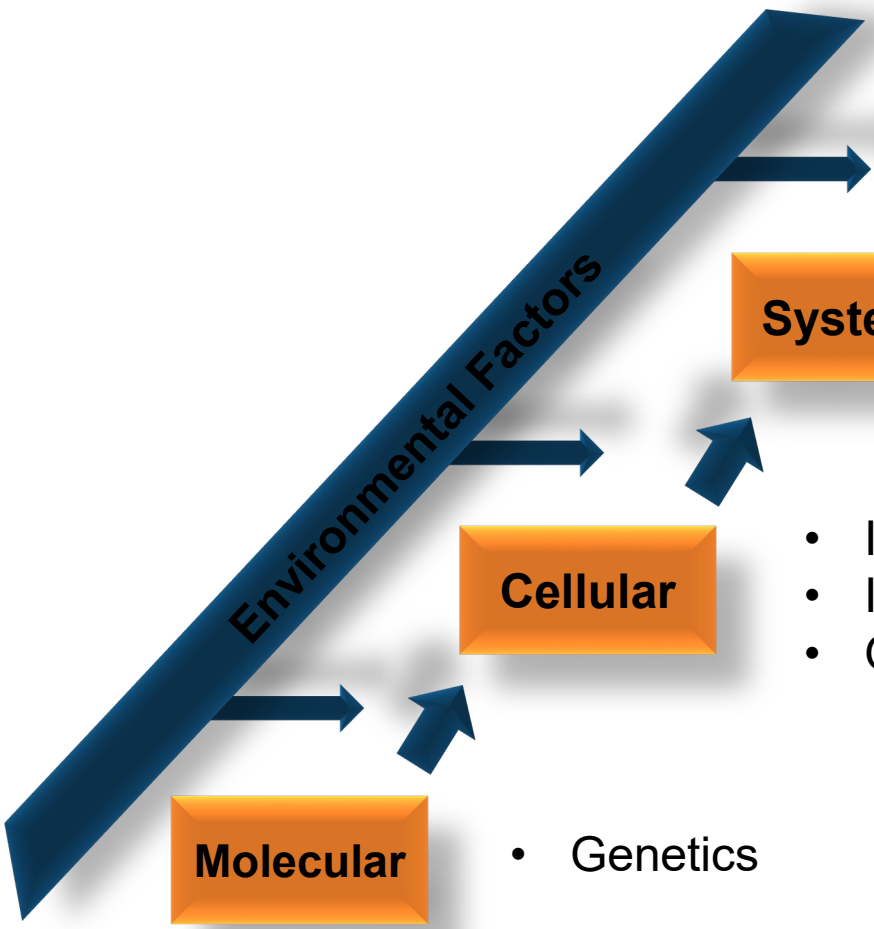
Part I.
Theories of Bipolar Disorder Pathophsiology

The Pathophysiology of Bipolar Disorder: Levels of Analysis[1]



- Cognitive Function
- Circadian Rhythm

- HPA Axis Hyperactivity
- Monoaminergic Pathways
- Regional Brain Anatomy
- Neurocircuitry

- Ion Dysregulation
- Immune System
- Glial-Neuron Interactions

- Genetics

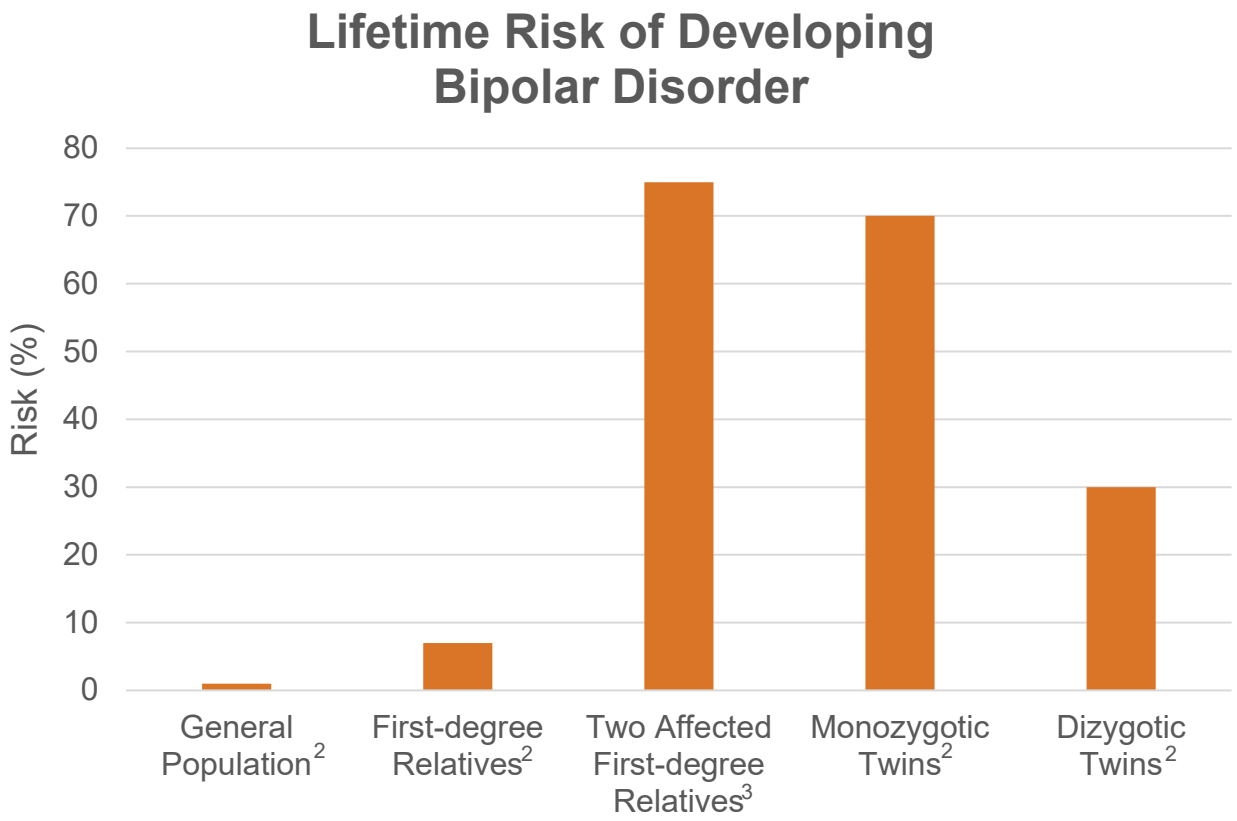
Image adapted from: Manji HK. 2000[1]

HPA, hypothalamic-pituitary-adrenal.

1. Manji HK, et al. *Biol Psychiatry*. 2000;48(6):518-30.

Lifetime Risk of Developing Bipolar Disorder

- Familial and identical twin studies have revealed a strong genetic basis for bipolar disorder (BD)[1]



1. Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.
2. Kelsoe JR. *J Affective Disord*. 2003;73:183-197.
3. Bechdolf A, et al. *J Affect Disord*. 2010;127(1-3):316-20.

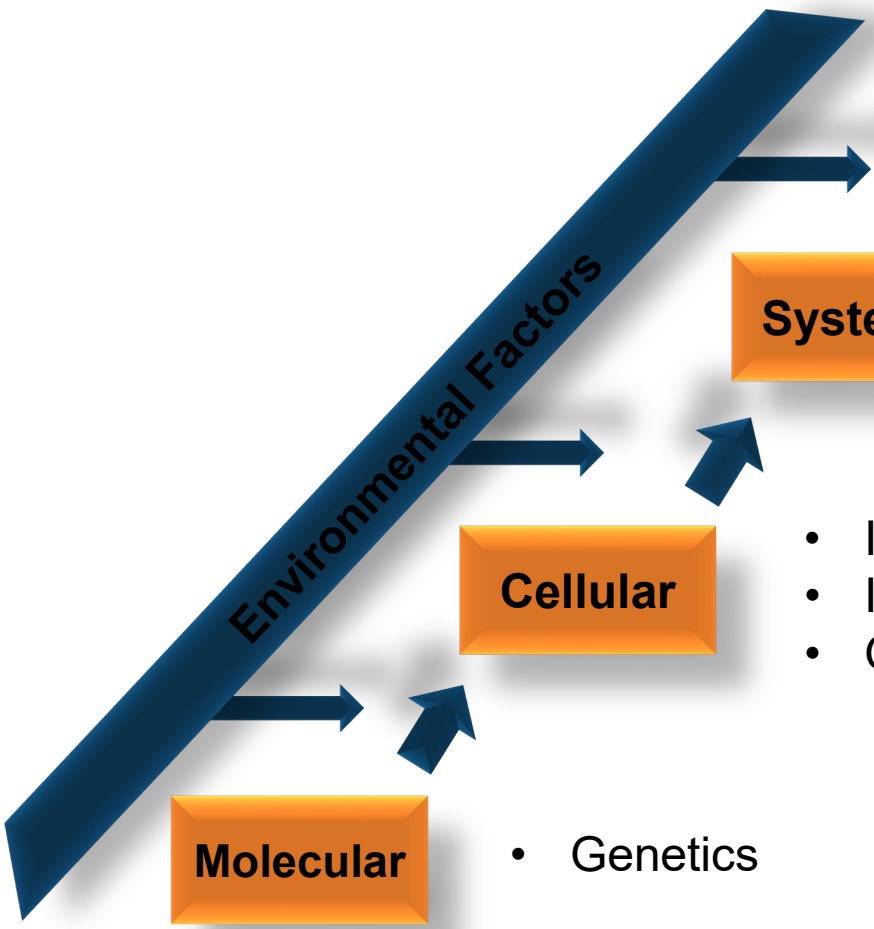
Genetics

- Identical-twin concordance rates for BD generally range from 40% to 70%, with the estimated heritability reaching as high as 90% in recent reports[1]
- Key genes
  - Genetic variations in COMT (enzyme involved in dopamine degradation) are strongly linked to BD[2]
  - Calcium channel signaling gene (*CACNA1C*) implicated across multiple psychiatric disorders[1]
  - Genetic implications for glutamate and GABA receptor subtypes and metabolic enzymes[3]

COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid.

1. Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.
2. Andreazza AC, et al. *Int J Neuropsychopharmacol*. 2014;17(7):1039-52.
3. Cherlyn SY, et al. *Neurosci Biobehav Rev*. 2010;34(6):958-77.

The Pathophysiology of Bipolar Disorder: Levels of Analysis[1]



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1. Manji HK, et al. *Biol Psychiatry*. 2000;48(6):518-30.

Ion Dysregulation

- Calcium ion
  - High intracellular calcium concentrations have been observed in BD (in both basal and receptor-regulated calcium conditions)[1]
  - Mood stabilizers are thought to attenuate and/or modulate calcium levels via multiple cellular signal transduction pathways[2,3]
- Sodium / potassium ions
  - Increased intracellular sodium concentrations have been observed in bipolar mania (partially attributed by altered sodium–potassium pump activity)[4]
  - Mood stabilizers via sodium-potassium pump interaction decreases intracellular sodium concentration[4,5]
  - Antipsychotics are thought to reduce / normalize sodium concentrations via D_2 receptor blockade[6]

D_2, dopamine 2 receptor.

1. Malhi GS, et al. *Can J Psychiatry*. 2004;49(12):813-9.
2. Sourial-Bassillious N, et al. *Neuroscience*. 2009;161(4):1126-34.
3. Wasserman MJ, et al. *Neuropsychopharmacology*. 2004;29(4):759-690.
4. Herman L, et al. *Neurosci Biobehav Rev*. 2007;31(6):874-81.
5. Marmol F, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(8):1761-71.
6. Roberts RJ, et al. *World J Biol Psychiatry*. 2010;11(2 Pt 2):181-7.

Immune System Hypothesis[1]

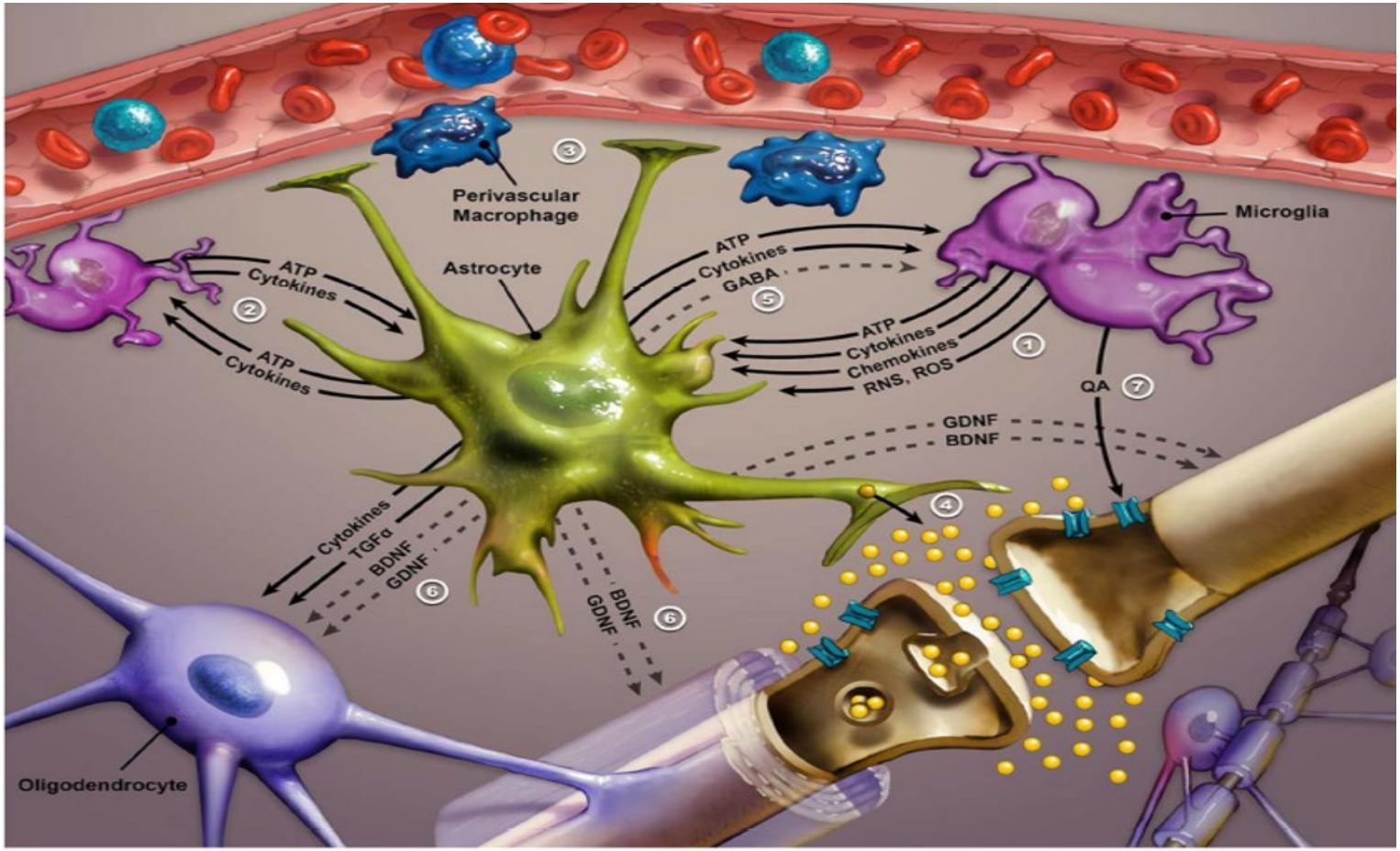


Image from: Maletic V, Raison C. 2014[1]

ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; QA, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGFα, transforming growth factor alpha.

1. Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.

Glial-Neuron Interactions[1]

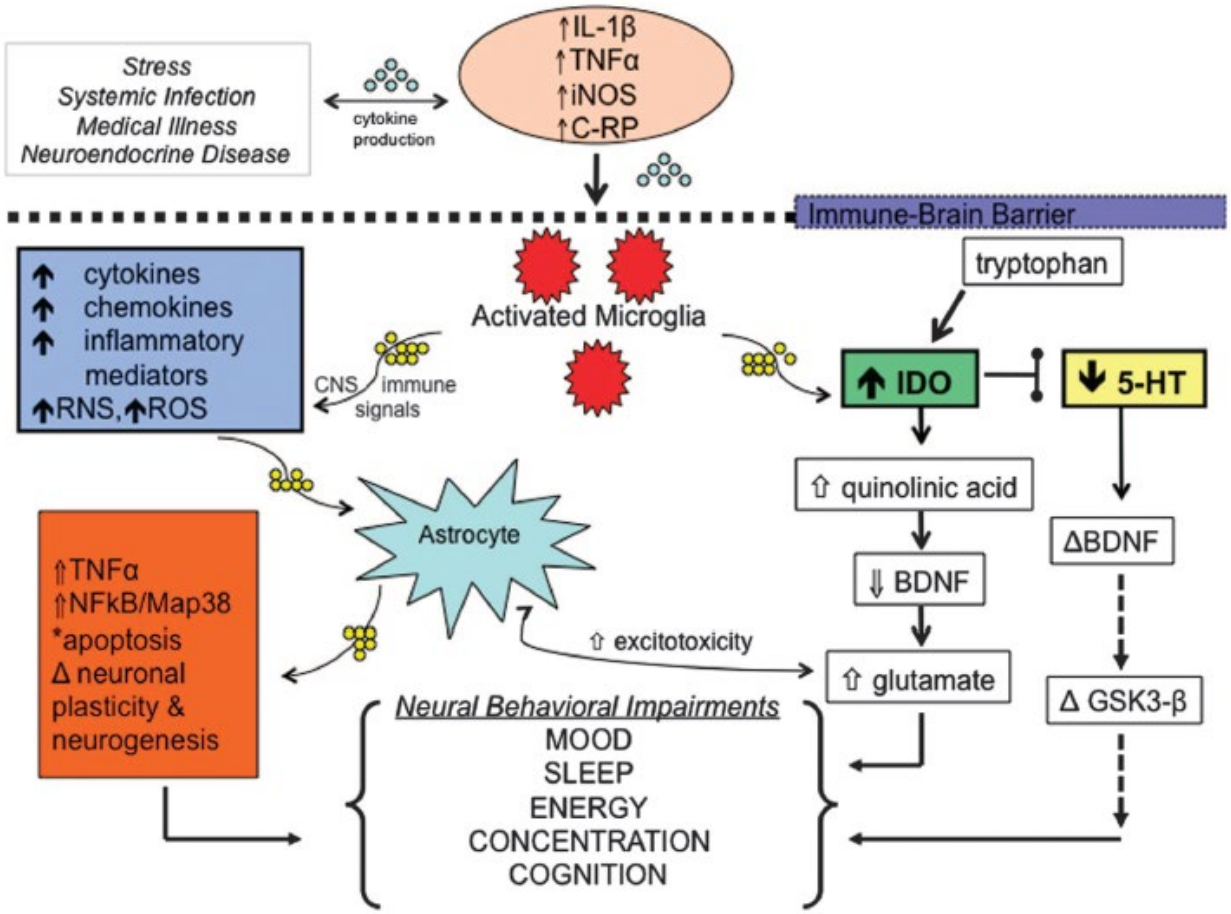
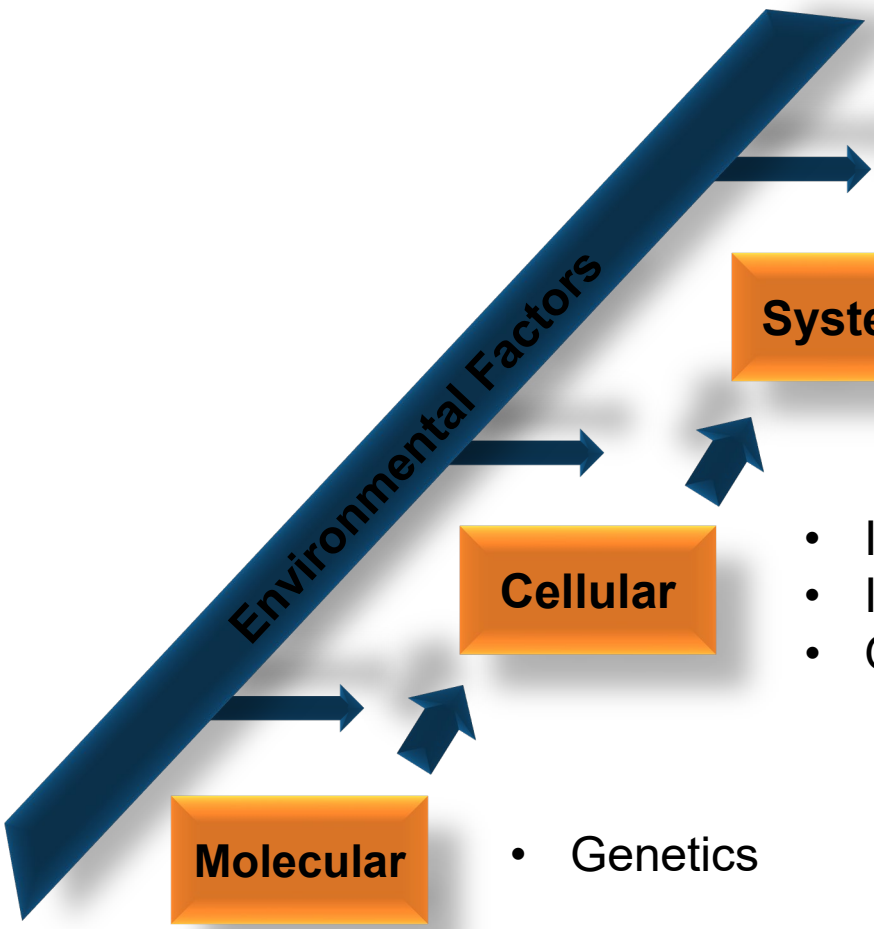


Image from: Watkins CC. 2014[1]

5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; C-RP, C-reactive protein; GSK3-β, glycogen synthase kinase 3 beta; IDO, indoindoleamine 2,3-dioxygenase; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; Map38, p38 mitogen-activated protein kinase; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha.

1. Watkins CC, et al. *Transl Psychiatry*. 2014;4:e350.

The Pathophysiology of Bipolar Disorder: Levels of Analysis[1]



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1. Manji HK, et al. *Biol Psychiatry*. 2000;48(6):518-30.

HPA Axis Hyperactivity Hypothesis

- **Cortisol / neuroendocrine dysfunction**
  - Early life adversity, leading to HPA axis activation, has been implicated in later mood disorders[1,2]
  - Evidence for HPA axis dysregulation in BD[2]
  - Modifying the HPA axis with stress reduction improves depressive symptoms[3,4]

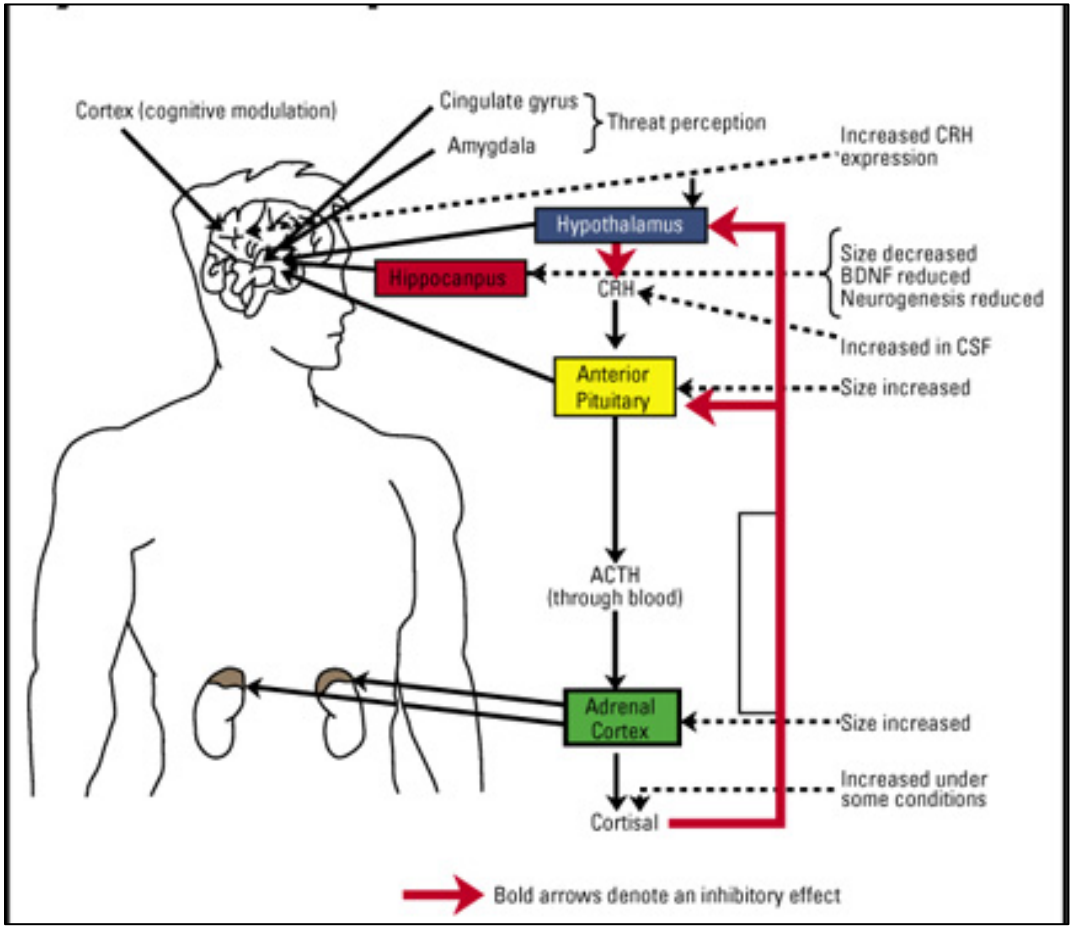
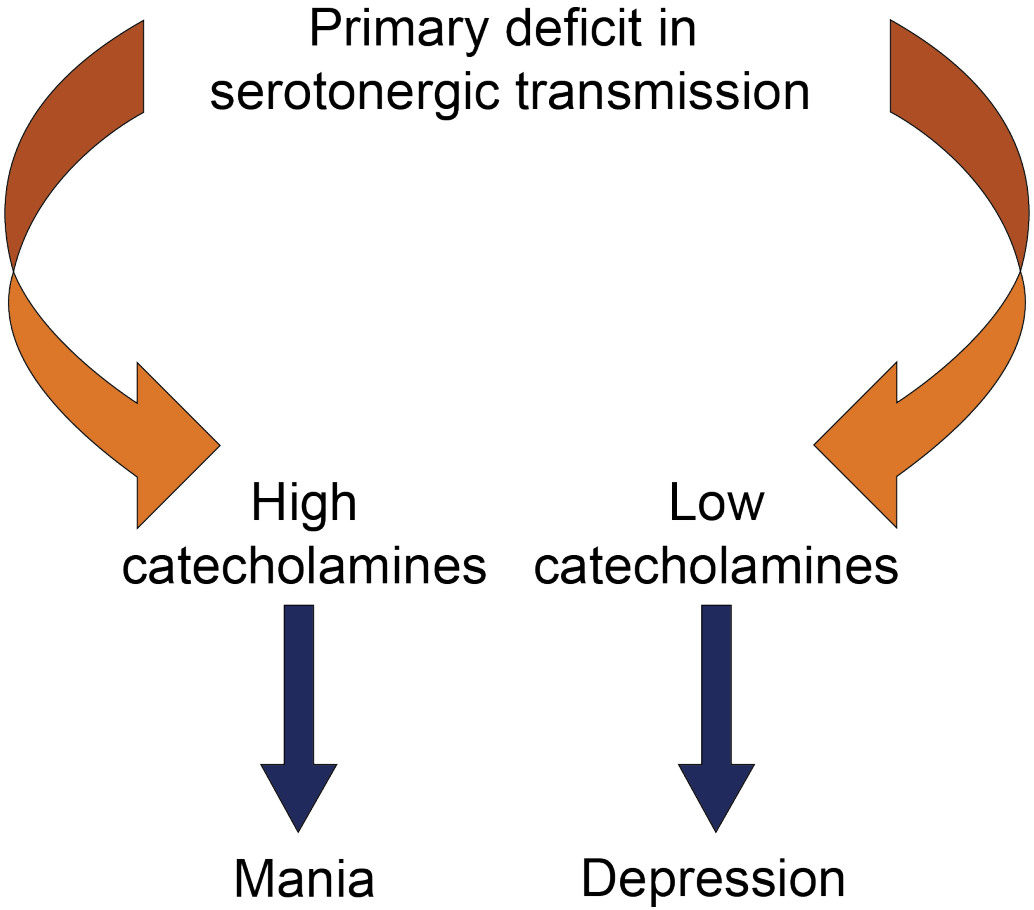


Image from: Belmaker RH. 2008[5]

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; HPA, hypothalamic-pituitary-adrenal.

1. Hasler G. *World Psychiatry*. 2010;9(3):155-61
2. Watson S, et al. *Br J Psychiatry*. 2004;184:496-502.
3. Naveen GH, et al. *Indian J Psychiatry*. 2013;55(Suppl 3):S400-4.
4. Kasala ER, et al. *Complementary Therapies in Clinical Practice*. 2013;30:1e7.
5. Belmaker RH. *CNS Spectr*. 2008;13(8):682-7.

Proposed Monoamine Dysregulation[1]



1. Prange, et al. *Arch Gen Psychiatry.* 1974;30:56-62.

Image adapted from: Prange AJ. 1974[1]

Brain Regions Implicated in Bipolar Disorder[1]

Neuroimaging studies have revealed compromised cognitive control and increased emotional reactivity in euthymic patients with BD

Areas in Red = Regions involved in emotion regulation show increased responsiveness

Areas in Blue = Regions involved in cognitive control show reduced responsiveness

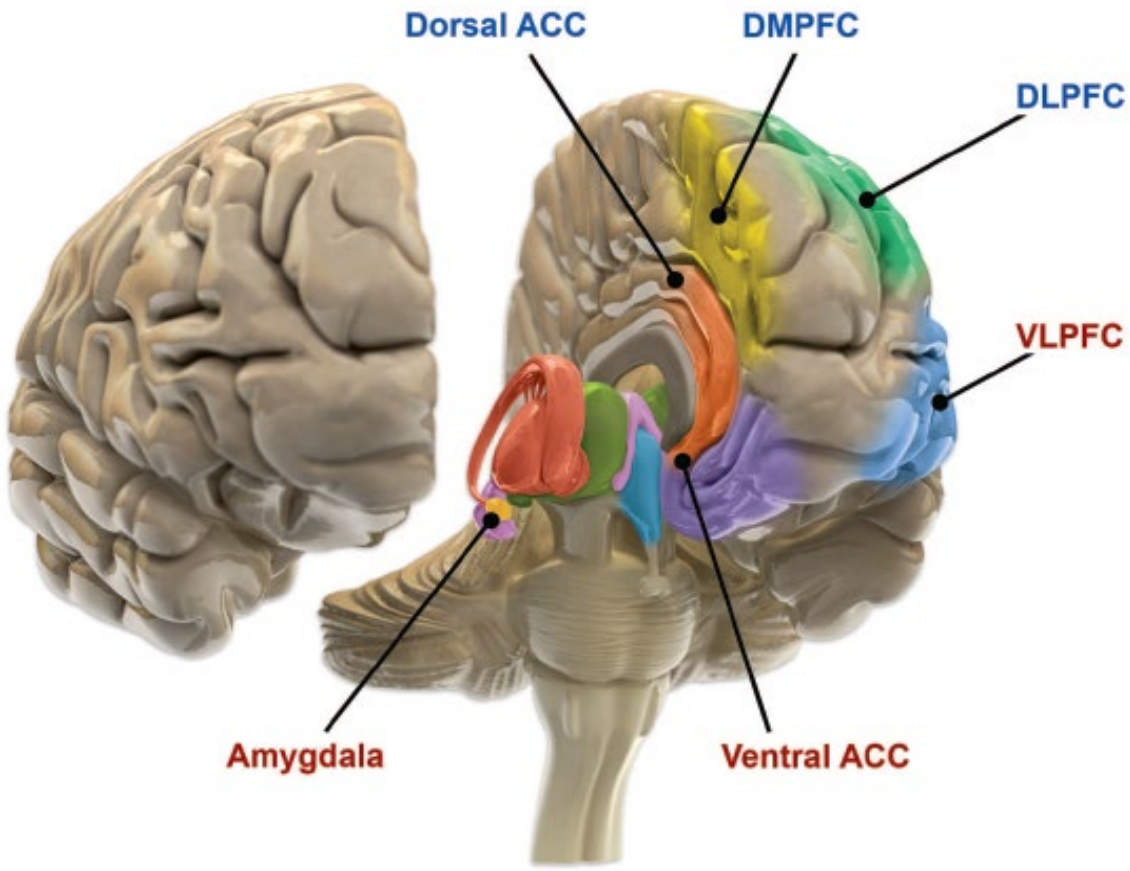


Image from: Maletic V, Raision C. 2014[1]

DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex
ACC: Anterior cingulate cortex

1. Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.

Proposed Altered Circuity: Prefrontal-Striatal-Thalamic Circuits

- Modulate executive functioning, attention, and verbal memory[1,2]
- Modulate emotion and social behavior[3]
- Compromised in BD[3,4]

Prefrontal Cortex: Executive Functioning[2]

Basal Ganglia: Verbal Memory[4]

Thalamus: Cortical Feedback[3,5]

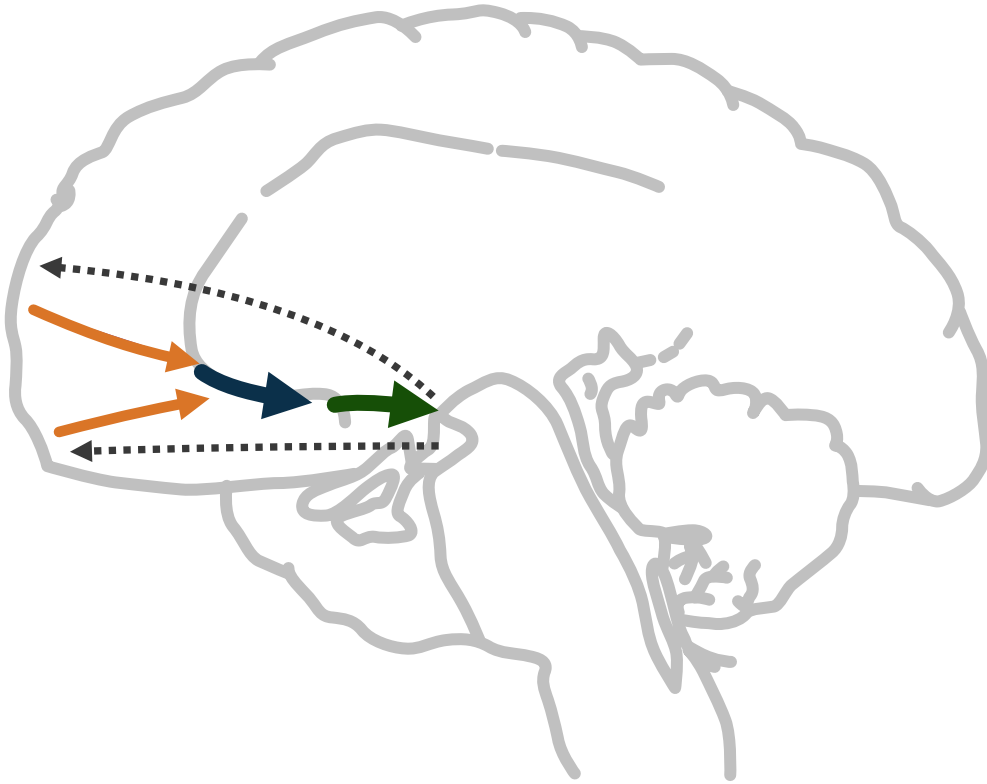


Image adapted from: Stahl S. 2013[6]

1. Osuji IJ, et al. *Psychiatr Clin North Am*. 2005;28(2):427-41.
2. Malhi Gs, et al. *Can J Psych*. 2004;49(12):813-819.
3. Strakowski SM, et al. *Molecular Psychiatry*. 2005;10:105-116.
4. Bearden, et al. *Bipolar Disord*. 2001;3:106-150.
5. Strakowski SM, et al. *Neuropsychopharmacology*. 2004;29(9):1734-40.
6. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013.

The Pathophysiology of Bipolar Disorder: Levels of Analysis[1]

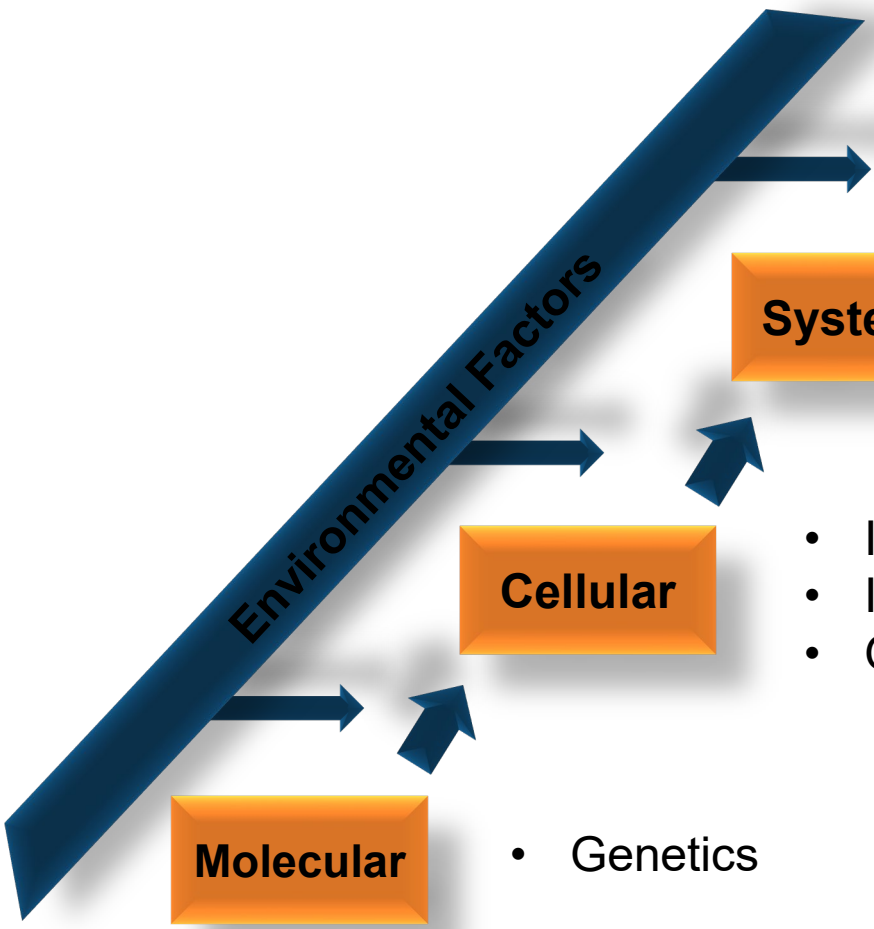


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Image adapted from: Manji. 2000[1]

HPA, hypothalamic-pituitary-adrenal.

1. Manji HK, et al. *Biol Psychiatry*. 2000;48(6):518-30.

Cognitive Function

- Cognitive deficits include impairments in attention; working, episodic, and verbal memory; and processing speed and executive functioning[1,2]
  - Prevalence rates of ~30% to 57% for cognitive impairment have been documented in recent meta-analyses[2,3]
- Cognitive function in patients with BD is negatively correlated to[1]:
  - Number of episodes suffered
  - Number of hospitalizations
  - Duration of illness
- Manic episodes are more strongly linked to deficits in delayed verbal memory and some measures of executive function versus depressed episodes; there is considerable overlap between BD-I and BD-II[1,2]
- Research suggests an increased incidence of dementia with every affective episode leading to psychiatric hospitalization[4]

1. Robinson LJ, et al. *Bipolar Disord*. 2006;8(2):103-16.
2. Cullen B, et al. *J Affective Disorders*. 2016; 205:165–181.
3. Szmulewicz AG, et al. *Archives of Clinical Psychiatry (São Paulo)*. 2015;42(5):139-46.
4. Kessing LV, et al. *J Neurol Neurosurg Psychiatry*. 2004;75(12):1662-6.

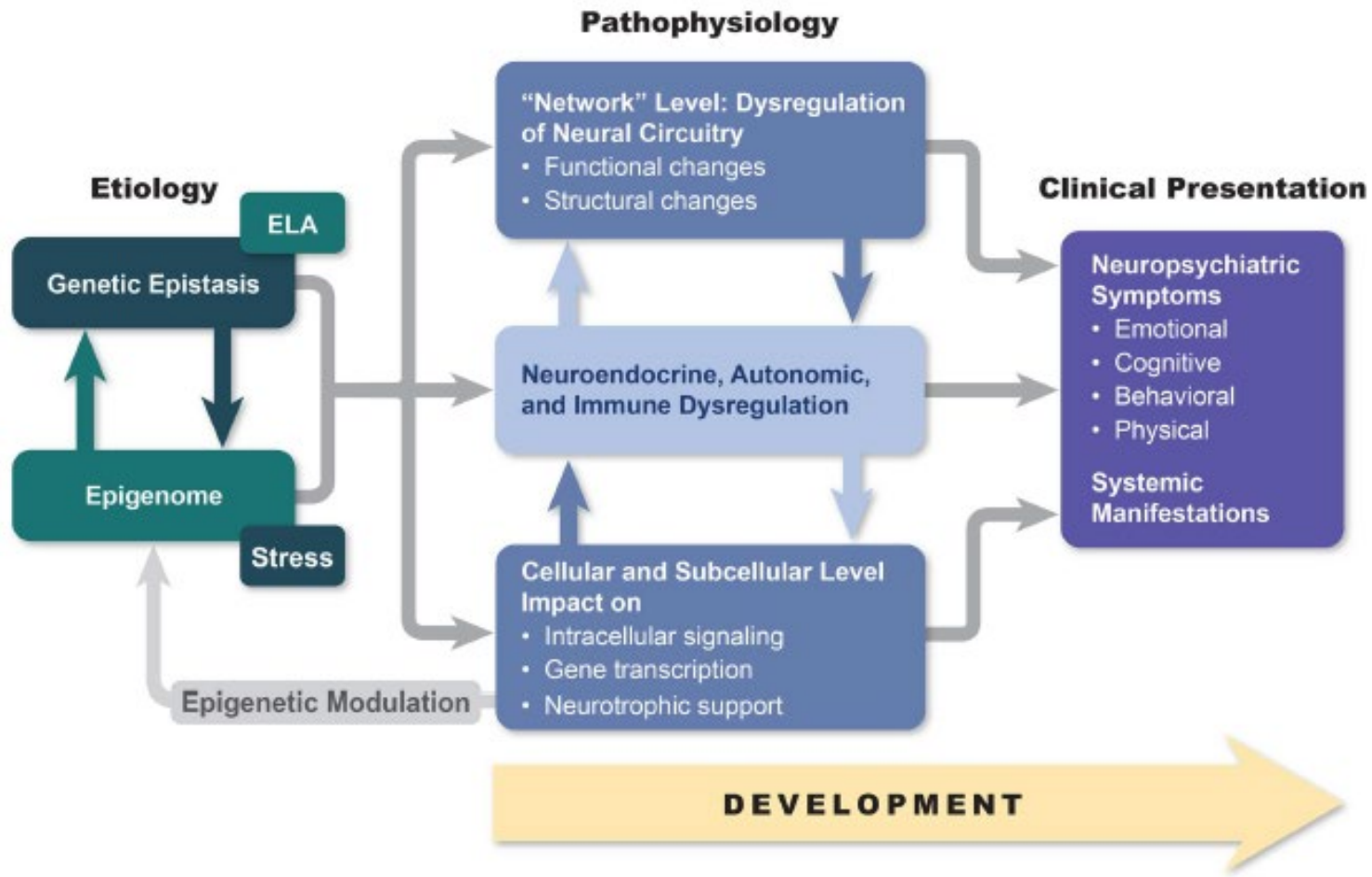
Sleep and Circadian Rhythms in Bipolar Disorder

- Sleep disturbances occur in individuals with bipolar disorders across lifespan and episode, even during periods of euthymia[1,2]
- During a manic episode there is a reduced need for sleep in 69–99% of patients and longer sleep onset latency[2]
- Total sleep time and sleep variability was associated with symptom severity and functioning in STEP-BD[3]
- Polymorphisms in circadian genes have been associated with symptoms of BD in preclinical and human studies[4]
- Circadian rhythm sleep-wake disorder is significantly associated with younger onset of BD and a family history of suicide[5]

STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

1. Sylvia LG, et al. *J Psychopharmacol*. 2012;26(8):1108-12.
2. Harvey AG, et al. *Clin Psychol (New York)*. 2009;16(2):256-277.
3. Gruber J, et al. *J Affect Disord*. 2011;134(1-3):416-20.
4. Murray G, et al. *Bipolar Disord*. 2010;12(5):459-72.
5. Takaesu Y, et al. *PLoS One*. 2016;11(7):e0159578.

Proposed Course of Bipolar / Mood Disorders[1]



1. Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.

Image from: Maletic V, Raison C. 2014[1]

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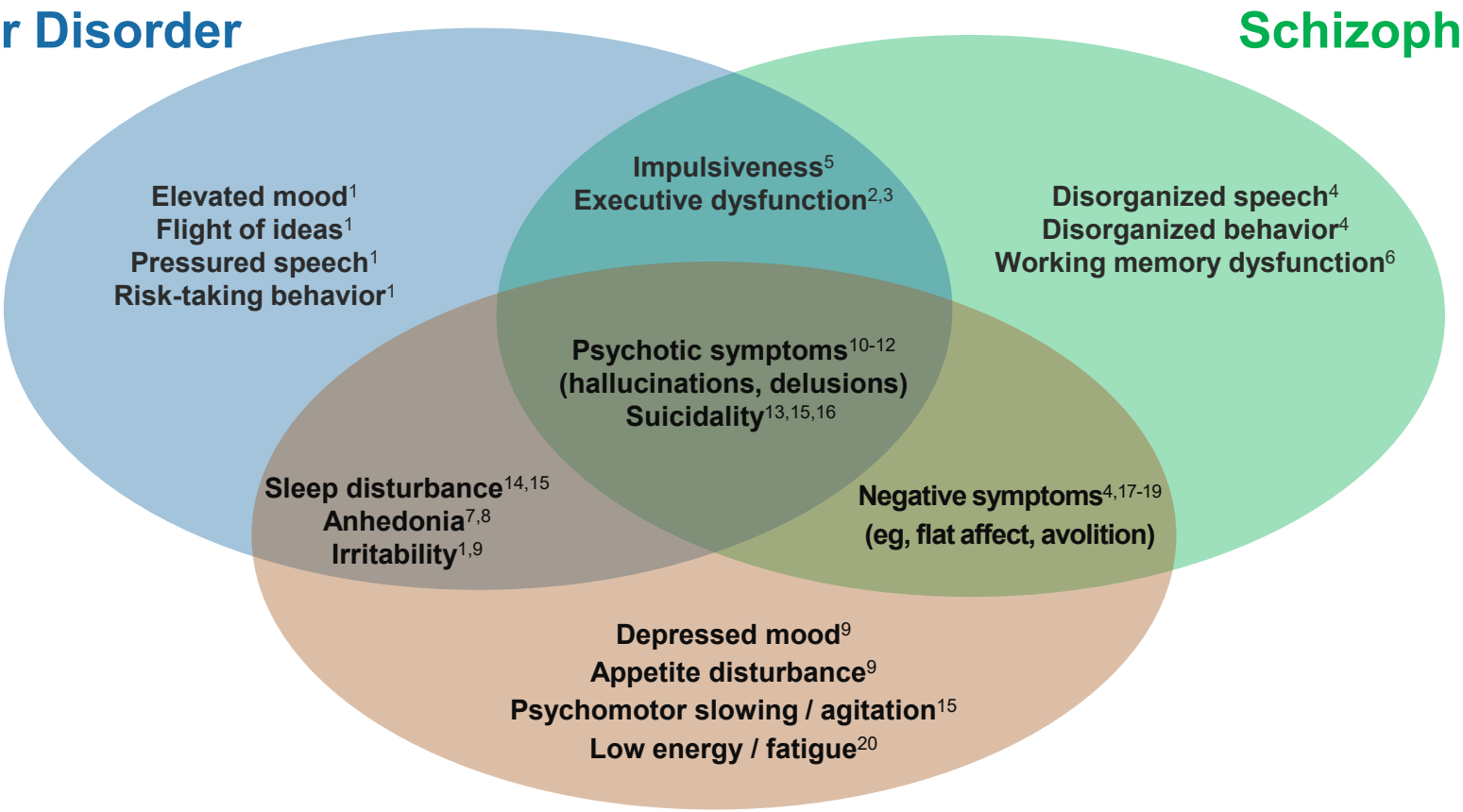
Part II. Potential Role of Neurotransmitters and Treatment Considerations in Bipolar Disorder

Clinical Overlap = Overlap of Symptoms



- Judd LL, et al. 2012.
- Barbosa IG, et al. 2012.
- Brown AS, et al. 2009.
- Kerns JG. 2006.
- Reddy LF, et al. 2014.

6. Forbes NF, et al. 2009.
7. Pizzagalli DA, et al. 2008.
8. Berlim MT, et al. 2004.
9. Farabaugh AH, et al.. 2004.
11. ISC, et al. 2009.
12. Santosh SV et al. 2014.
13. MacKinnon DF, et al. 2005.
14. Harvey AG, et al. 2009.
16. Hor K, et al. 2010.
17. Foussias G, et al. 2010.
18. Pizzagalli DA, et al. 2002.
19. Bracht T, et al. 2012.

Proposed Anatomical Localization of Manic Symptoms

Label	Region	Manic Symptom
1	Prefrontal Cortex	• Racing thoughts • Grandiosity • Distractibility • Talkative / pressured speech • Mood • Risks
2	Basal Forebrain	• Decreased sleep / arousal
3	Nucleus Accumbens	• Racing thoughts • Goal directed • Grandiosity
4	Striatum	• Motor/agitation
5	Amygdala	• Mood
6	Hypothalamus	• Decreased sleep / arousal

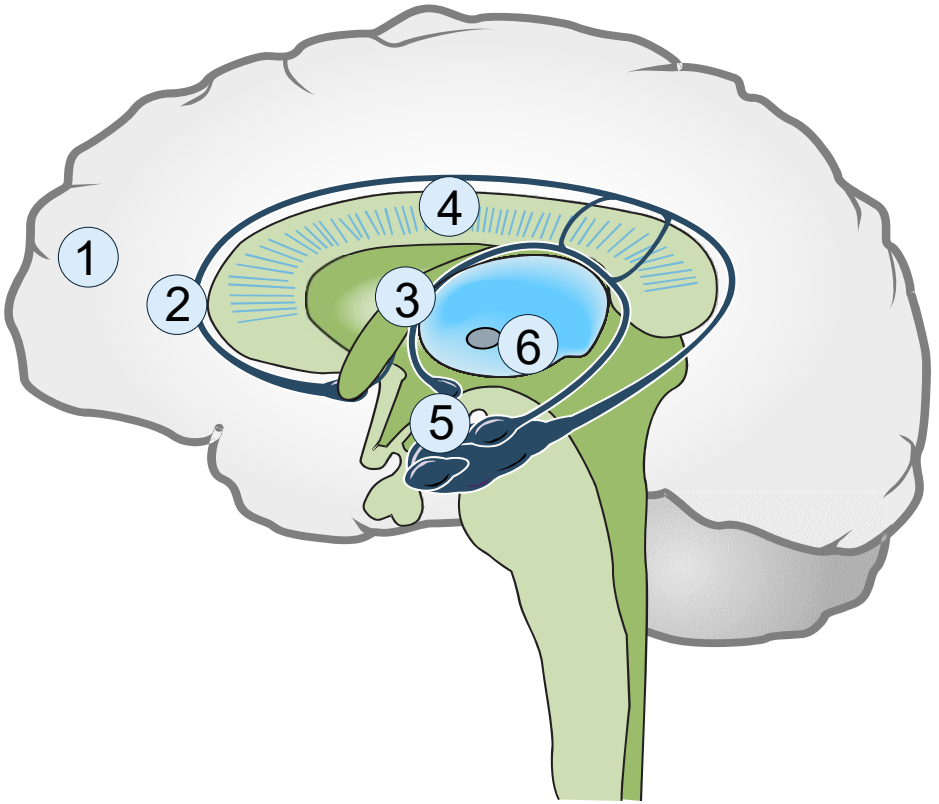


Figure adapted from Stahl SM. 2013

Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.

Proposed Anatomical Localization of Depressive Symptoms

Label	Region	Depressive Symptom
1	Prefrontal Cortex	• Concentration • Interest/pleasure • Psychomotor • Fatigue (mental) • Guilt • Suicidality • Worthlessness • Mood
2	Nucleus Accumbens	• Pleasure • Interests • Fatigue/energy
3	Striatum	• Psychomotor • Fatigue (physical)
4	Amygdala	• Guilt • Suicidality • Worthlessness • Mood
5	Hypothalamus	• Sleep • Appetite
6	Cerebellum	• Psychomotor
7	Spinal cord	• Fatigue (physical)

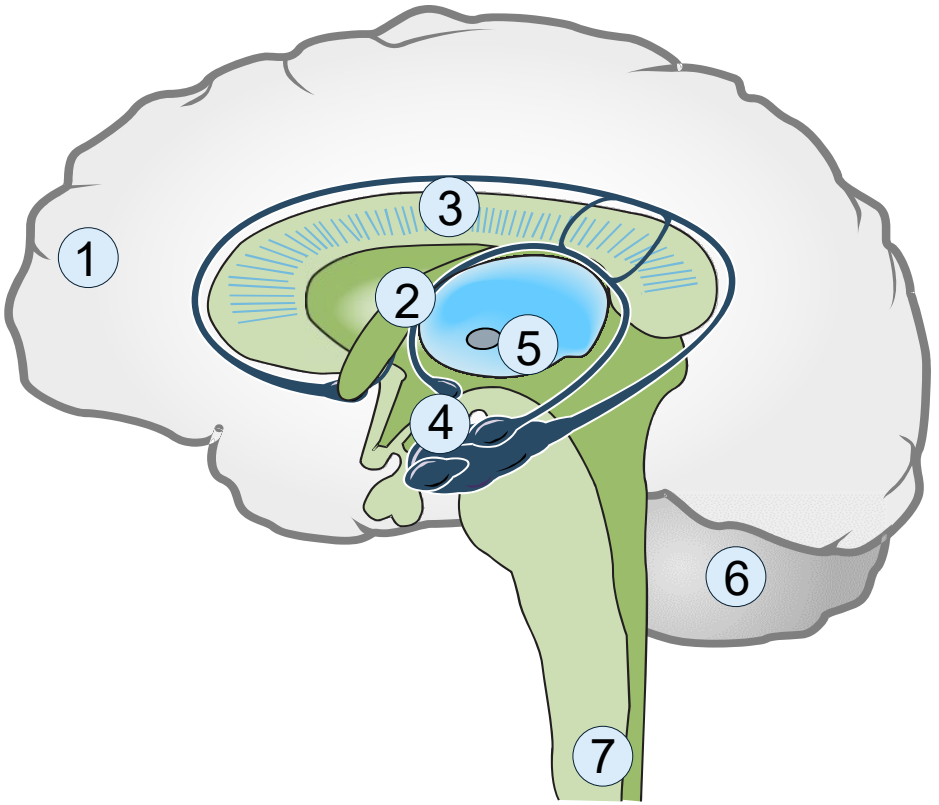


Figure adapted from Stahl SM. 2013

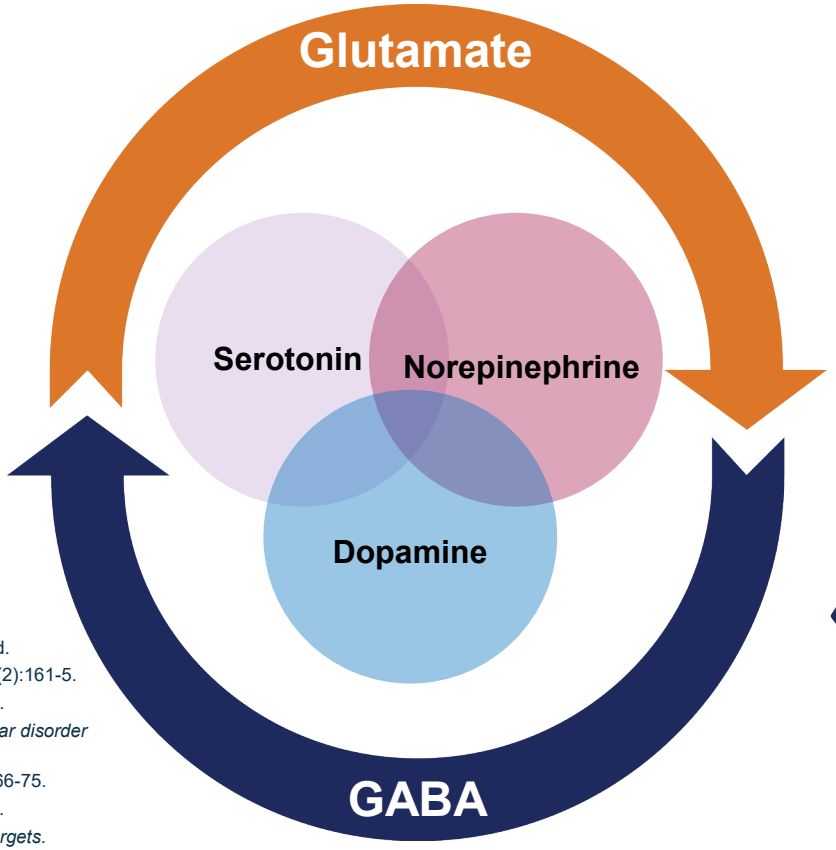
Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 4th edition. Cambridge University Press; 2013.

GABA and Glutamate

- The major inhibitory and excitatory neurotransmitters[1]

Glutamate

- Major excitatory neurotransmitter in the CNS[2]
- Regulates synaptogenesis and neurogenesis[2]
- Synaptic plasticity[3]



GABA

- Major inhibitory neurotransmitter in the CNS[4]
- Target of anti-anxiety drugs[4]
- Involved in sleep-wake cycle[5,6]

CNS, central nervous system; GABA, gamma-aminobutyric acid.

- Rainesalo S, et al. *Brain Res Mol Brain Res*. 2005;141(2):161-5.
- Boulland JL, et al. *J Comp Neurol*. 2004;480(3):264-80.
- Manji, HK, et al (eds). *Behavioral neurobiology of bipolar disorder and its treatment*. Springer, 2011
- D'Hulst C, et al. *Drug Discov Today*. 2009;14(17-18):866-75.
- Nitz D, et al. *Am J Physiol*. 1996;271(6 Pt 2):R1707-12.
- Murillo-Rodríguez E, et al. *CNS Neurol Disord Drug Targets*. 2009;8(4):245-53.

Potential Role of GABA

- In 1980, Emrich and colleagues proposed the GABA hypothesis for mood disorders, in which a potential GABAergic deficiency underlies mood disorders1
- Cerebrospinal fluid (CSF), plasma, and metabolite levels of GABA are altered (often decreased) in bipolar disorder (alterations may be dependent on current episode)1
- GABA system changes occur in specific brain regions: hippocampus, prefrontal cortex, and anterior cingulate cortex1
- Neuroimaging techniques assessing specific chemicals in certain brain regions (including GABA-related enzymes) may provide a means to differentiate between bipolar and unipolar depression1,2
- Drugs effective in the treatment of bipolar disorder have direct effects on the GABA system including increasing GABA levels in specific brain regions and altering several key metabolic enzymes1

1. GABA, gamma-aminobutyric acid.
2. Brambilla P, et al. Mol Psychiatry. 2003;8(8):721-37, 715.
3. Maletic V, Raison C. Front Psychiatry. 2014;5(98):1-24.

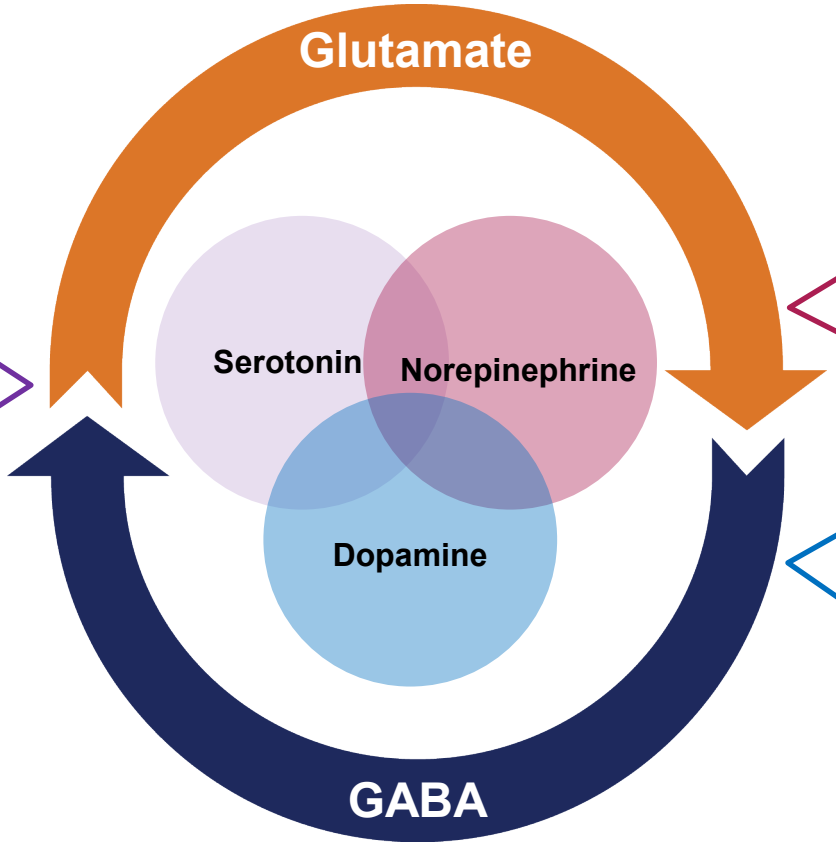
Potential Role of Glutamate

- Evidence from genetic, postmortem, biochemical, and imaging studies points to a principal role of glutamatergic dysregulation in the etiopathogenesis of bipolar disorder[1]
- Studies show an increase in glutamatergic transmission in the frontal cortex and hippocampus of bipolar subjects relative to control groups[1]
- Studies reveal elevation of various glutamate/GABA metabolites in the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), parieto-occipital cortex, insula, and hippocampus across bipolar mood states and euthymic individuals[1]
- Drugs effective in bipolar disorder impact glutamatergic neurotransmission[2]
- An increased understanding of glutamate-dopamine (DA) interactions may enhance drug development efforts[3]

GABA, gamma-aminobutyric acid.

1. Muneer A. *Psychiatry Investig*. 2016;13(1):18-33.
2. Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.
3. de Bartolomeis A, et al. *J Psychopharmacol*. 2014;28(6):505-26.

Serotonin, Norepinephrine, and Dopamine



Serotonin

- Impulsive behavior
- Anxiety, irritability
- Sex, appetite, aggressive behavior
- Mood, emotion, cognitive function

Norepinephrine

- Energy, interest
- Anxiety, irritability
- Motivation
- Mood, emotion, cognitive function

Dopamine

- Drive
- Sex, appetite, aggressive behavior
- Motivation
- Mood, emotion, cognitive function

GABA, gamma-aminobutyric acid.

Zajecka J, et al. *J Clin Psychiatry*. 2013;74:407-414.

Potential Role of Dopamine

- In the mid-1960's, the catecholamine hypothesis of bipolar disorder (CHBD) emerged due to pharmacological observations[1]
  - Excessive DA neurotransmission involved in development of mania-like behavior[2]
  - Phase-related altered levels of DA and DA metabolite (HVA) found in CSF and urine[3]
  - Decreased DA transport (DAT) levels observed in frontal cortex of patients with bipolar disorder versus healthy control participants[4]
- Psychostimulants
  - Administration in healthy volunteers can produce a hypomanic-like state[2]
  - MOA of the psychostimulant amphetamine — reverses the direction of DAT[5]
  - Mood stabilizers are thought to alter DA neurotransmission[2]
- Catechol-O-methyltransferase (COMT, DA metabolic enzyme) — genetic variations linked to bipolar disorder[6]

MOA, mechanism of action; HVA, homovanillic acid.

1. Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.
2. Berk M, et al. *Acta Psychiatr Scand Suppl*. 2007;(434):41-9.
3. Cousins DA, et al. *Bipolar Disord*. 2009;11(8):787-806.
4. Rao JS, et al. *J Affect Disord*. 2012;136(1-2):63-71.
5. Berman SM, et al. *Mol Psychiatry*. 2009;14(2):123-42.
6. Andreazza AC, et al. *Int J Neuropsychopharmacol*. 2014;17(7):1039-52.

Potential Role of Norepinephrine

- Plasma and urine norepinephrine (NE) levels and NE metabolite levels are lower in patients with bipolar depression compared with those with unipolar depression, and is higher in the manic phase versus the depressed phase[1]
- Plasma NE levels are lower in response to orthostatic challenge in bipolar depression versus unipolar depression[2,3]
- Elevated NE metabolite levels are observed in postmortem bipolar brains[4]

1. Manji HK, et al. *World Psychiatry*. 2003;2(3):136-46.
2. Roy A, et al. *Arch Gen Psychiatry*. 1985;42(12):1181-5.
3. Rudorfer MV, et al. Arch Gen Psychiatry. 1985;42(12):1186-92.
4. Young LT, et al. *Biol Psychiatry*. 1994;35(2):121-7.

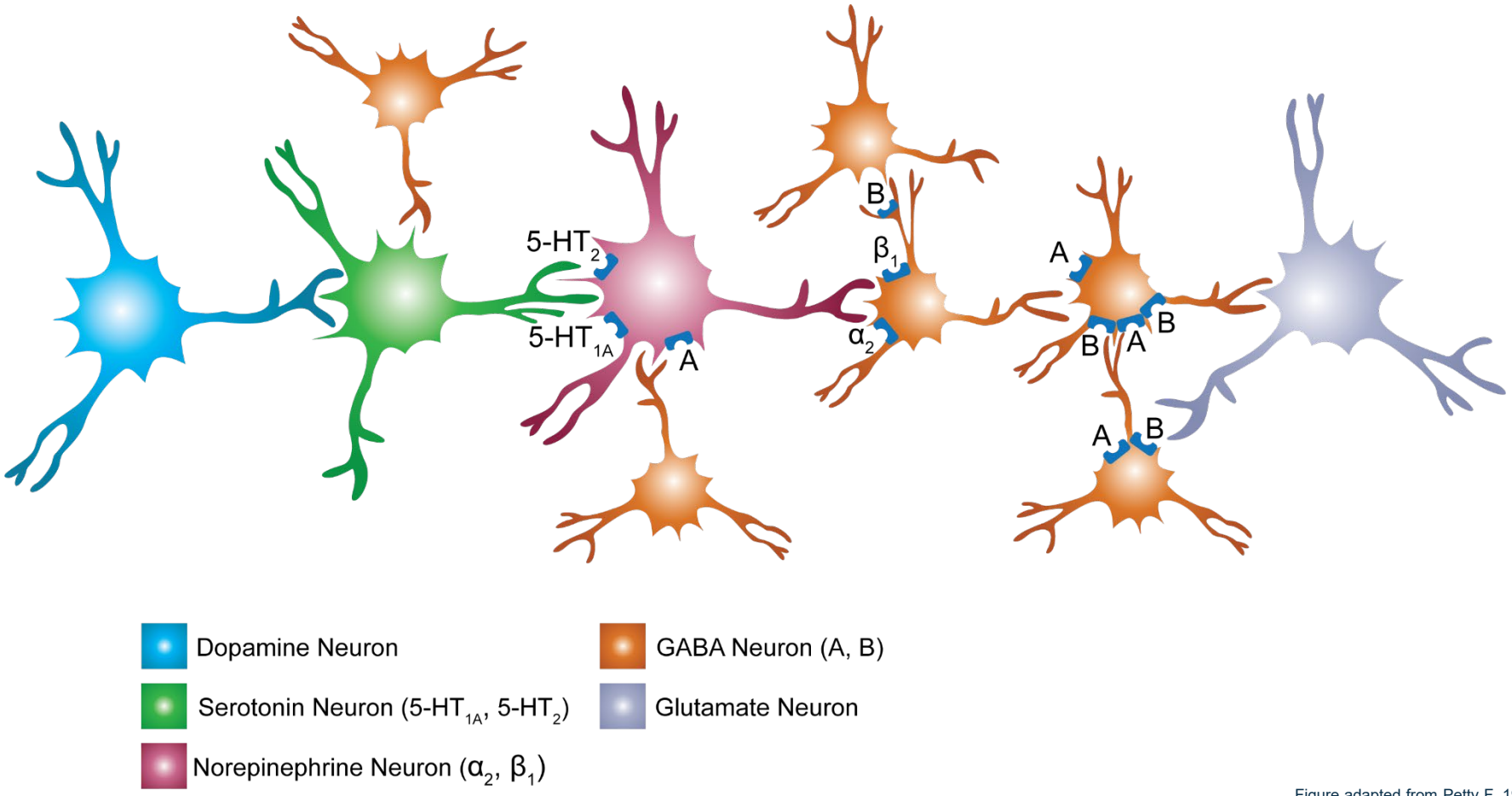
Potential Role of Serotonin

- No simple model for serotonergic involvement in bipolar exists
  - Deficient serotonin (5-HT) signaling seems to contribute to both depressive and manic symptoms
    - Low energy, anhedonia, altered sleep, and appetite
    - Impulsivity, interpersonal aggression
  - Increased 5-HT signaling implicated in some symptoms of mania
    - Increased hedonic behavior, decreased need for sleep, increased energy
- Postmortem studies show reduced levels of 5-HIAA
- Neuroimaging research implications:
  - Reduced 5-HT transporter binding in midbrain of depressed bipolar patients has been shown, extent of alterations correlates with aggressive symptoms in patients with bipolar II
  - One study reveals reduced 5-HT_{2A} receptor binding in manic patients
- Genetics: Two gene variants in 5-HTT have modest associations with bipolar
  - Short allele of 5-HTTLPR & intron two variable number of tandem repeats (VNTR)

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT_{2A}, serotonin receptor 2A; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin-transporter-linked polymorphic region.

Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.

Neurotransmitter Interactions



Petty F. *J Affect Disord*. 1995;34(4):275-81.

Figure adapted from Petty F. 1995

Historical Perspective of Pharmacologic Treatments for Bipolar Disorder

- Anticonvulsants: Used for mood stabilization, starting in 1960s, clinical trials began in 1980s
- Antipsychotics: Phenothiazines both oral and intramuscular standard treatment used for acute mania in 1970s
- Benzodiazepines: Possible use as adjunctive agents in acute mania in the 1960s

Hirschowitz J, Kolevzon A, Garkani A. *Harv Rev Psychiatry*. 2010;18(5):266-78.

Pharmacologic Treatment of Bipolar Disorder

US FDA-approved Therapies	Proposed Mechanism of Action
Mood stabilizers	Mechanism of action is complex and not fully understood.[1] Suppresses formation of secondary messengers (eg, IP_3, by inhibiting IMPase).[1] Reduces DA and Glu neurotransmission, enhances 5-HT and GABA neurotransmission[1]
Anticonvulsants	Blocks Na^+ and Ca^{2+} channels, enhances GABA receptor functions, enhances 5-HT neurotransmission[2,3]
Atypical antipsychotics	Antagonist and/or partial agonist activity at D_2, 5-HT_{2A}, 5-HT_{1A} receptors and other DA, 5-HT, and NE targets[4,5]

5-HT, serotonin; 5-HT_X, serotonin receptor X; Ca, calcium; D_x, dopamine receptor X; DA, dopamine; FDA, Food and Drug Administration: GABA, gamma-aminobutyric acid; Glu, glutamate; IMPase; inositol monophosphatase; IP_3, inositol triphosphate; Na, sodium; NE, norepinephrine; US, United States.

1. Malhi GS, et al. *CNS Drugs*. 2013;27(2):135-53.
2. Schloesser RJ, et al. *Trends Neurosci*. 2012;35(1):36-46.
3. Nugent AC, et al. *J Psychopharmacol*. 2013;27(10):894-902.
4. Li X, et al. *Neuropsychopharmacology*. 2012;37(1):77-101.
5. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.

Summary

- While the pathophysiology of bipolar disorder is not completely understood, several theories have been proposed on both the molecular and cellular level[1,2]
- Various systems such as the HPA axis, monoaminergic pathways, and specific brain regions and circuits have also been implicated[1,2]
- Neurotransmitters thought to be involved in bipolar disorder include GABA, glutamate, serotonin, norepinephrine, and dopamine[1-3]
- Pharmacologic treatment options for bipolar disorder include mood stabilizers, anticonvulsants, and atypical antipsychotics[4]

1. Manji HK, et al. *Biol Psychiatry*. 2000;48(6):518-30.
2. Maletic V, Raison C. *Front Psychiatry*. 2014;5(98):1-24.
3. Soares JC. *Bipolar Disorders: Basic Mechanisms and Therapeutic Implications*. 3rd edition. Cambridge University Press; 2016.
4. Li X, et al. *Neuropsychopharmacology*. 2012;37(1):77-101.

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