Circadian Rhythms and Bipolar Disorder

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What is Bipolar Disorder

- Chronic psychiatric disorder characterized by the occurrence of one or more manic or mixed episodes
- May also experience depressive states
- High rates of co-morbidity with other disorders
- Equally affects men and women
- Median age of onset ~25 and prevalence is between 2-4%
What Causes Bipolar Disorder?

Genes + Environment

Genetics: 80-90% of bipolar patients have a family history of Bipolar disorder, major depression or schizophrenia

<table>
<thead>
<tr>
<th>Relation to Person w/ Bipolar</th>
<th>Risk of Developing Bipolar</th>
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<tbody>
<tr>
<td>General Population</td>
<td>1%</td>
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<td>2nd degree relative (i.e. aunt/uncle)</td>
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<td>Sibling</td>
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<td>Fraternal Twin</td>
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<td>One Parent</td>
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<td>Both Parents</td>
<td>50-75%</td>
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<td>Identical Twin</td>
<td>70%</td>
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12 AM Midnight

- Deepest sleep
- Bowel movements suppressed
- Melatonin secretion starts

6 AM

- Sharpest rise in blood pressure
- Lowest body temperature

6 PM

- Highest blood pressure
- Highest body temperature

Noon 12 PM

- Best coordination
- Fastest reaction time
- Greatest cardiovascular activity

High alertness

Highest testosterone secretion

Bowel movement likely

Melatonin secretion stops
The master pacemaker is located in the SCN.
Light at night                  Shift Work                  Puberty/Aging
Travel across time zones       Inconsistent sleep/wake schedule
Genetics                      Early school start times       Electronic devices
The circadian clock consists of a feedback loop that controls gene expression and all daily rhythms.

*Sleep/wake cycle
*Hormonal rhythms
*Body temperature rhythms
*Rhythms in appetite and metabolism
*Rhythms in drug responses
*Rhythms in mood
*Seasonal rhythms

Disruptions cause jet lag, sleep problems, and mood disorders.
People with psychiatric disorders have abnormal clocks

- Depression, bipolar disorder and schizophrenia are associated with major disruptions in sleep and activity.

- Changes in schedule precipitate manic or psychotic episodes

- Depression is diurnal, often seasonal, and occurs more frequently in areas of the world where there is little daylight for long periods of time

- People with a preference toward “eveningness” (Owls vs Larks) are more susceptible to depression, and the vast majority of bipolar subjects are evening types.

- Polymorphisms in several circadian genes associate with bipolar disorder, depression, and seasonal affective disorder. The CLOCK gene in particular has an association with bipolar disorder.
Circadian Rhythm Phase Shifts

- Delayed Sleep Phase
- Advanced Sleep Phase
- Normal Sleep Phase
- Irregular Sleep-Wake Rhythm
- Non-24 Hour Sleep-Wake Rhythm

Blue bars represent sleep periods.
Healthy Control
Bipolar Patient
Reduced rhythm amplitude is associated with increased depression scores

(Souetre et al 1989)
Circadian Rhythms and Mood Disorders

In 1968, Franz Halberg suggested that some, but not all, circadian rhythms in bipolar patients were not synchronized with the 24-hour day-night cycle. Halberg’s hypothesis was that the interaction between the unsynchronized, “free-running” rhythms and the normally synchronized “entrained” rhythms causes switches back and forth between mania and depression.
Social Zeitgeber Theory
Ehlers, Frank, Kupfer (1988)
Molecular rhythms are disrupted in major depressive disorder

Circadian patterns of gene expression in the human brain and disruption in major depressive disorder


Department of Human Genetics and Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI 48109; Department of Psychiatry and Human Behavior, University of California, Irvine, CA 92697; Center for Neuroscience, University of California, Davis, CA 95616; Department of Psychiatry, Weill Cornell Medical College, New York, NY 10017; Department of Psychiatry, Stanford University, Palo Alto, CA 94305; and HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806
Rhythmic gene expression is disrupted in MDD patients

Edgar and McClung, 2013

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The direction of travel across time zones influences mood state.

**East-West** = greater depression

**West-East** = greater hypomania


**Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport.**

Jauhar P, Weller MP.

**Abstract**

In a two-year period, 186 patients were admitted from Heathrow Airport to the nearest psychiatric hospital. Affective illness was related to time zone change. Depression was diagnosed significantly more often on flights from east to west (P less than 0.012 east to west versus west to east; P less than 0.015 north to south combined with south to north versus east to west, Fisher's exact probability test, two tailed). Hypomania was inversely related to depression in an east to west comparison (P less than 0.025). No other associations with direction of travel were seen in other diagnoses. Ninety-three (50 per cent) were diagnosed as schizophrenic; 24 of these had been aimlessly wandering. Twenty patients had been admitted at least once before under similar circumstances. Schizophrenic patients from Heathrow constituted 20 per cent of the total number of schizophrenic patients admitted to the hospital during that period.
Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder


EBioMedicine, 2016, Available online 13 August 2016

Fig. 1. The shifting of acrophases of circadian rhythms in bipolar disorder patients. Note that the acrophase is the timing of the peak of the best-fitting sine curve.
The *Clock* mutant mouse

*Clock* was identified in a screen of mutagenized mice done in the lab of Joe Takahashi (Vitaterna et al., 1994).
How do you feel?
Anxious? Depressed?
Models of Depression, Anxiety, Exploratory Drive and Reward in Mice

Forced Swim Test  Learned Helplessness  Open field  Elevated Plus Maze

Conditioned Place Preference  Light/dark test  Sucrose preference
The *Clock* mutant mice display similarities with bipolar mania and other psychiatric disorders.

**Bipolar patients**
- Hyperactivity
- Decreased need for sleep
- Feelings of euphoria
- Excessive involvement in activities that have a high potential for painful consequences.
- Propensity towards drug use and abuse

**Clock mutant mice**
- Hyperactivity
- Sleep less than wild type mice
- Less depression-like behavior
- Have increased impulsivity, novelty seeking, risk taking in behavioral models
- Are more sensitive to the rewarding effects of cocaine, sucrose, and brain stimulation

* Lithium or VPA treatment reverses these phenotypes

ClockΔ19 mice display rapid mood cycling with manic-like behavior during the day and euthymic-like behavior at night.

Sidor et al., Mol Psych, 2015
Dopamine is important in psychiatric disorders

- Mania is associated with increased dopaminergic transmission in striatal regions, while some models of depression produce decreased dopamine.
- Antipsychotic drugs antagonize Drd2 receptors
- All drugs of abuse activate the VTA dopamine system. Stimulants like cocaine directly bind to the dopamine transporter
Clock mutant mice have an increase in VTA dopamine cell firing and this is rescued by chronic lithium treatment.

Coque et al., Neuropsychopharm (2011)
ClockΔ19 mice have a large increase in daytime dopaminergic activity

Sidor et al., Mol Psych 2015
Clock knockdown mice have higher rates of dopamine cell firing

Mukherjee et al, Biological Psychiatry, 2010
Clock knock-down in the VTA increases alcohol preference

Ozburn et al., Neuropsychopharm, 2013
Viral expression of functional CLOCK in the VTA is able to rescue their behavioral abnormalities.

Clock mutant mice have increased DA in VTA, NAc, dSTR but decreased DA in mPFC

Logan et al., Molecular Psychiatry, in press
How does lithium work?

Arey et al., Mol. Psych 2013

Tanganelli et al., 2001
CCK levels are increased in the VTA of bipolar patients on meds

Local knock-down of Cck in the VTA leads to manic-like behavior

Cck knock-down in the Clock mutant mice prevents lithium from restoring normal behavior

Arey et al, Mol. Psych 2013
Most treatments for depression and bipolar disorder affect the circadian clock:

- Bright light therapy
- Total sleep deprivation
- Social Rhythm Therapy
- Melatonin/Agomelatin
- Lithium/SSRIs/valproate
# Social Rhythm Metric

**Directions:**
- Write the **ideal** target time you would like to do these daily activities.
- Record the **time** you actually did the activity each day.
- Record the **people** involved in the activity: 0 = Alone; 1 = Others present; 2 = Others actively involved; 3 = Others very stimulating

<table>
<thead>
<tr>
<th>Activity</th>
<th>Target Time</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Time</td>
<td>People</td>
<td>Time</td>
<td>People</td>
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<td>Out of bed</td>
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<td>First contact with other person</td>
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<td>Start work/school/volunteer/family care</td>
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Rate MOOD each day from −5 to +5
−5 = very depressed
+5 = very elated

**Date (week of):**
Interpersonal and Social Rhythm Therapy leads to greater occupational functioning in a shorter amount of time than traditional psychotherapy

Change in Occupational Functioning Over Course of Acute and Maintenance Treatment in Patients Assigned to Acute Phase Interpersonal and Social Rhythm Therapy Versus Intensive Clinical Management

*Lower scores indicate improved occupational functioning.
Fig. 3 When the patient slept during long, rigidly scheduled dark periods, the lunar periodicity disappeared and his mood cycles stopped. Indications are the same as in Fig. 1.

Wehr et al., *Translational Psychiatry*, 2018
Treatment of a Rapidly Cycling Bipolar Patient by Using Extended Bed Rest and Darkness to Stabilize the Timing and Duration of Sleep

Thomas A. Wehr, Erick H. Turner, Jeffrey M. Shimada, Catherine H. Lowe, Charles Barker, and Ellen Leibenuft

14 hrs then 10 hrs
In bed after dark
Daily bright light therapy at midday (12-2:30pm) helps people with bipolar depression

\[\text{Percentage of Patients Remitted}\]

\[\text{Week}\]

\[\text{Active treatment}\]
\[\text{Inactive treatment}\]

\[\text{Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio}=7.50, 95\% \text{ CI}=1.80, 31.28, p=0.003; \text{ adjusted odds ratio}=12.64, 95\% \text{ CI}=2.16, 74.08, p=0.004).\]

Sit et al., Am J Psychiatry 2018
Lithium and VPA increase molecular rhythm amplitude

Li et al., 2012

Johansson et al. 2011
CK1 ε/δ inhibitors increase rhythm amplitude under compromised conditions

**A**
- Bioluminescence (cps) vs. TIME (d)
- Graph showing the effect of Vehicle and PF670462 on bioluminescence.

**B**
- VEHICLE
- PF-670462 (30mg/kg)
- Graphs showing duration of rhythms under different treatments.

**C**
- Graphs showing temporal distribution of rhythms under constant light conditions.

Vipr2 -/-

Constant light

Meng et al., 2010
CK01 normalizes anxiety-related behavior and partially normalizes depression-like behavior in the *ClockΔ19* mice.

Arey et al., 2012
Conclusions

- Bipolar disorder is associated with major disruptions to the circadian system and an altered circadian clock could be a causative factor in the disorder.
- Disruptions to normal sleep/wake schedules can precipitate episodes (particularly manic episodes)
- We are learning more about how circadian genes regulate dopamine and other brain functions that regulate mood
- We are learning more about how mood stabilizing medications act on in the brain
- Stabilization and amplification of the circadian clock represents a therapeutic target for the treatment of bipolar disorder
The McClung lab (current)

Chelsea Vadnie
Kyle Ketchesin
Lauren Eberhardt
Mariah Hildebrand
Alyssa Miguelino
Shruti Bidani
Sam Moon Kim
Jessica Brandon
Laura Holesh
Jennifer Burns
Lauren DePoy
Kelly Cahill
Darius Becker-Krail
Wesley Dehaven

Duke: Kafui Dzirasa
Wash U: Jun Yoshino
Mt. Sinai: Ming-Hu Han

Past members

Angela Ozburn
Rachel Arey
Michelle Sidor
Kole Roybal
Shibani Mukherjee

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Collaborators at Pitt

Caleb Ho
Marianne Seney
George Tseng
Joey Chen
Charles Ma
David Lewis
John Enwright
Yanhua Huang
Mary Torregrossa
Ryan Logan
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