Circadian Rhythms and Bipolar Disorder

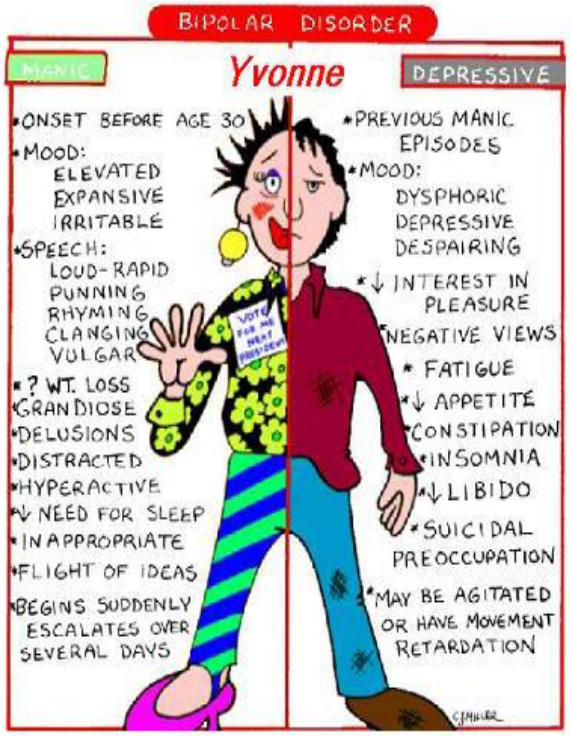
Colleen A. McClung, Ph.D.
Professor
Department of Psychiatry
Clinical and Translational Science
Translational Neuroscience Program
Center for Neuroscience
University of Pittsburgh School of Medicine

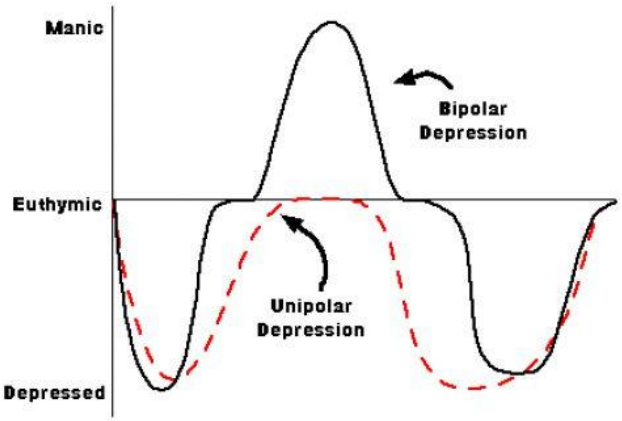
UNIVERSITY OF PITTSBURGH
Center for Sleep and Circadian Science

McCLUNG LAB

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%



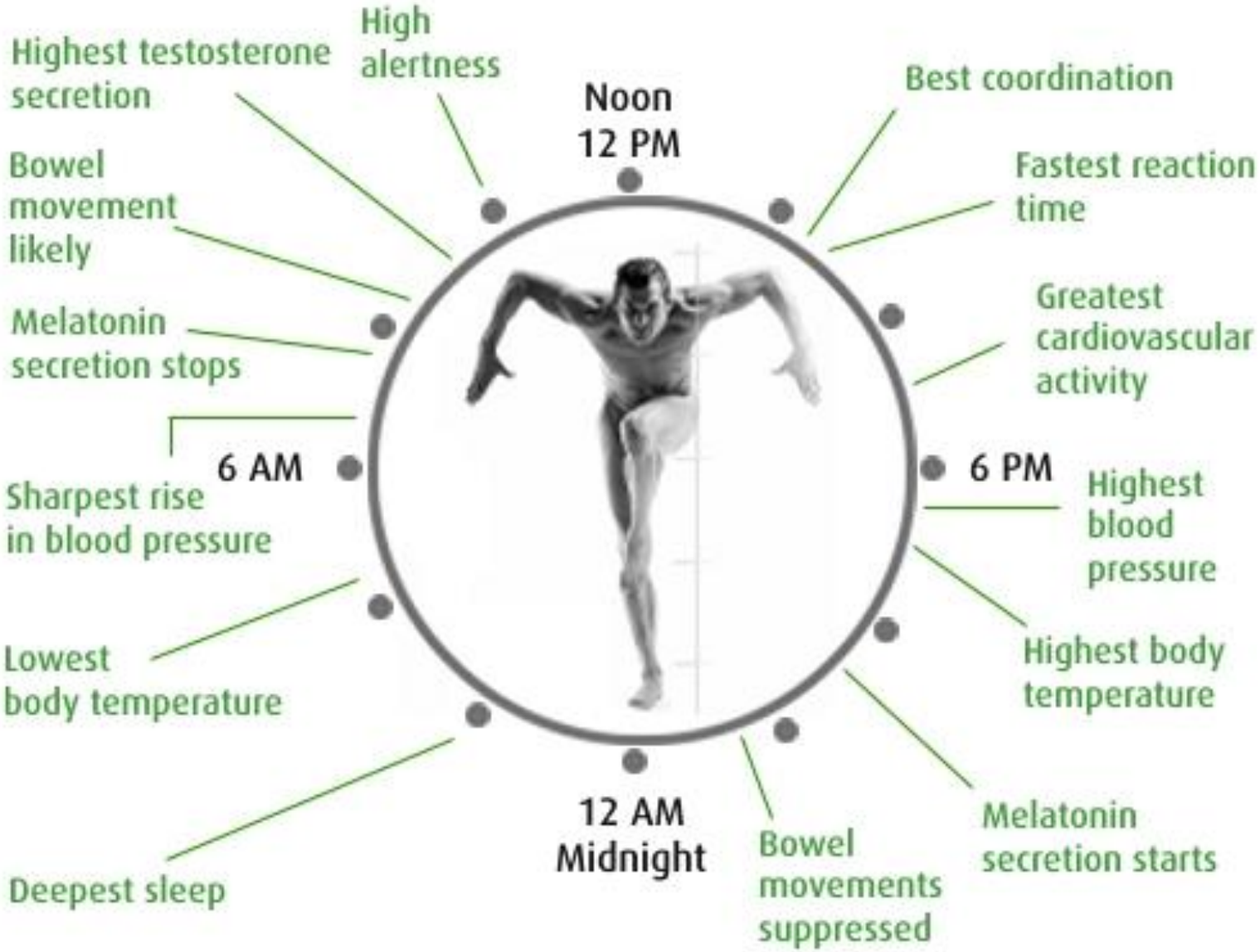


What Causes Bipolar Disorder?

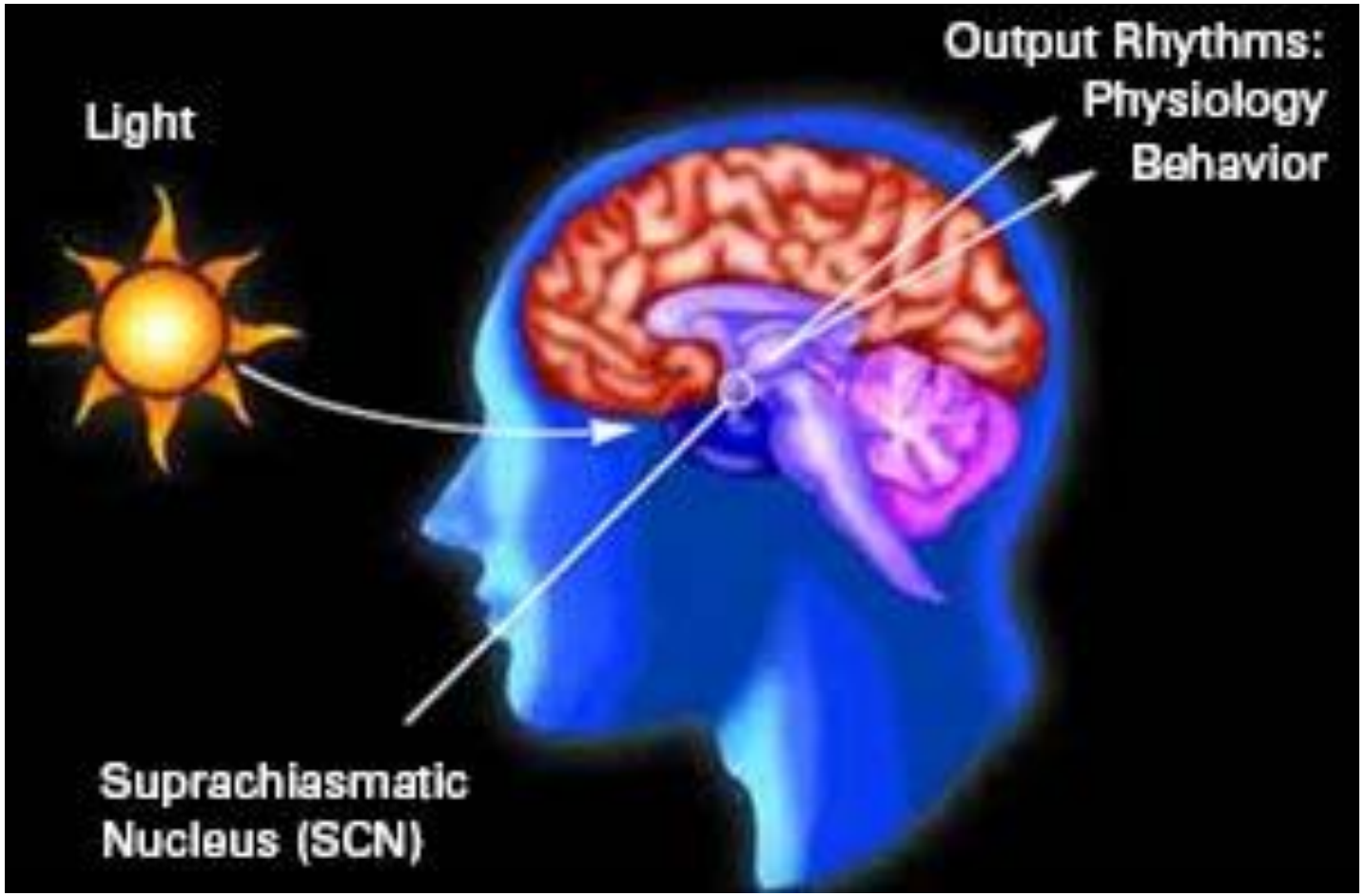
Genes + Environment

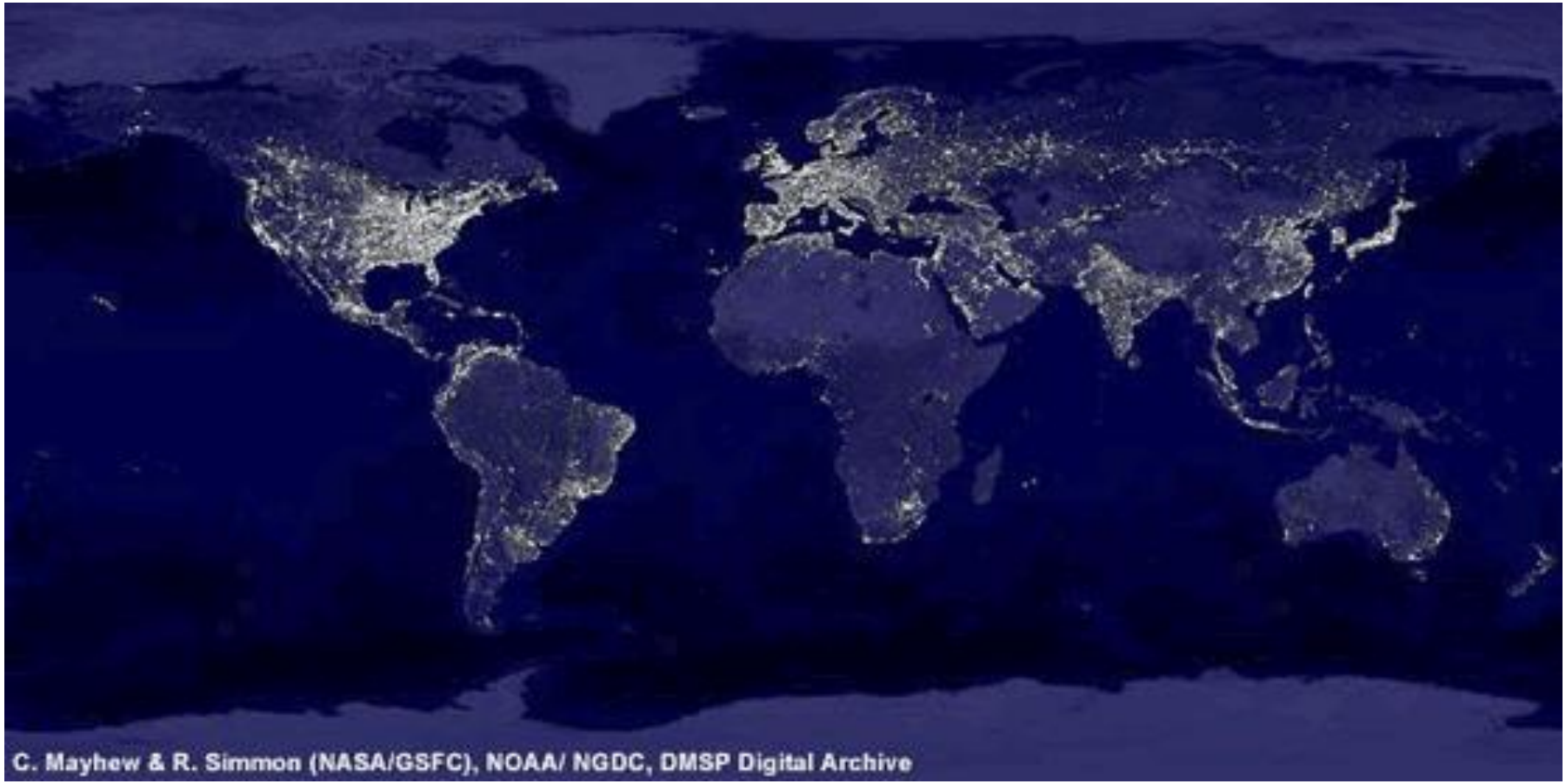
Genetics: 80-90% of bipolar patients have a family history of Bipolar disorder, major depression or schizophrenia

Relation to Person w/ Bipolar	Risk of Developing Bipolar
General Population	1%
2nd degree relative (i.e. aunt/uncle)	3-7%
Sibling	15-25%
Fraternal Twin	15-25%
One Parent	15-30%
Both Parents	50-75%
Identical Twin	70%


Noon
12 PM
High alertness
Highest testosterone secretion
Best coordination
Bowel movement likely
Fastest reaction time
Melatonin secretion stops
Greatest cardiovascular activity
6 AM
6 PM
Sharpest rise in blood pressure
Highest blood pressure
Lowest body temperature
Highest body temperature
12 AM
Midnight
Deepest sleep
Bowel movements suppressed
Melatonin secretion starts

The master pacemaker is located in the SCN





Light at night

Shift Work

Puberty/Aging

Travel across time zones

Inconsistent sleep/wake schedule

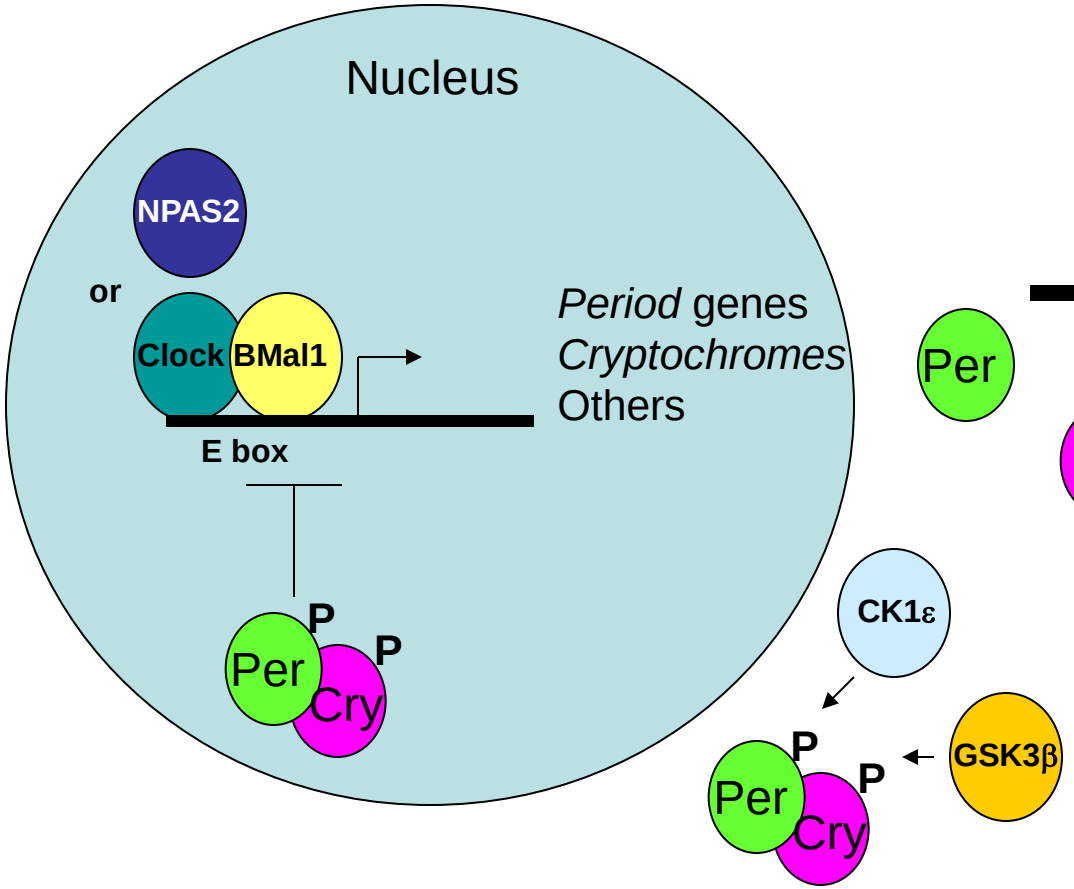
Genetics

Early school start times

Electronic devices

The circadian clock consists of a feedback loop that controls gene expression and all daily rhythms

Neuroendocrinology Group,
University of Surrey, UK

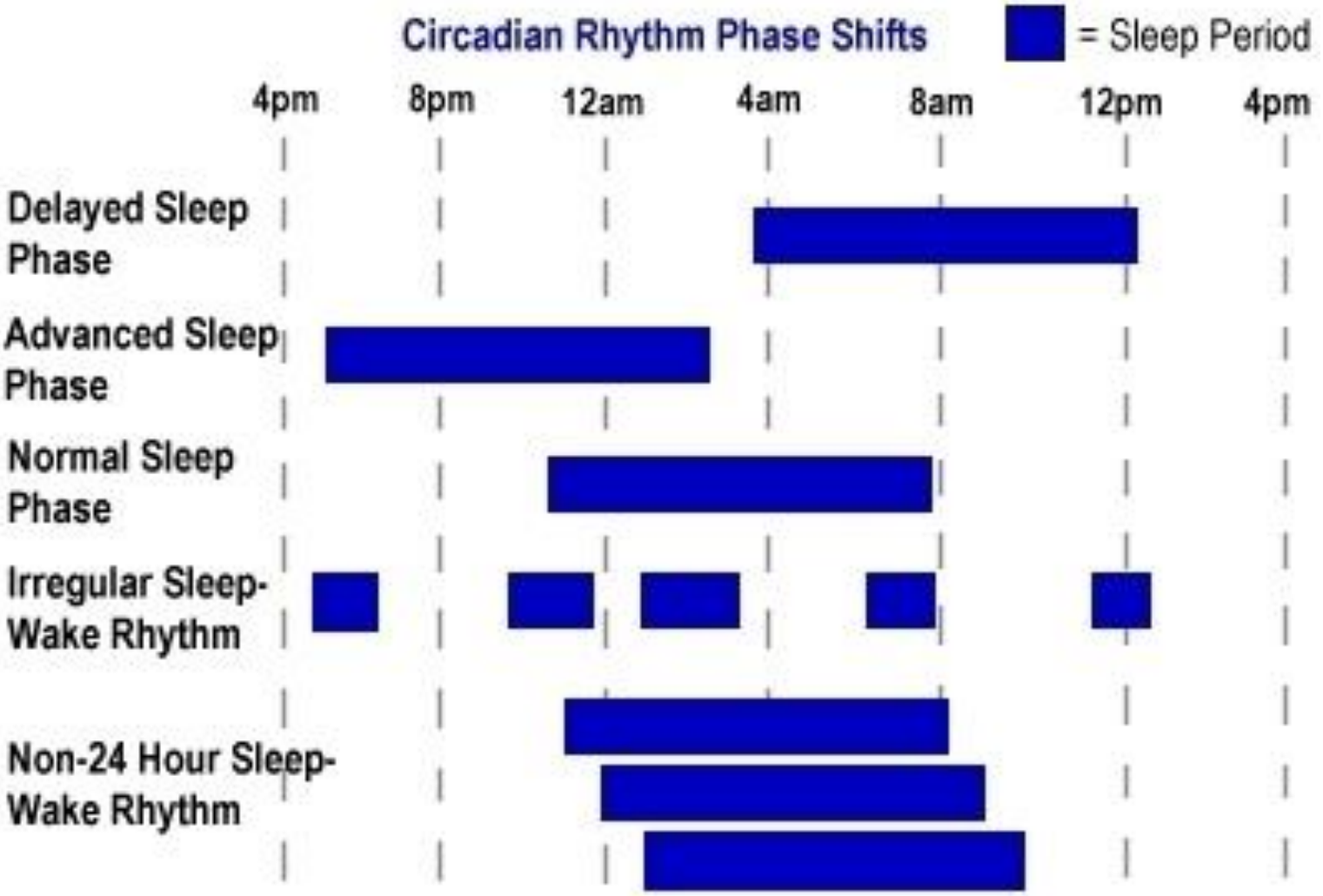


*Sleep/wake cycle
*Hormonal rhythms
*Body temperature rhythms
*Rhythms in appetite/
and metabolism
*Rhythms in drug responses
*Rhythms in mood
*Seasonal rhythms

Disruptions cause jet lag, sleep problems, and mood disorders

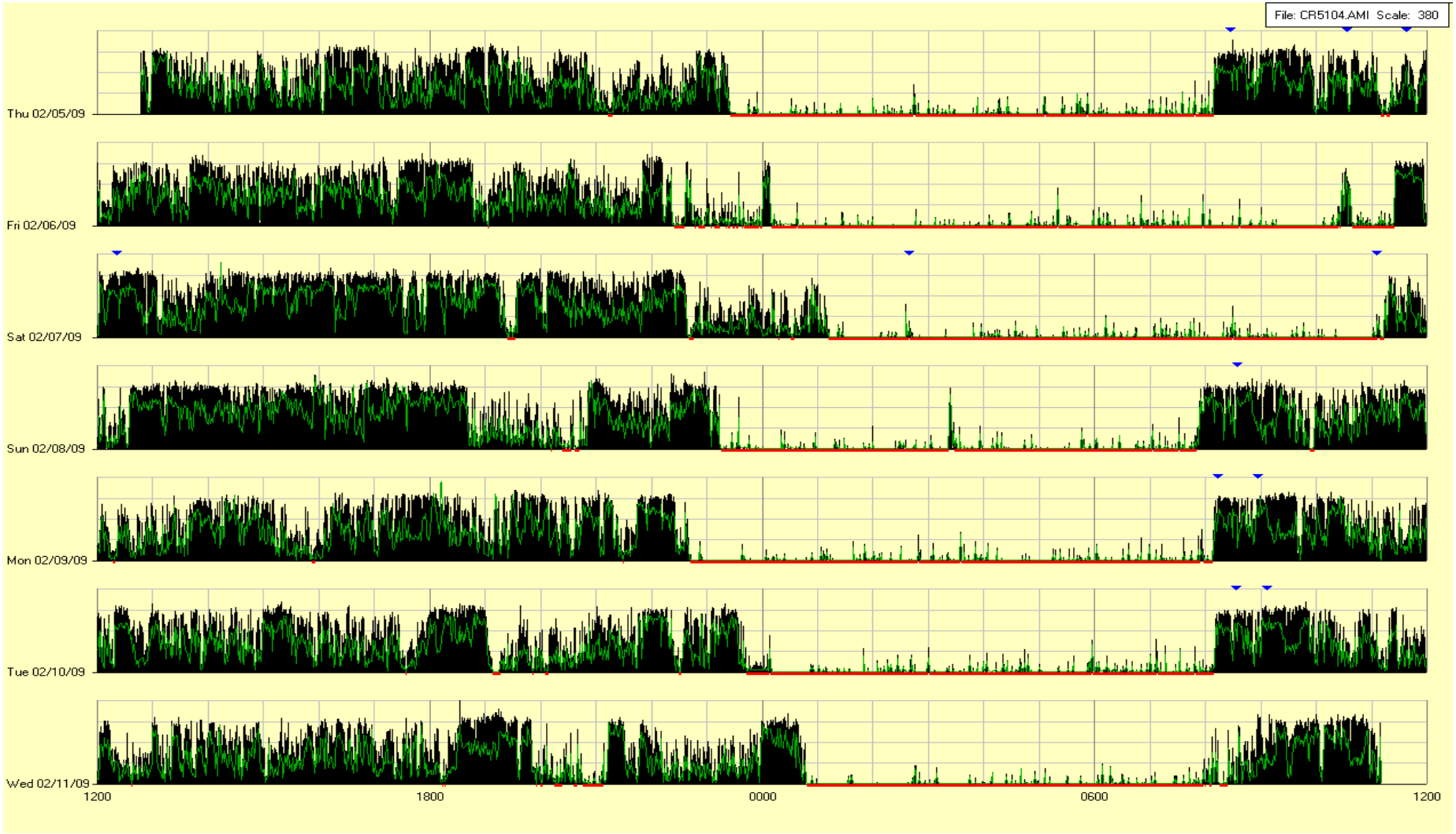
People with psychiatric disorders have abnormal clocks

- 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.

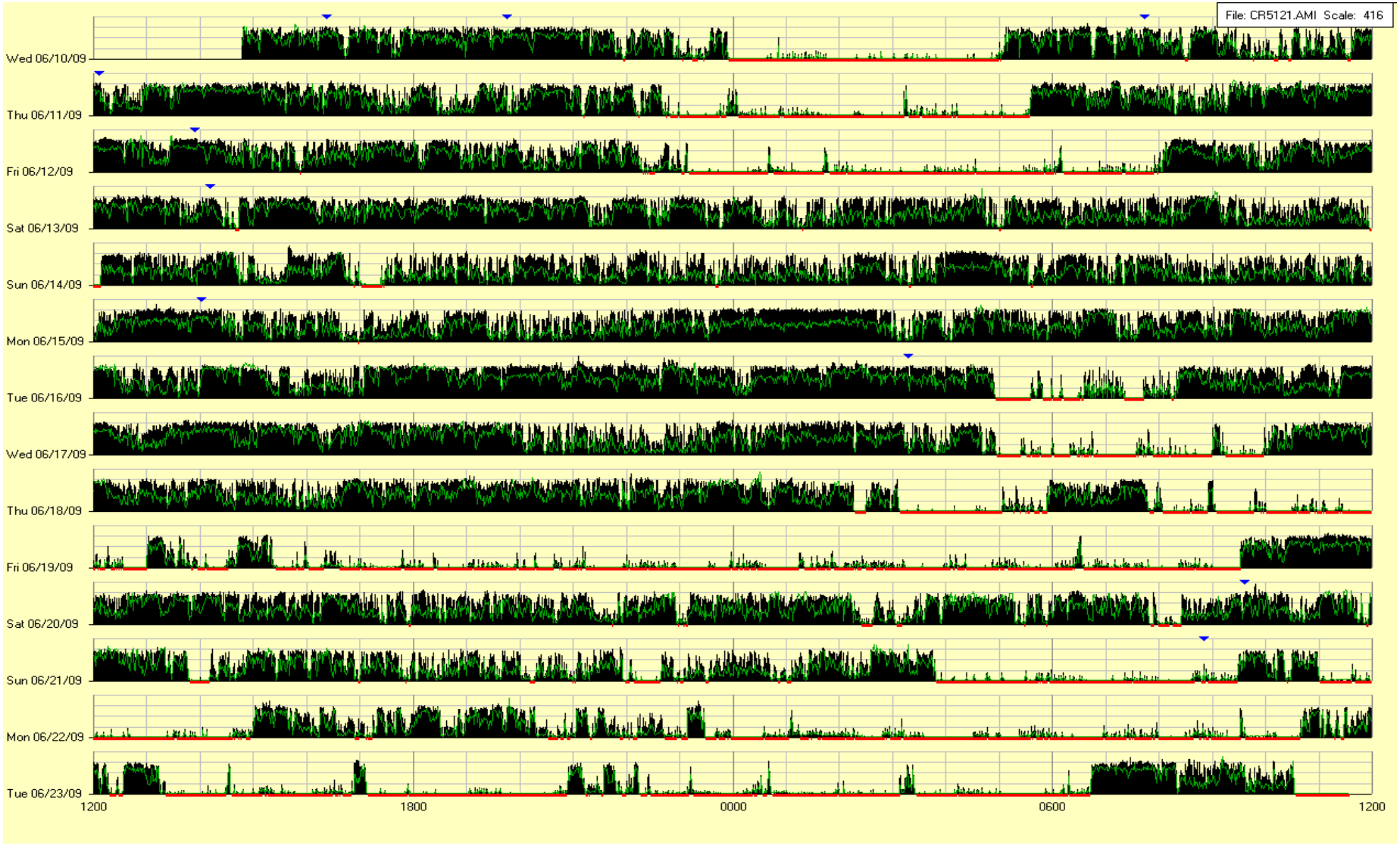

Circadian Rhythm Phase Shifts
= Sleep Period
4pm
8pm
12am
4am
8am
12pm
4pm
Delayed Sleep Phase
Advanced Sleep Phase
Normal Sleep Phase
Irregular Sleep-Wake Rhythm
Non-24 Hour Sleep-Wake Rhythm

Robert Gonzalez, MD
UTSW

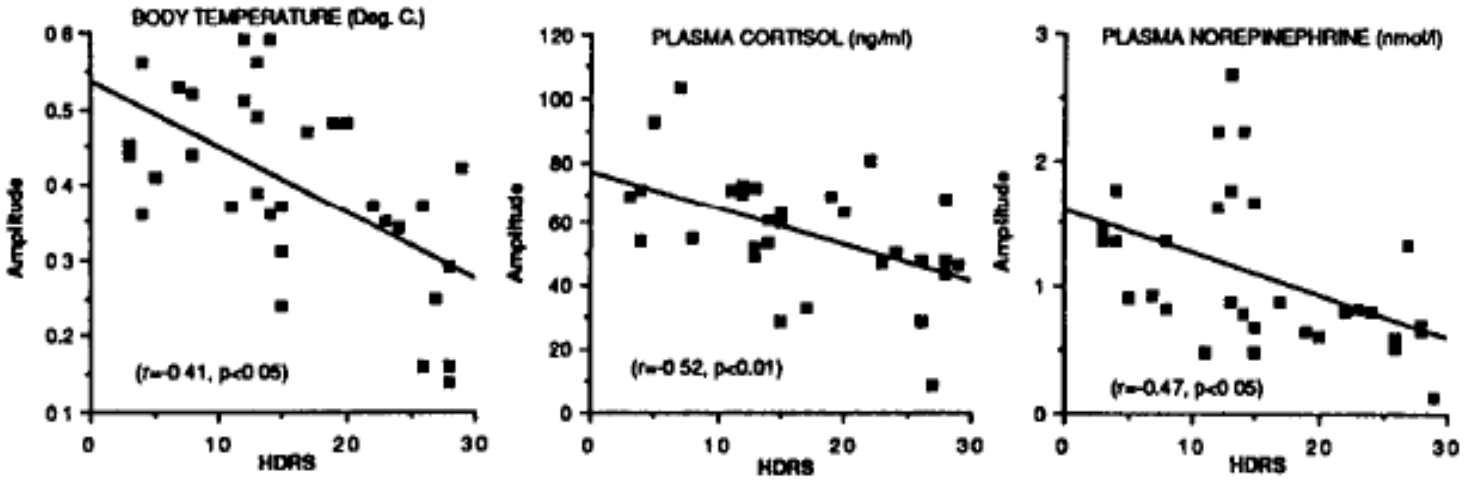
Healthy Control



Bipolar Patient



Reduced rhythm amplitude is associated with increased depression scores

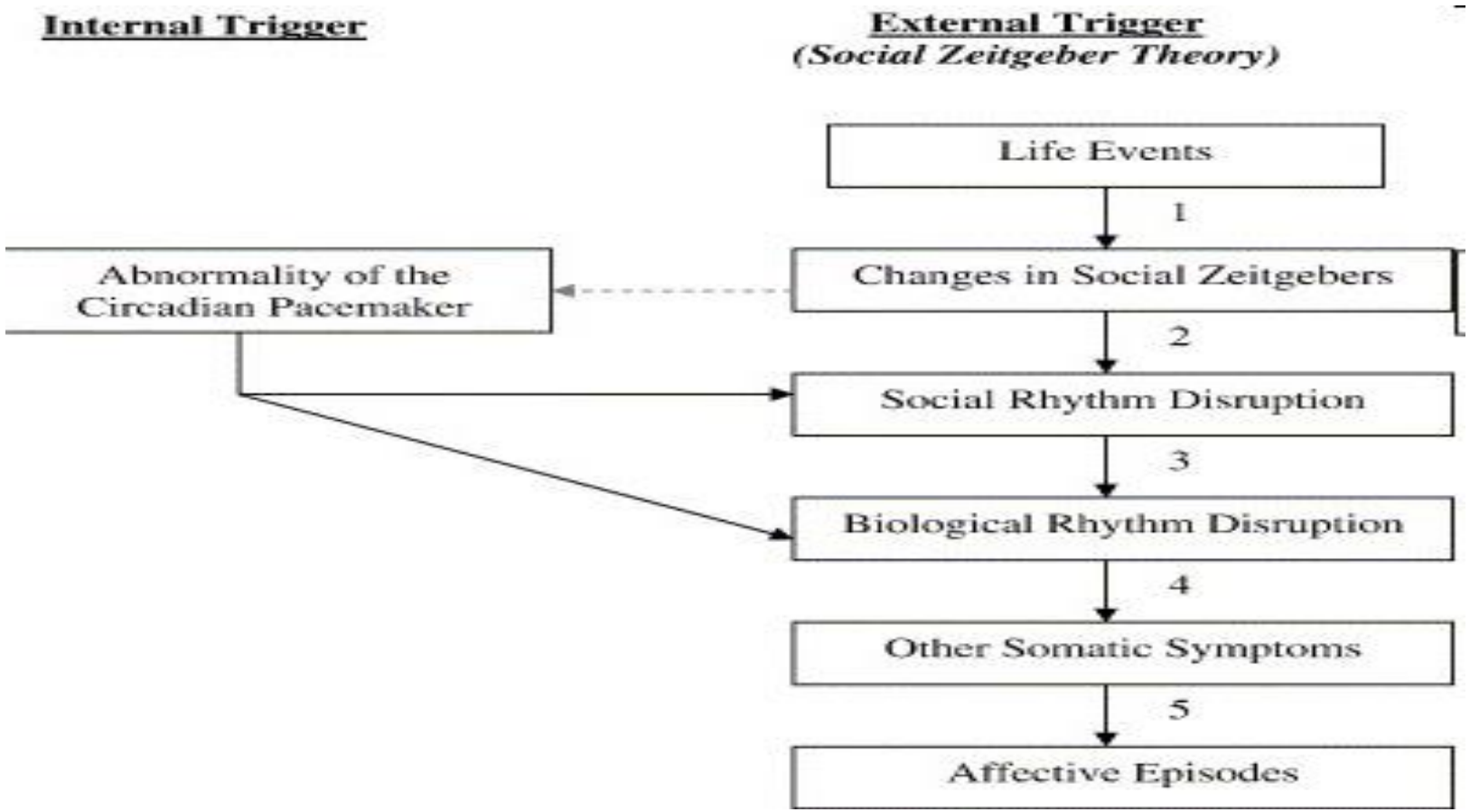


(Souetre et al 1989)

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

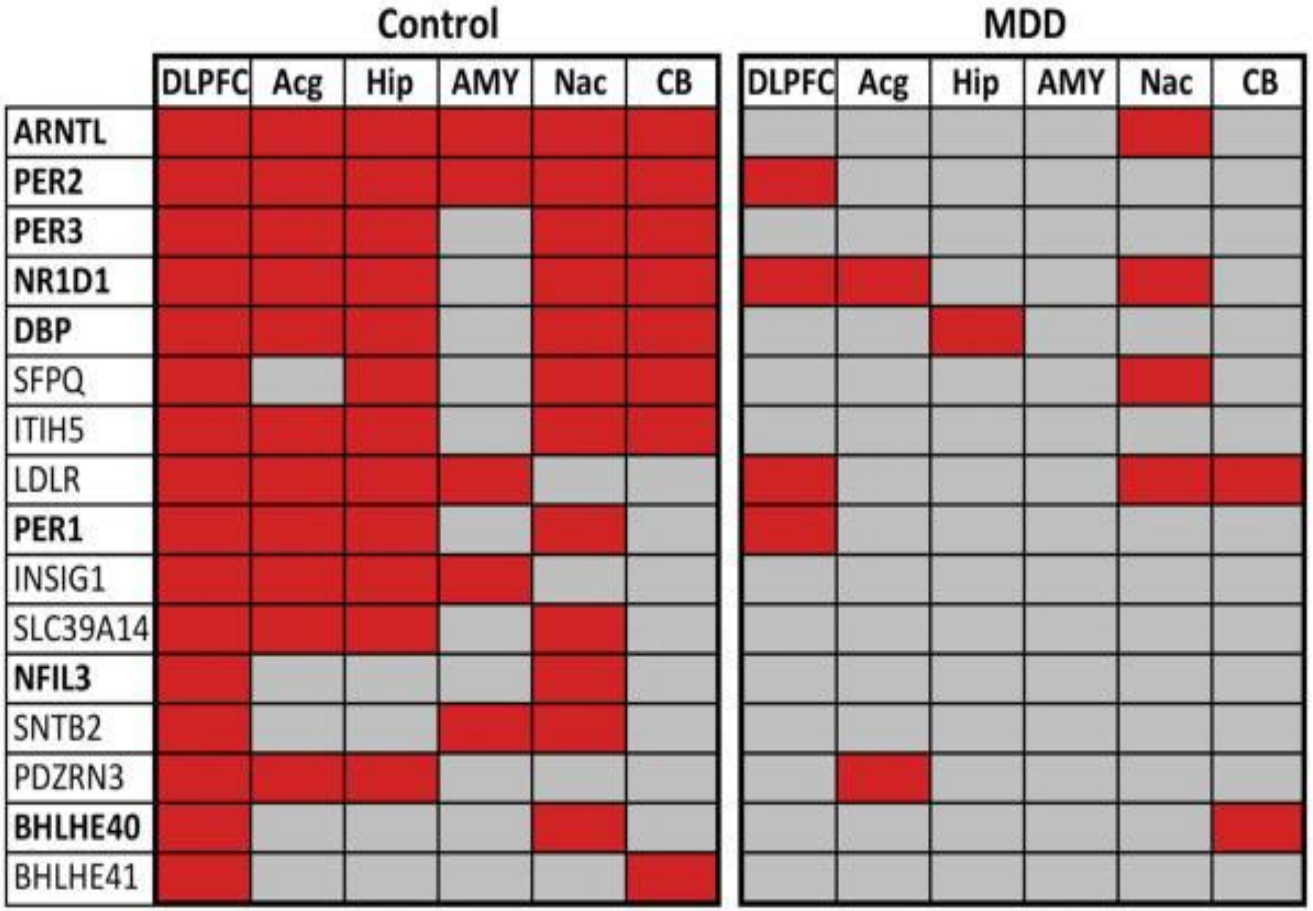
PNAS

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

Jun Z. Li[a,1], Blynn G. Bunney[b], Fan Meng[c], Megan H. Hagenauer[c], David M. Walsh[b], Marquis P. Vawter[b], Simon J. Evans[c], Prabhakara V. Choudary[d], Preston Cartagena[b], Jack D. Barchas[e], Alan F. Schatzberg[f], Edward G. Jones[d,2], Richard M. Myers[g], Stanley J. Watson, Jr.[c], Huda Akil[c,1], and William E. Bunney[b]

[a]Department of Human Genetics and [c]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI 48109; [b]Department of Psychiatry and Human Behavior, University of California, Irvine, CA 92697; [d]Center for Neuroscience, University of California, Davis, CA 95616; [e]Department of Psychiatry, Weill Cornell Medical College, New York, NY 10017; [f]Department of Psychiatry, Stanford University, Palo Alto, CA 94305; and [g]HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806

Rhythmic gene expression is disrupted in MDD patients



Edgar and McClung, 2013

The direction of travel across time zones influences mood state

Br J Psychiatry. 1982 Mar;140:231-5.

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.

East-West= greater depression

West-East= greater hypomania

Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder

Joung-Ho Moon, Chul-Hyun Cho, Gi Hoon Son, Dongho Geum, Sooyoung Chung, Hyun Kim, Seung-Gul Kang, Young-Min Park, Ho-Kyoung Yoon, Leen Kim, Hee-Jung Jee, Hyonggin An, Daniel.F. Kripke, Heon-Jeong Lee

EBioMedicine, 2016, Available online 13 August 2016

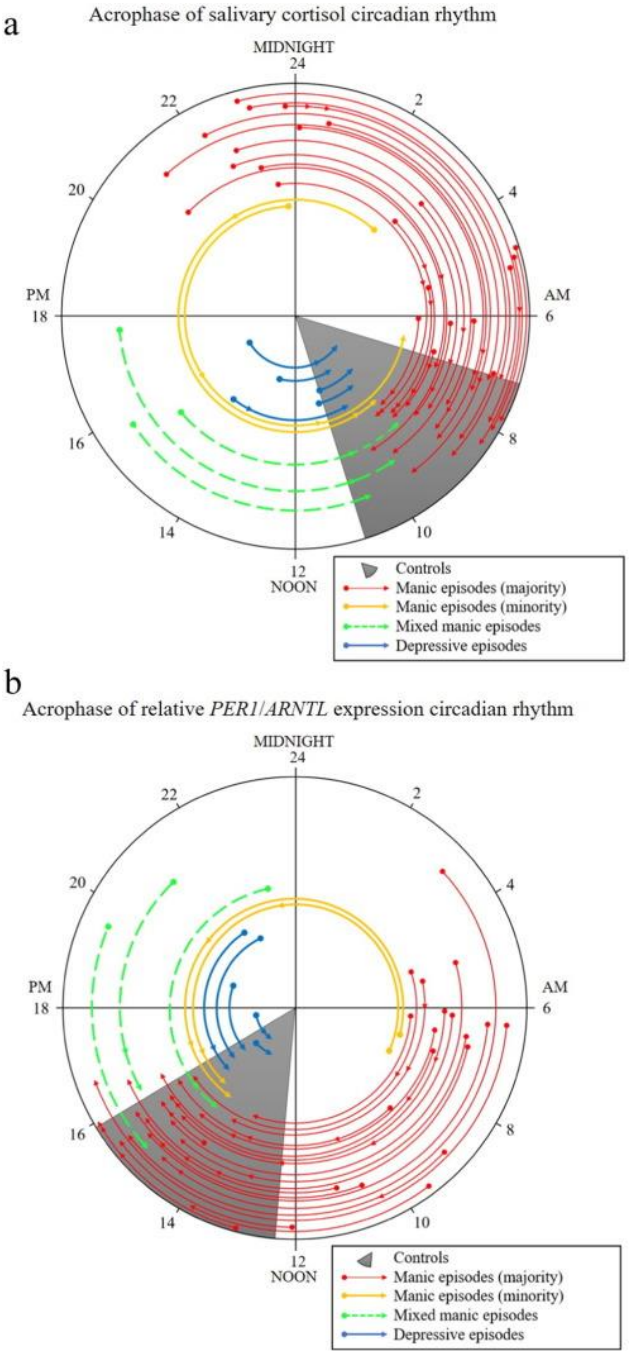
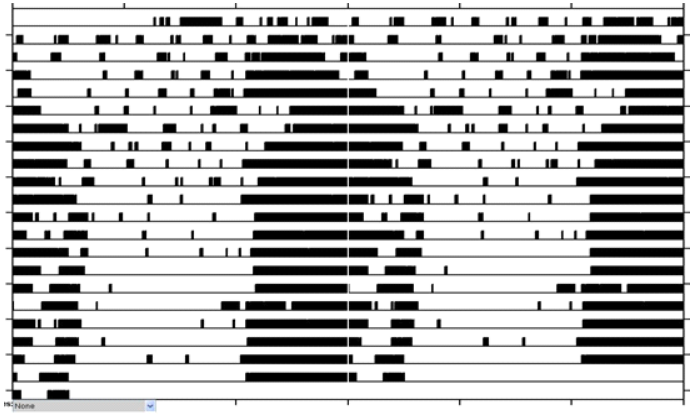


Fig. 1. The shifting of acrophases of circadian rhythms in bipolar disorder patients. Note that the acrophase is the timing of the peak of the best-fitting sine curve.

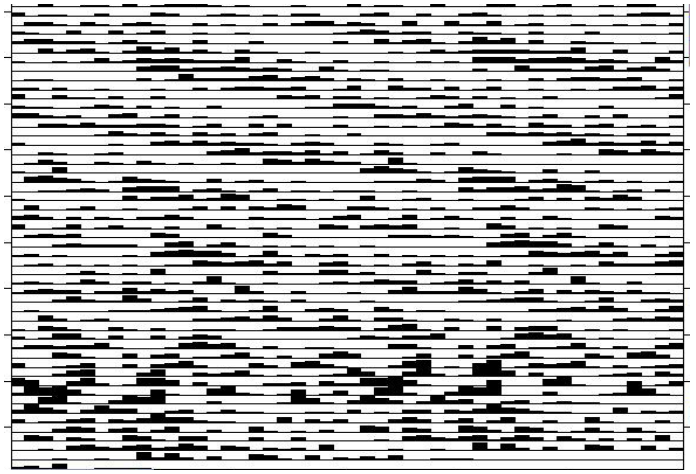
The *Clock* mutant mouse

Clock was identified in a screen of mutagenized mice done in the lab of Joe Takahashi (Vitaterna et al.,1994).

Normal mouse



Clock mutant mouse



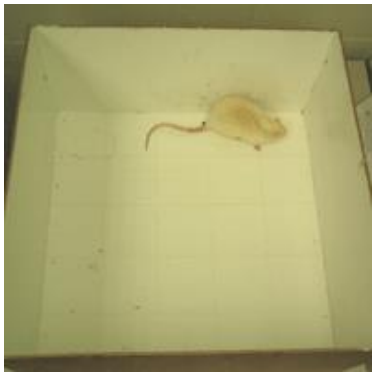

How do you feel?
Anxious? Depressed?

Models of Depression, Anxiety, Exploratory Drive and Reward in Mice

Forced Swim Test

Learned Helplessness

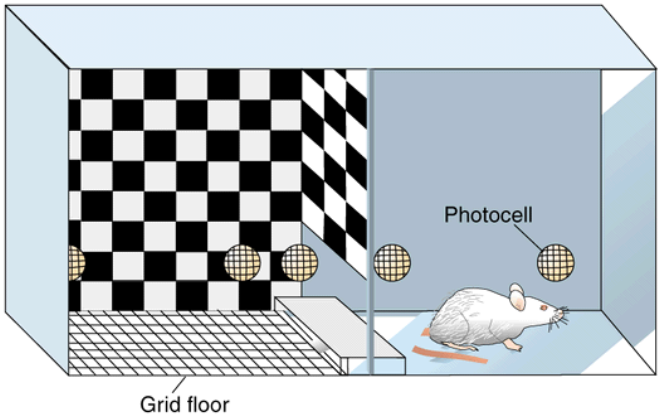
Open field



Elevated Plus Maze

Light/dark test

Conditioned Place Preference



Sucrose preference

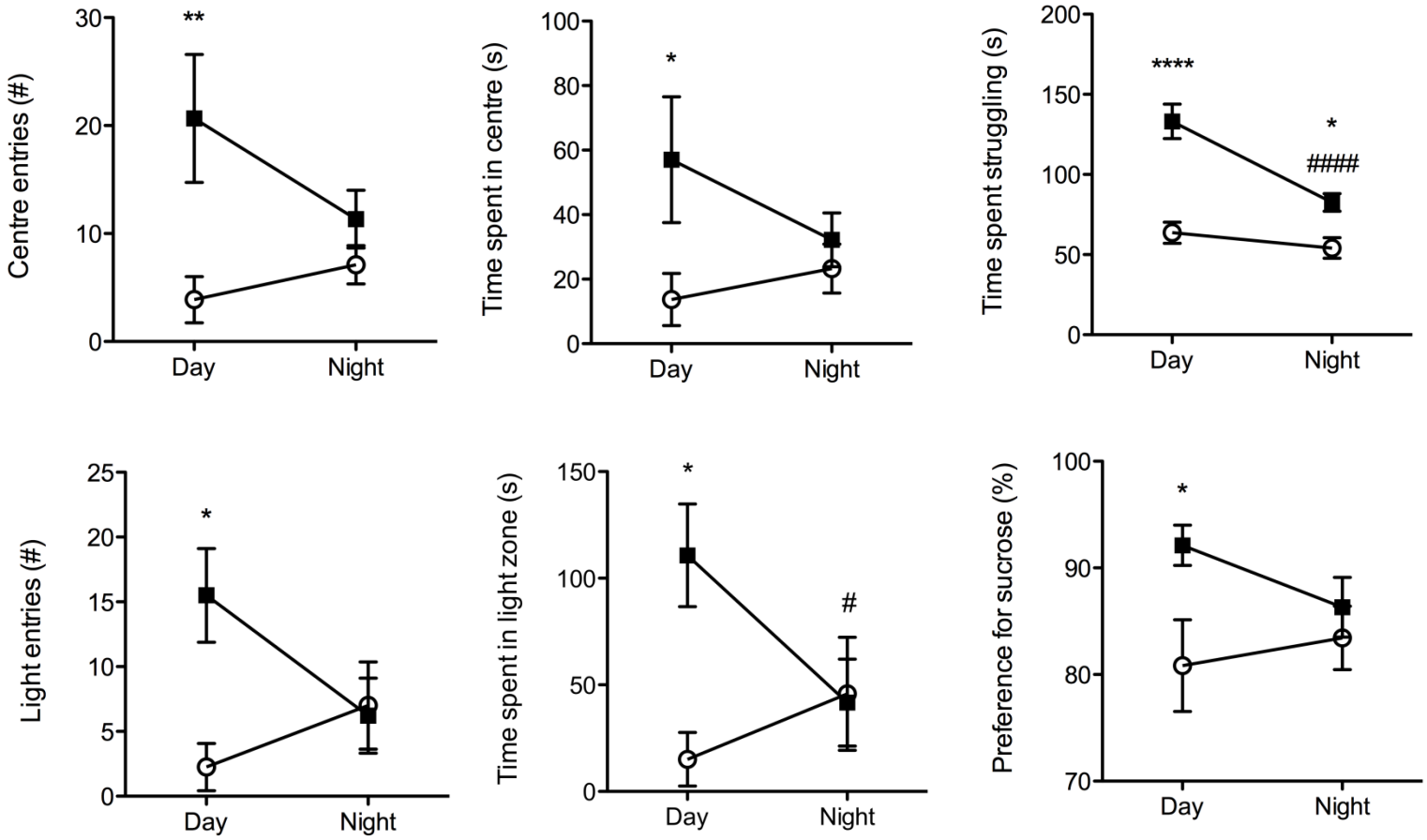
The *Clock* mutant mice display similarities With bipolar mania and other psychiatric disorders

Bipolar patients	***Clock* mutant mice**
Hyperactivity	Hyperactivity
Decreased need for sleep	Sleep less than wild type mice
Feelings of euphoria	Less depression-like behavior
Excessive involvement in activities that have a high potential for painful consequences.	Have increased impulsivity, novelty seeking, risk taking in behavioral models
Propensity towards drug use and abuse	Are more sensitive to the rewarding effects of cocaine, sucrose, and brain stimulation

Lithium or VPA treatment reverses these phenotypes

Roybal *et al*., *PNAS* (2007); Ozburn et al., *NPP* (2013); Arey et al., *Mol Psych* (2014); Ozburn et al., *Psychopharm* (2012); Coque et al., *NPP* (2011); Naylor et al., J Neurosci (2000); Easton et al., *Genes Brain Behav* (2003); McClung et al., *PNAS* (2005); Van Enkhuizen et al., *Behav Brain Res* (2013)

*Clock*Δ19 mice display rapid mood cycling with manic-like behavior during the day and euthymic-like behavior at night

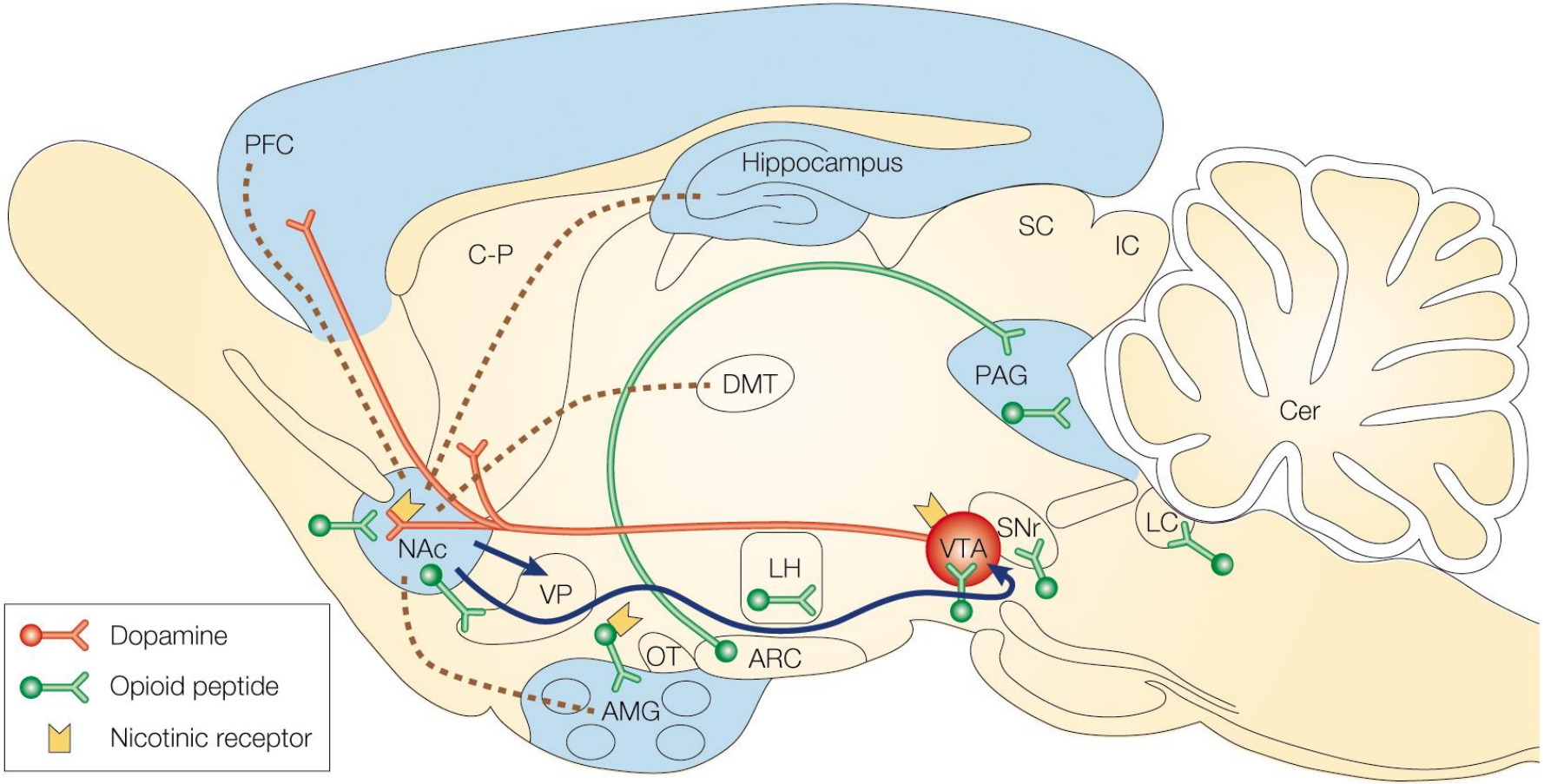


Sidor et al., Mol Psych, *2015*

Dopamine is important in psychiatric disorders

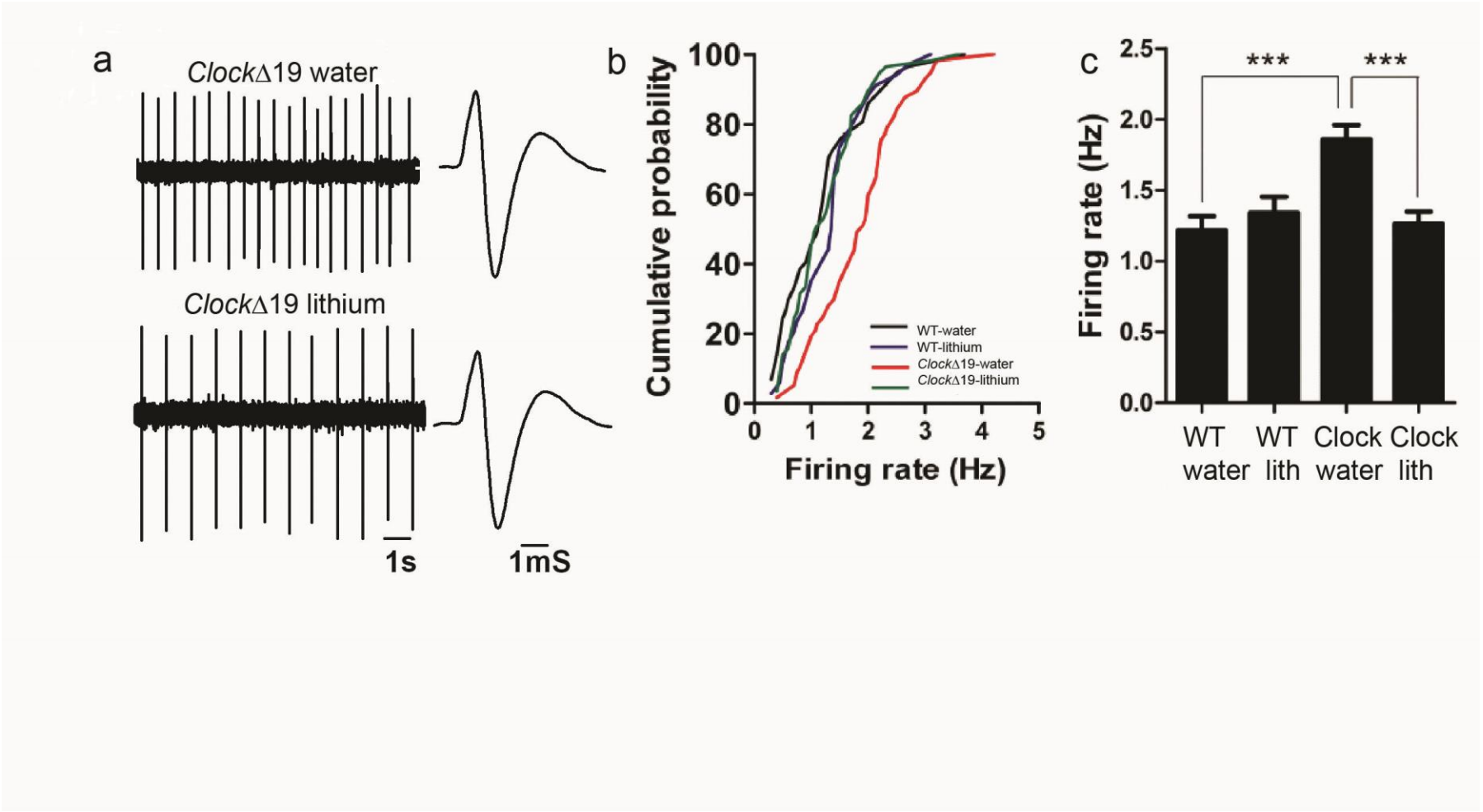
- Mania is associated with increased dopaminergic transmission in striatal regions, while some models of depression produce decreased dopamine.
- Antipsychotic drugs antagonize Drd2 receptors
- All drugs of abuse activate the VTA dopamine system. Stimulants like cocaine directly bind to the dopamine transporter

BRAIN REWARD REGIONS



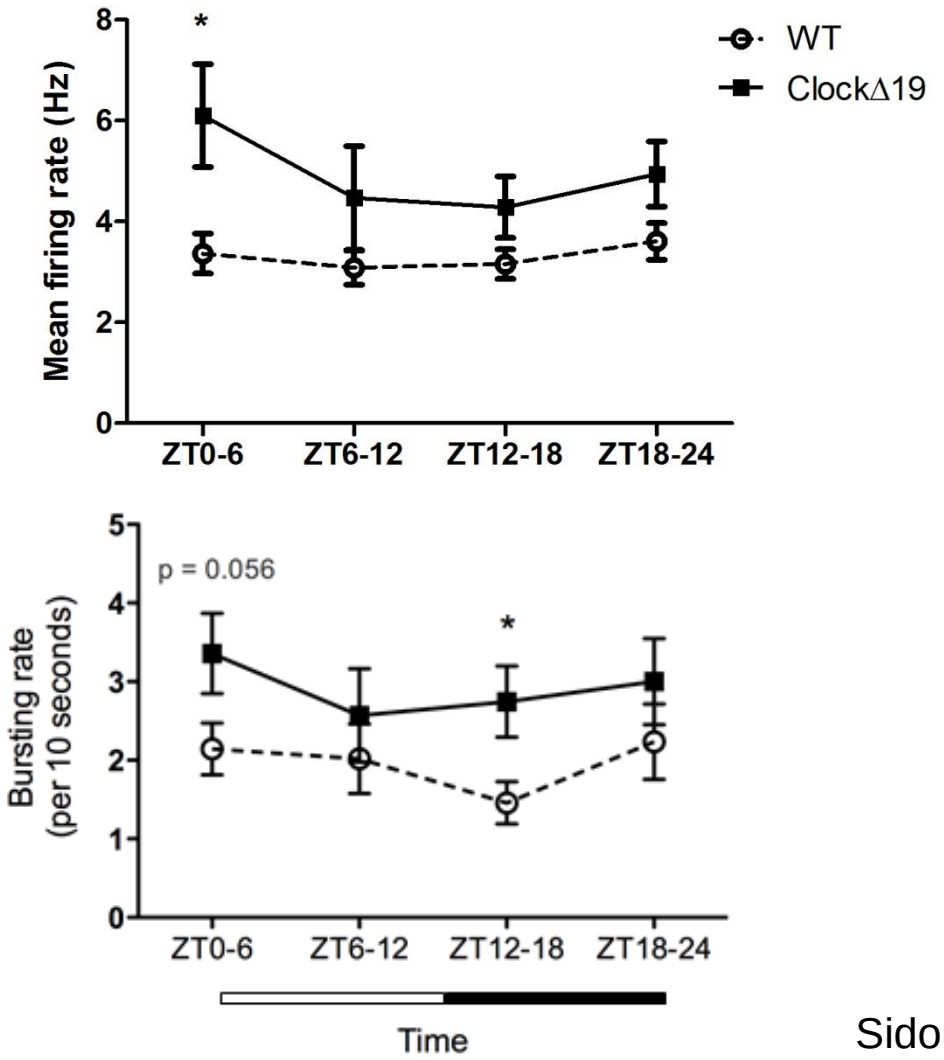
Nestler et al., (2003)

Clock mutant mice have an increase in VTA dopamine cell firing and this Is rescued by chronic lithium treatment



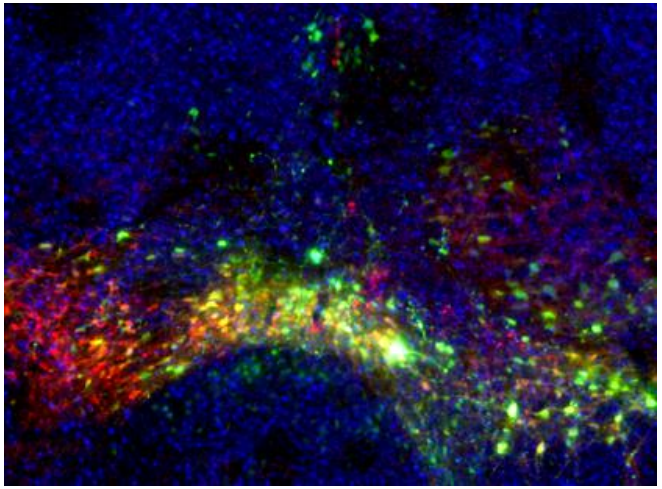
Coque et al., *Neuropsychopharm (*2011)

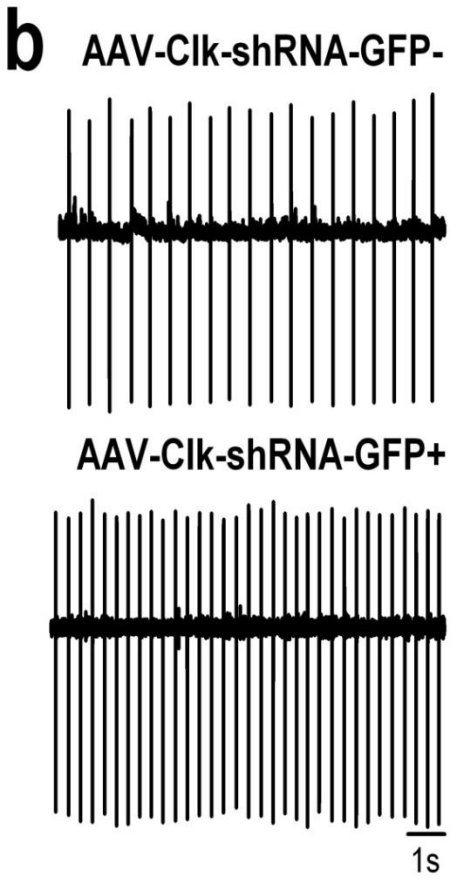
*Clock*Δ19 mice have a large increase in daytime dopaminergic activity

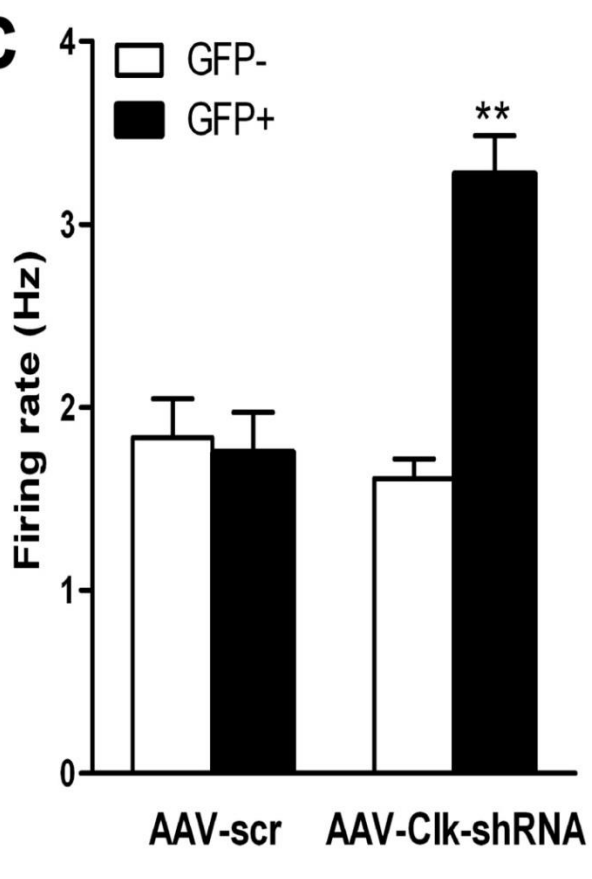


Sidor et al., *Mol Psych 2015*

Clock knockdown mice have higher rates of dopamine cell firing

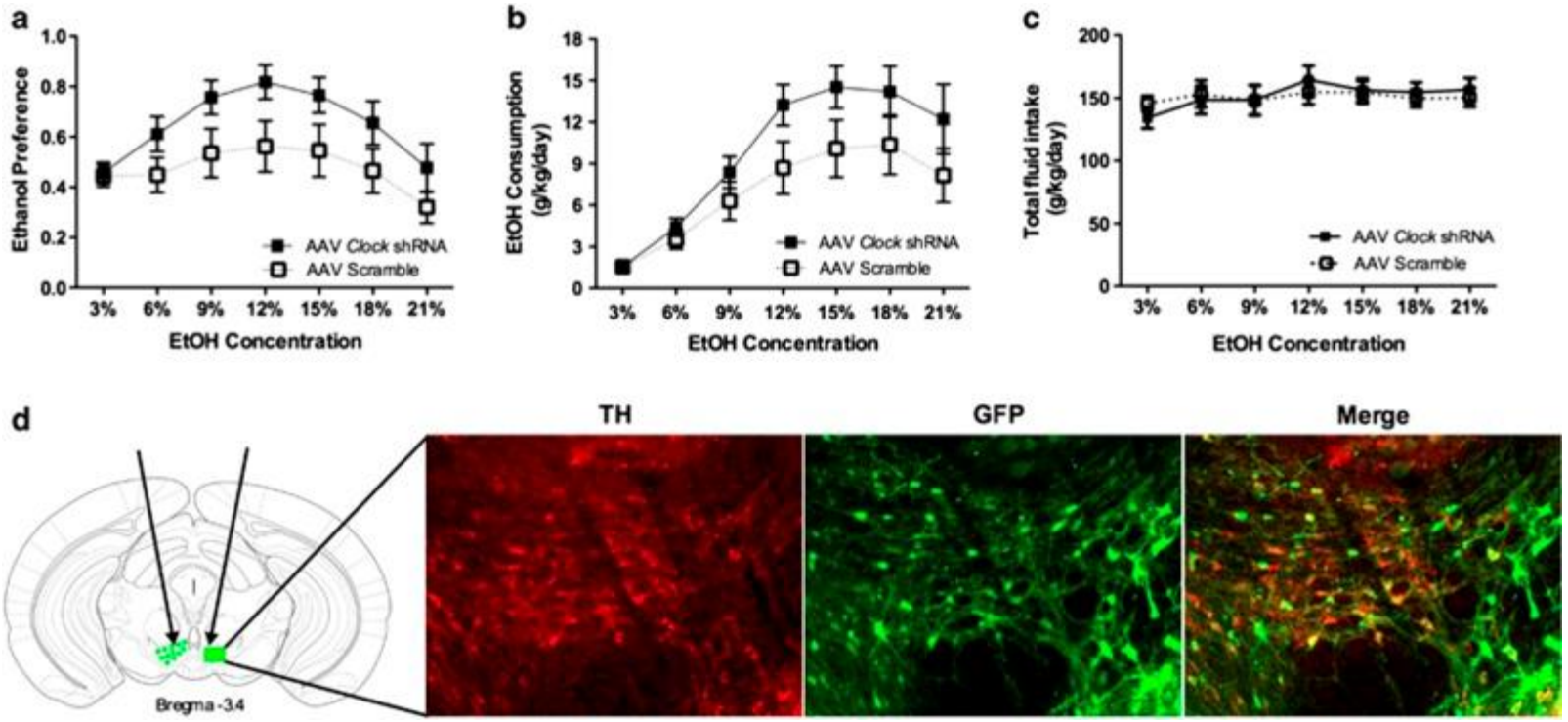






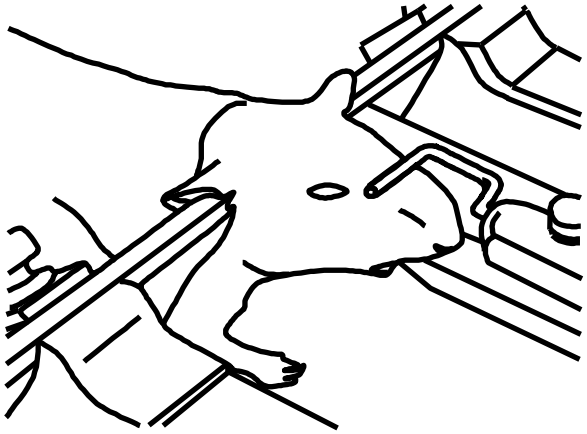
Mukherjee et al, *Biological Psychiatry, 2010*

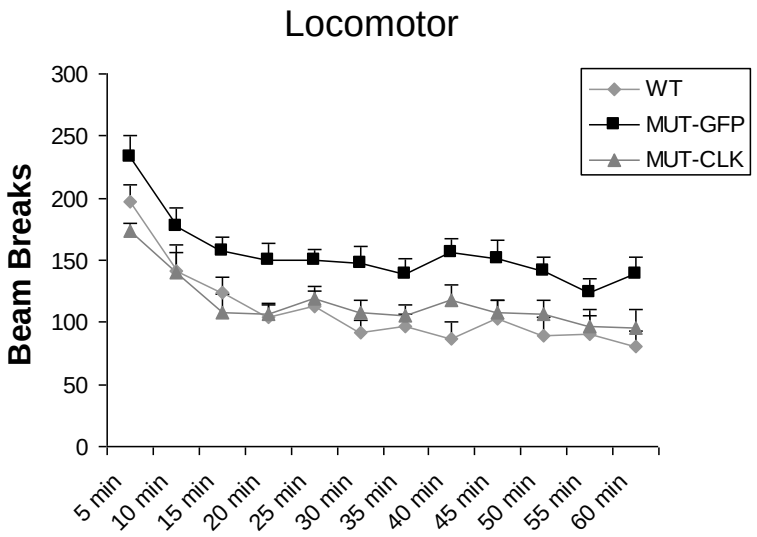
Clock knock-down in the VTA increases alcohol preference

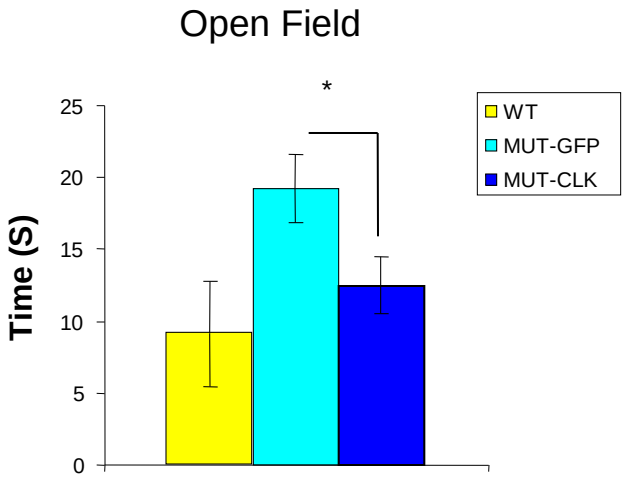


Ozburn et al., Neuropsychopharm, 2013

Viral expression of functional CLOCK in the VTA is able to rescue their behavioral abnormalities

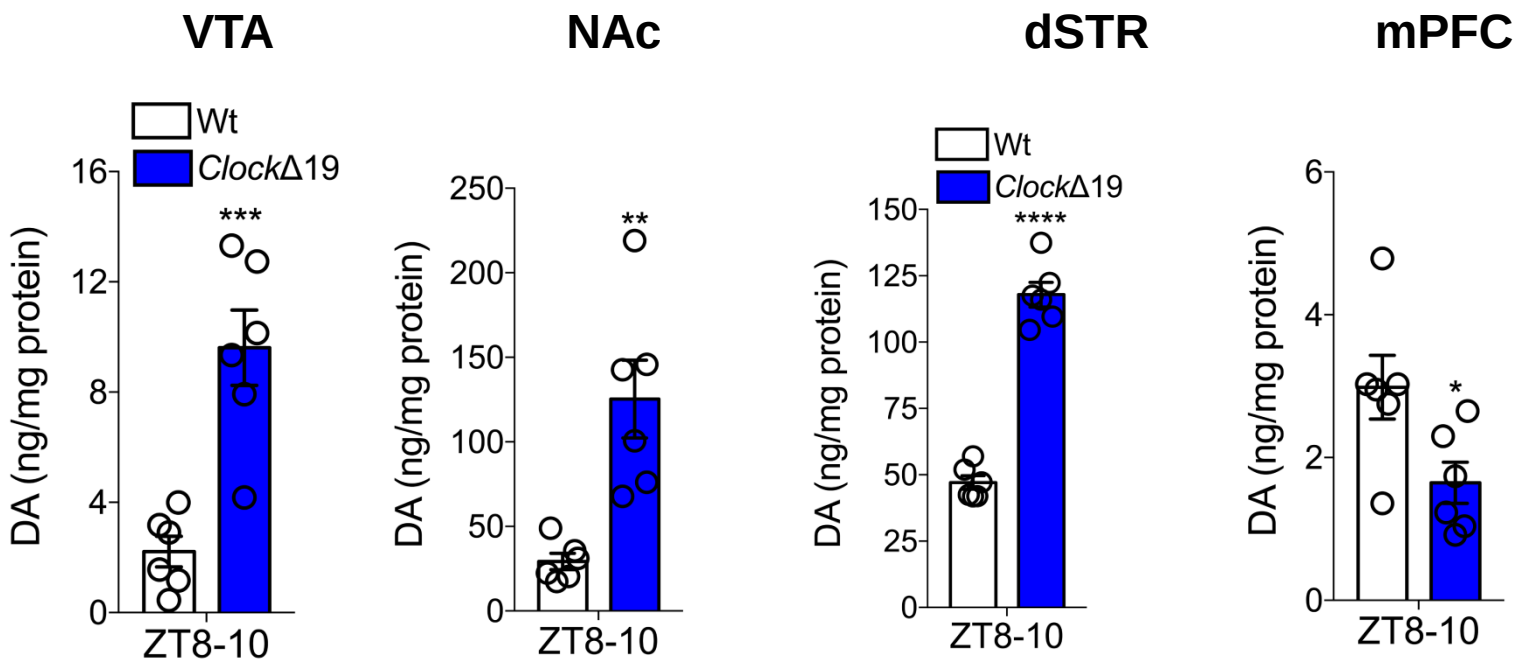






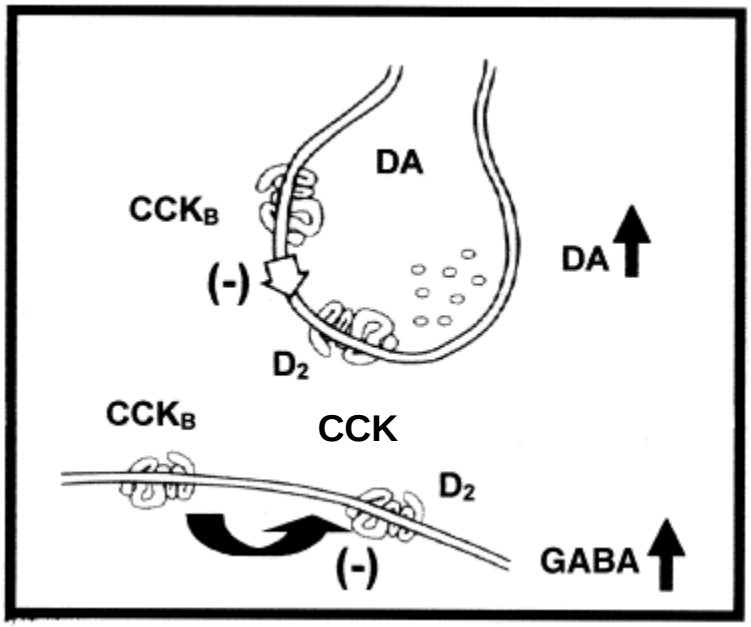
Roybal *et al*., *Proc. Natl. Acad. Sci.* (2007)

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

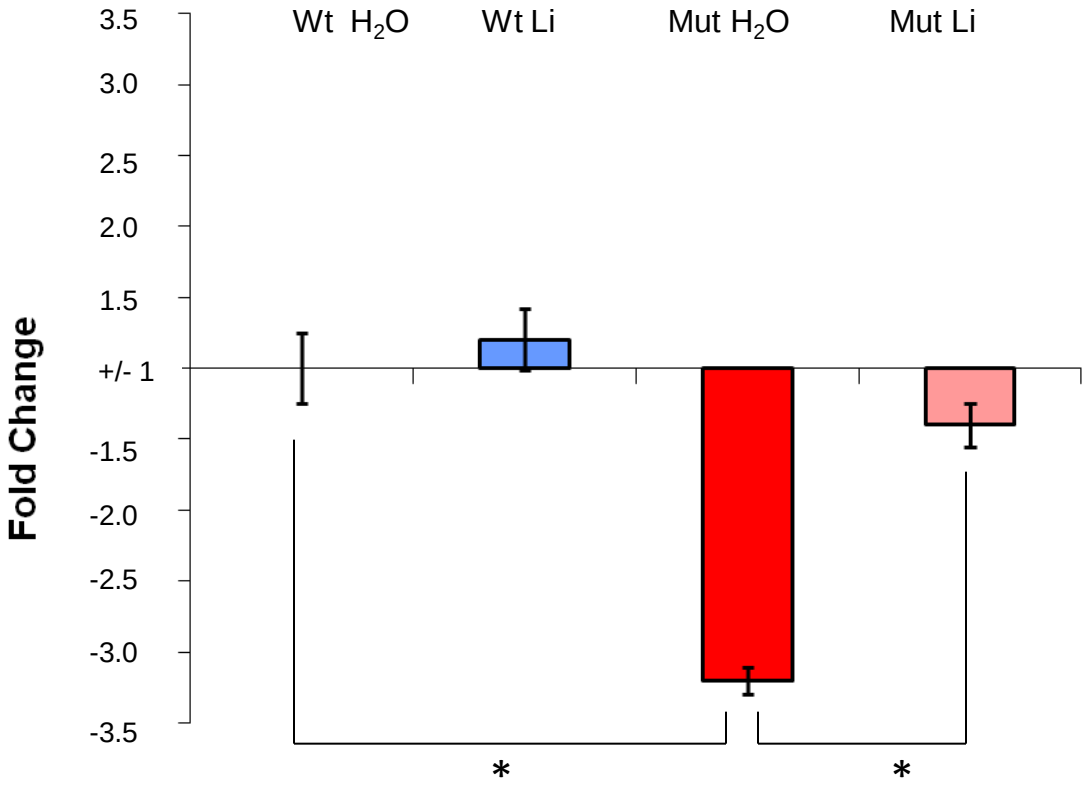


Logan et al., *Molecular Psychiatry, in press*

How does lithium work?

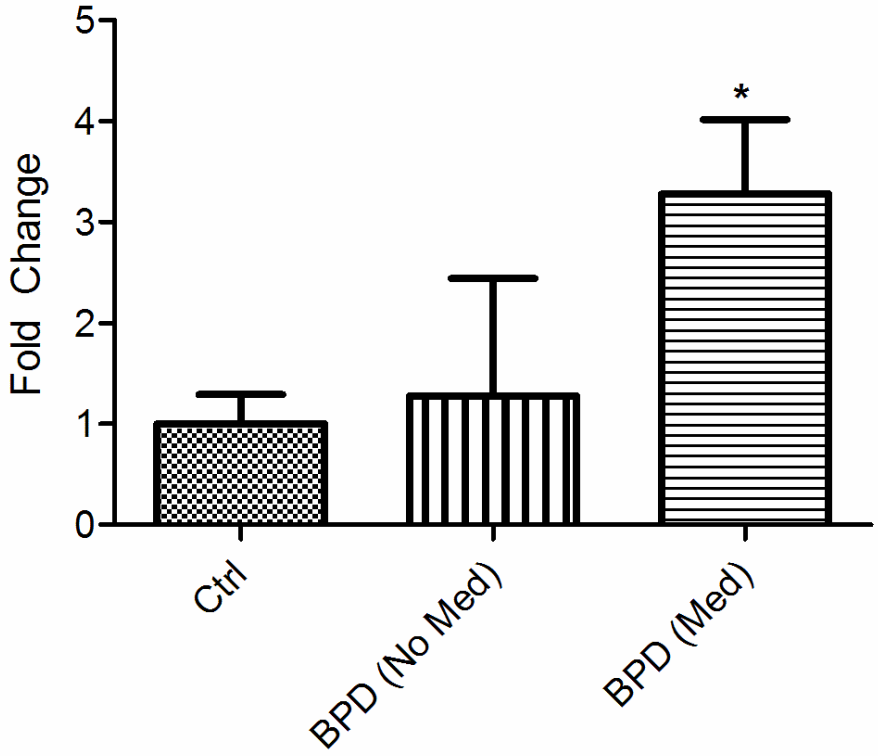


Tanganelli et al., 2001

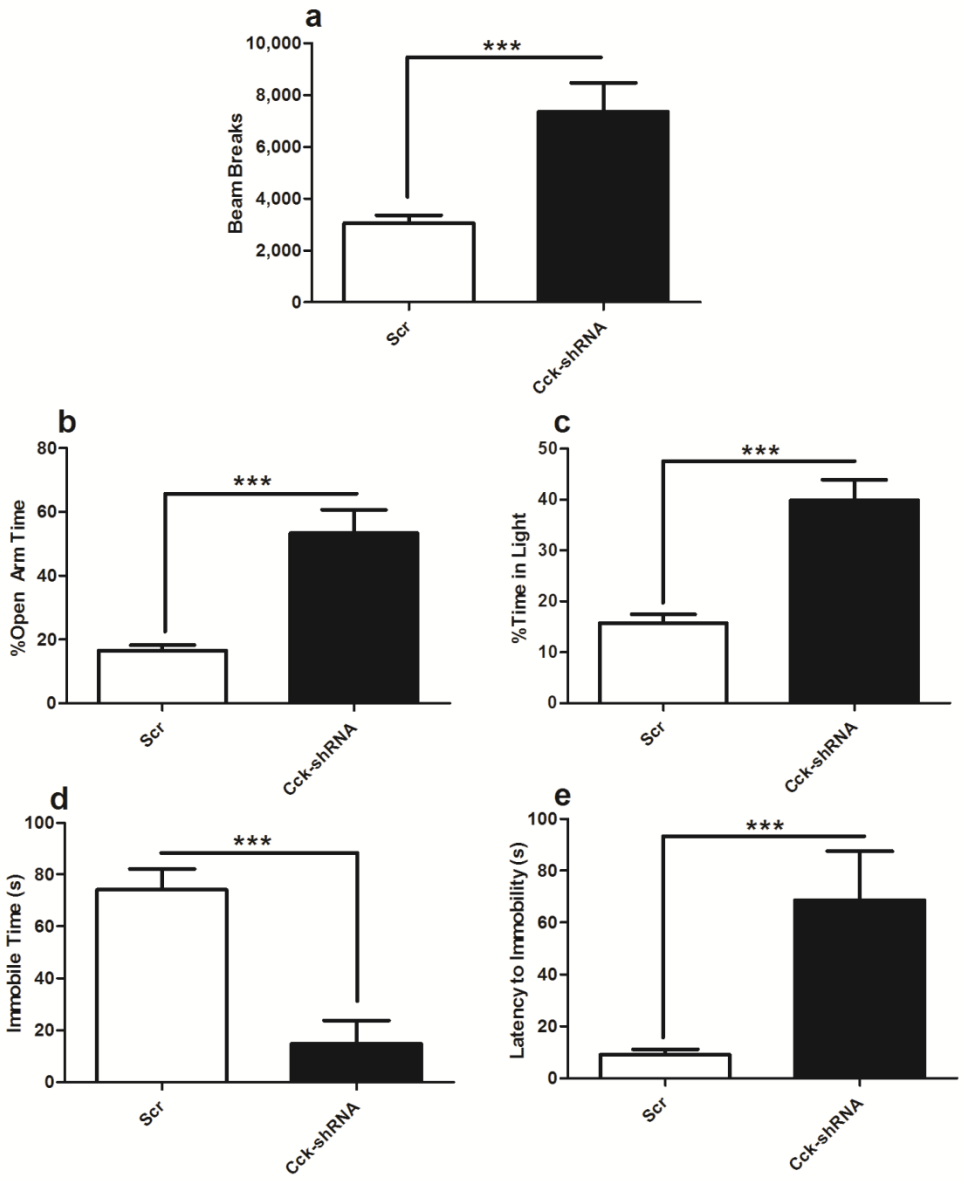


Arey et al, *Mol. Psych 2013*

CCK levels are increased in the VTA of bipolar patients on meds

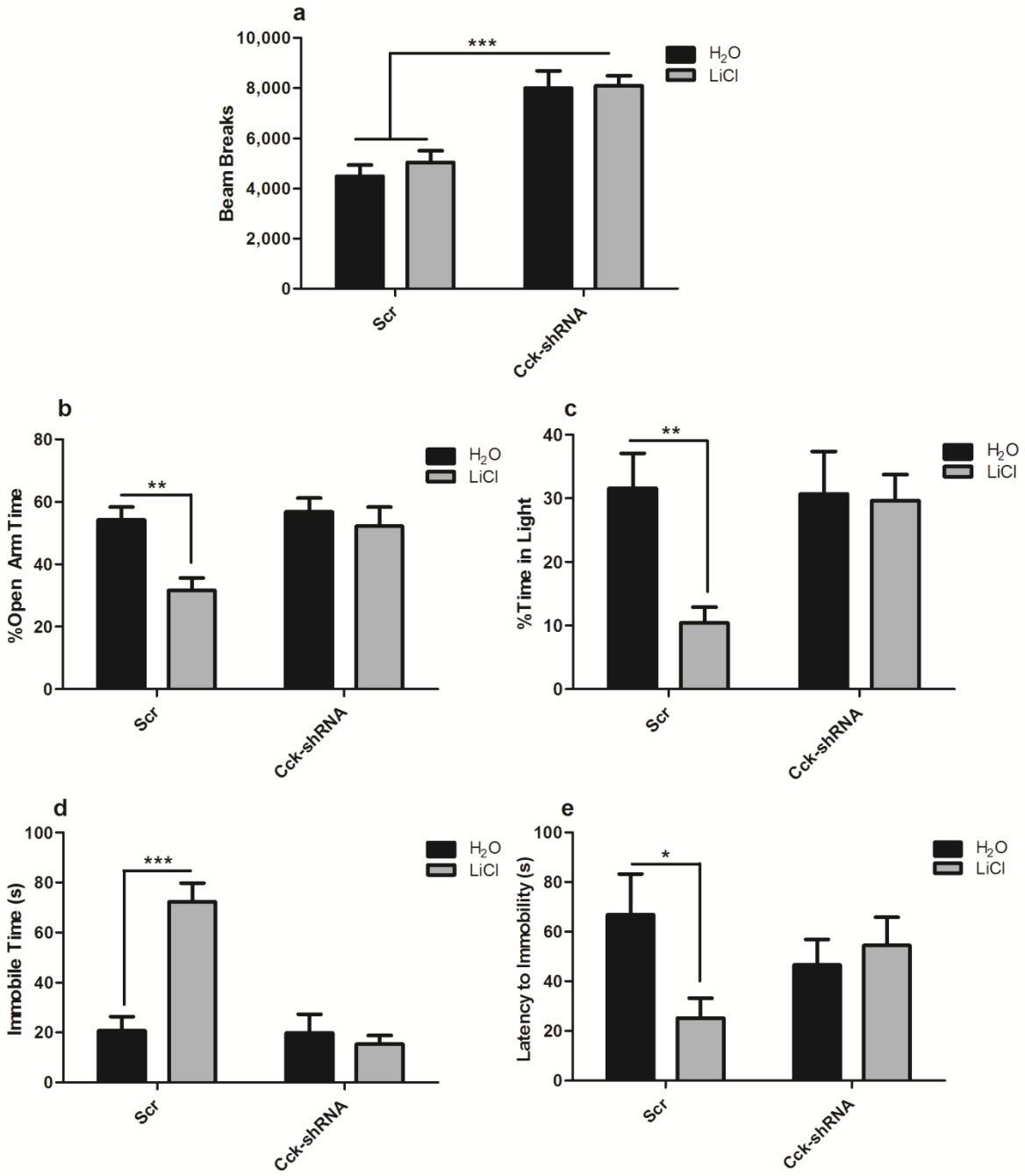


Arey et al, *Mol. Psych 2013*



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

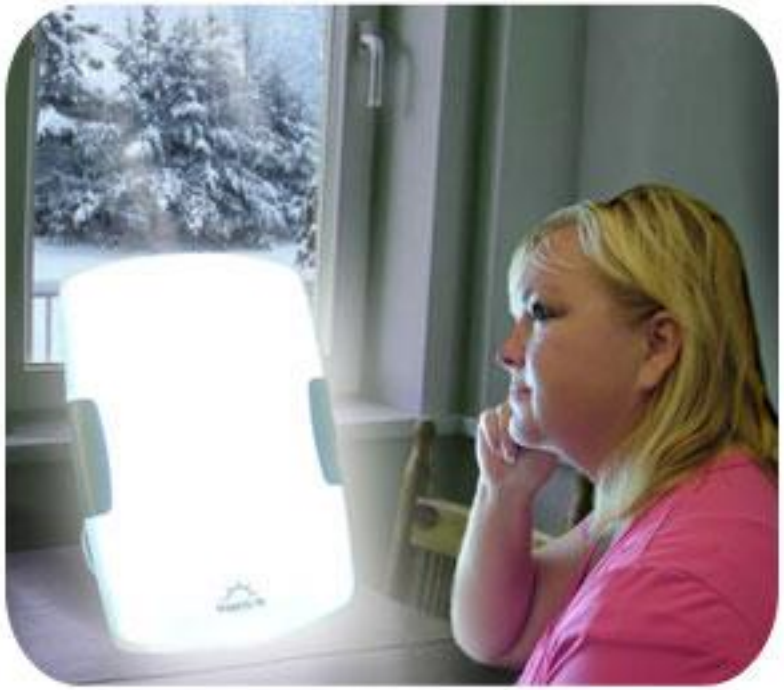
Arey et al, *Mol. Psych 2013*



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

SRM II–5

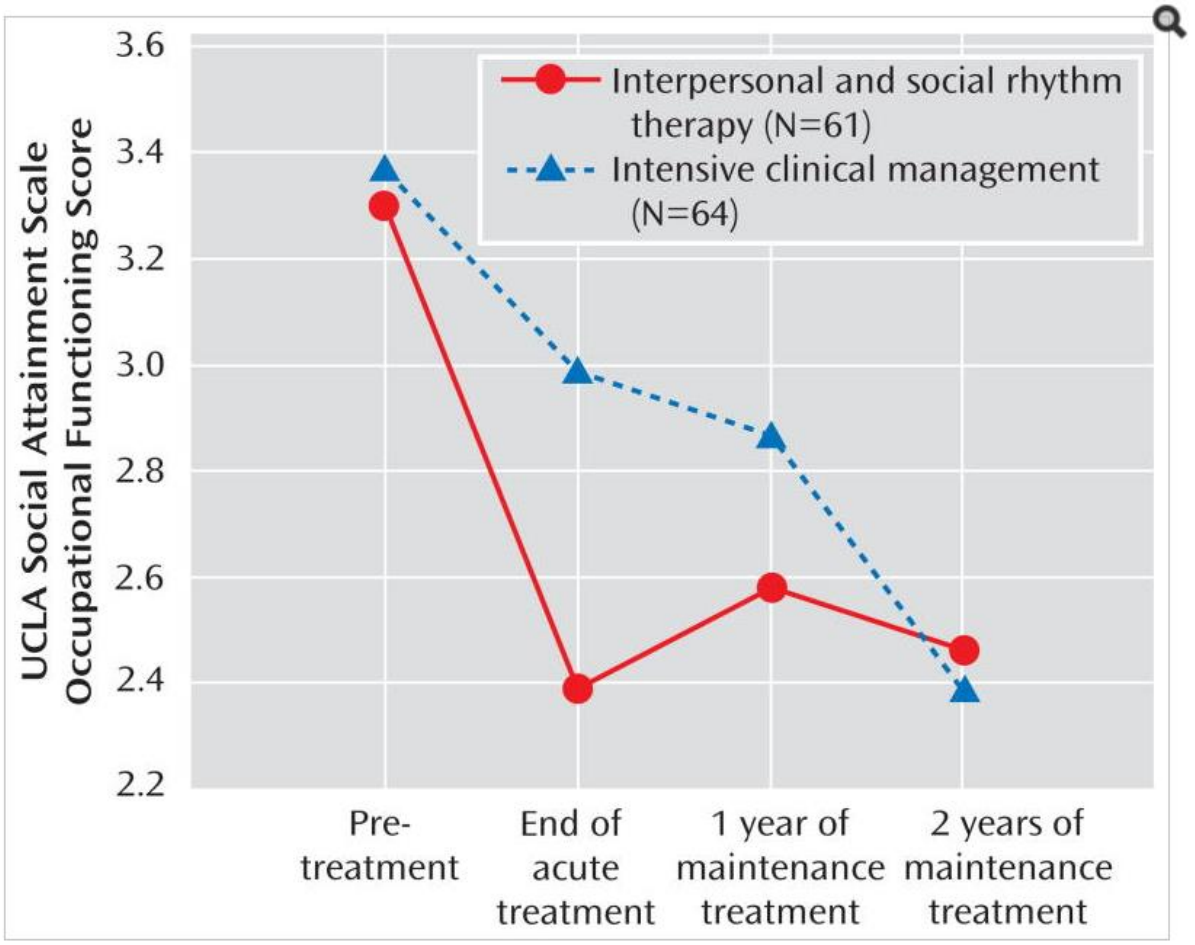
Directions:

- 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

Date (week of):

Activity	Target Time	Sunday		Monday		Tuesday		Wednesday		Thursday		Friday		Saturday	
		Time	People	Time	People	Time	People	Time	People	Time	People	Time	People	Time	People
Out of bed															
First contact with other person															
Start work/school/ volunteer/family care															
Dinner															
To bed															
Rate MOOD each day from –5 to +5 –5 = very depressed +5 = very elated															

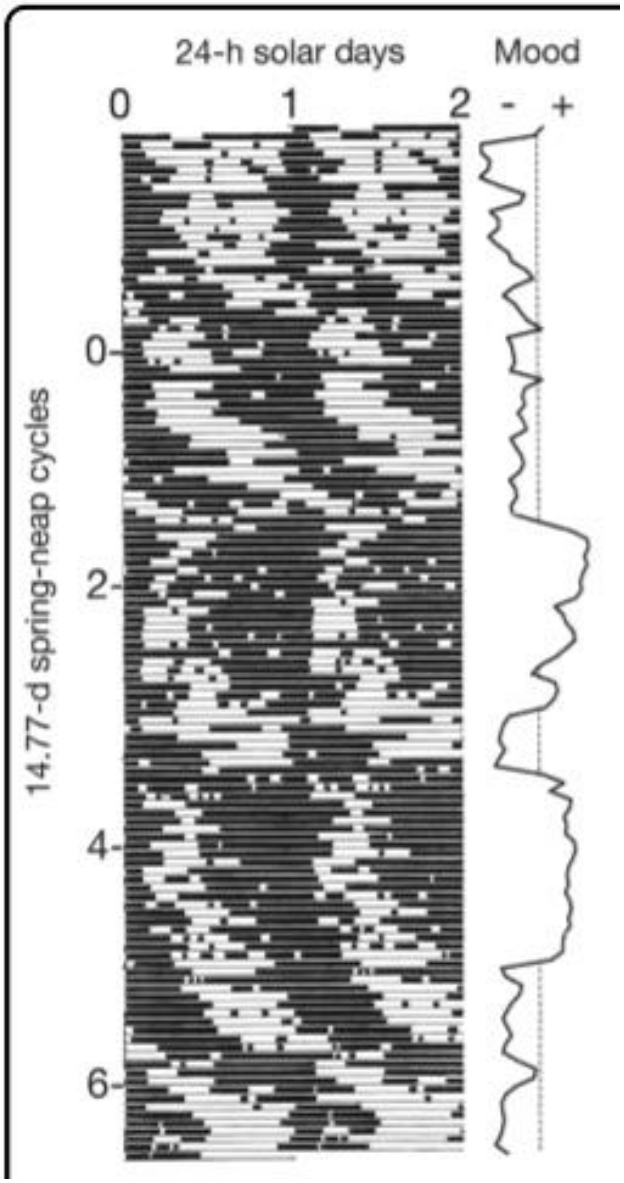
Interpersonal and Social Rhythm Therapy leads to greater occupational functioning in a shorter amount of time than traditional psychotherapy



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[a]

[a] Lower scores indicate improved occupational functioning.

Frank et al., 2008



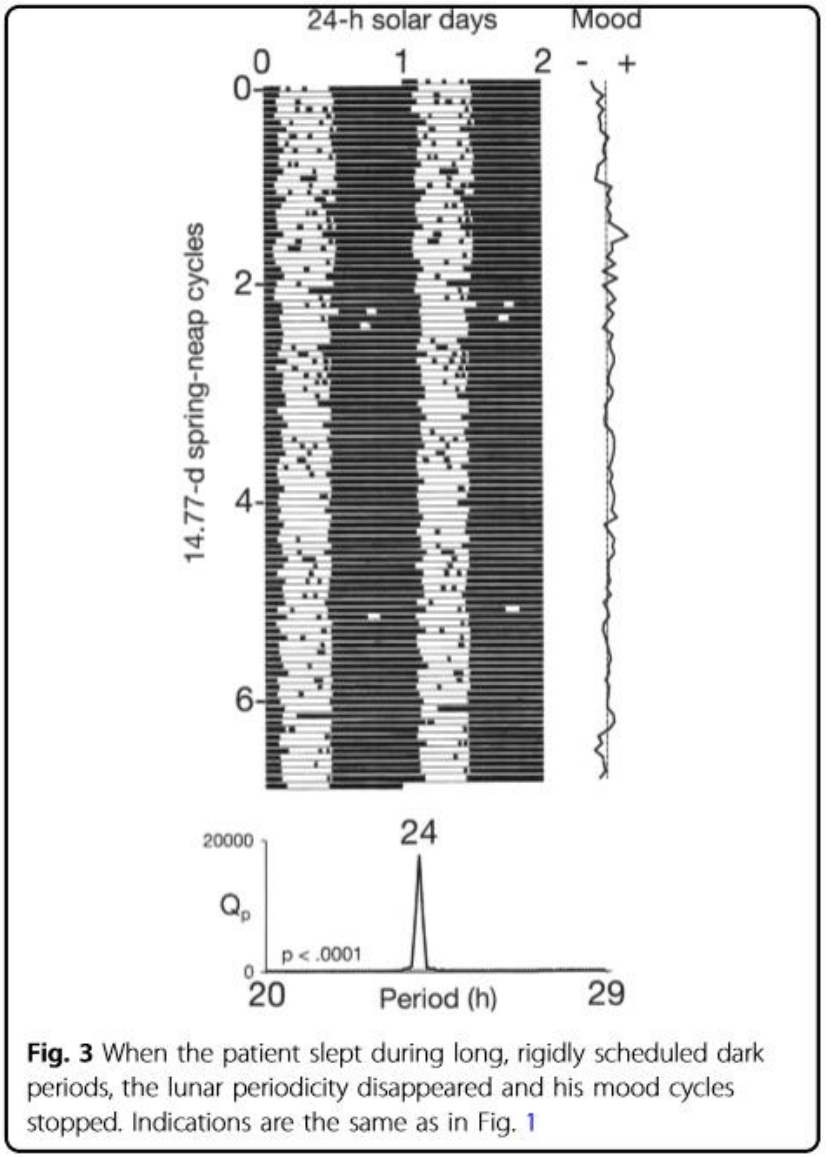


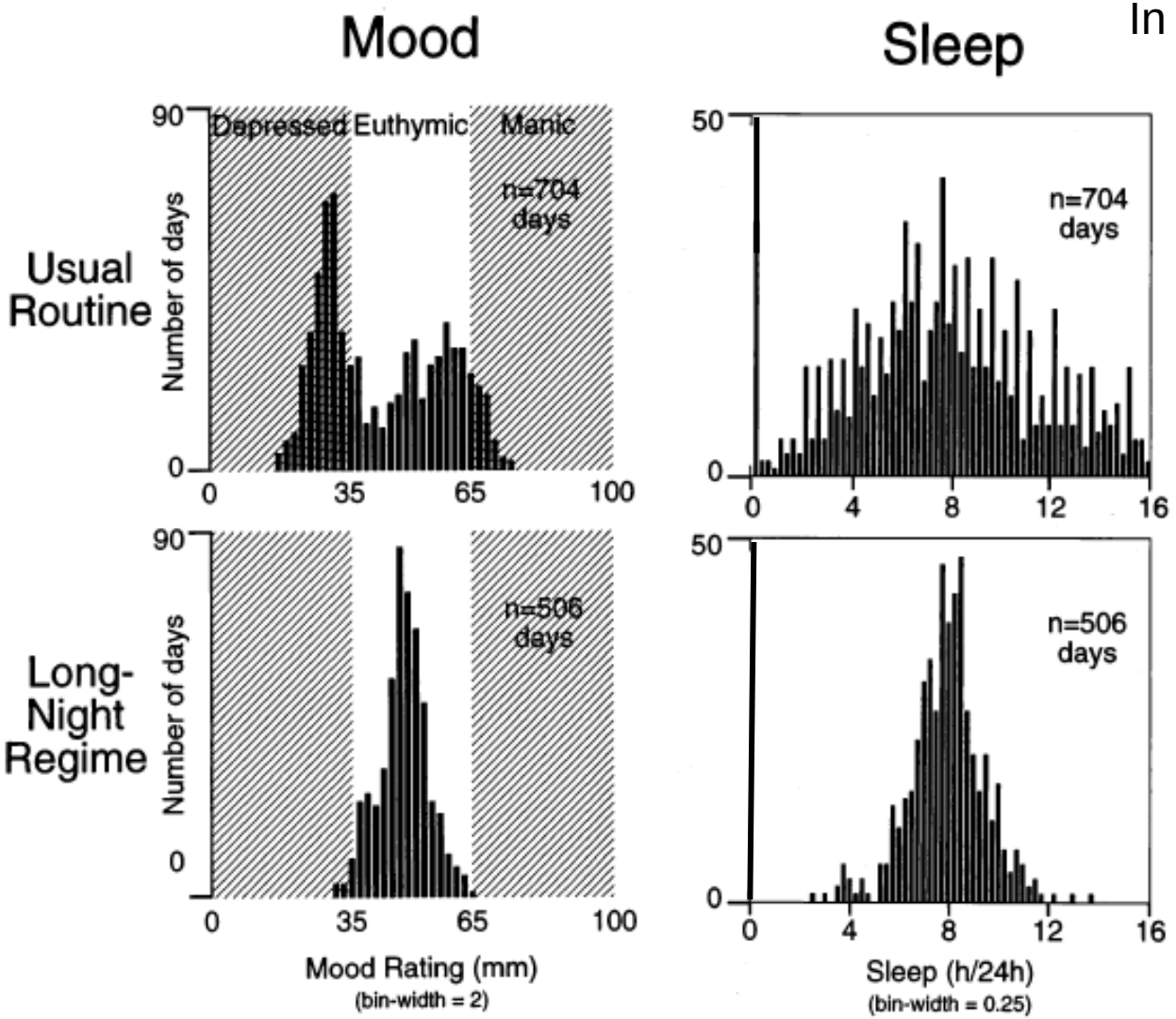
Fig. 3 When the patient slept during long, rigidly scheduled dark periods, the lunar periodicity disappeared and his mood cycles stopped. Indications are the same as in Fig. 1

Wehr et al., *Translational Psychiatry*, 2018

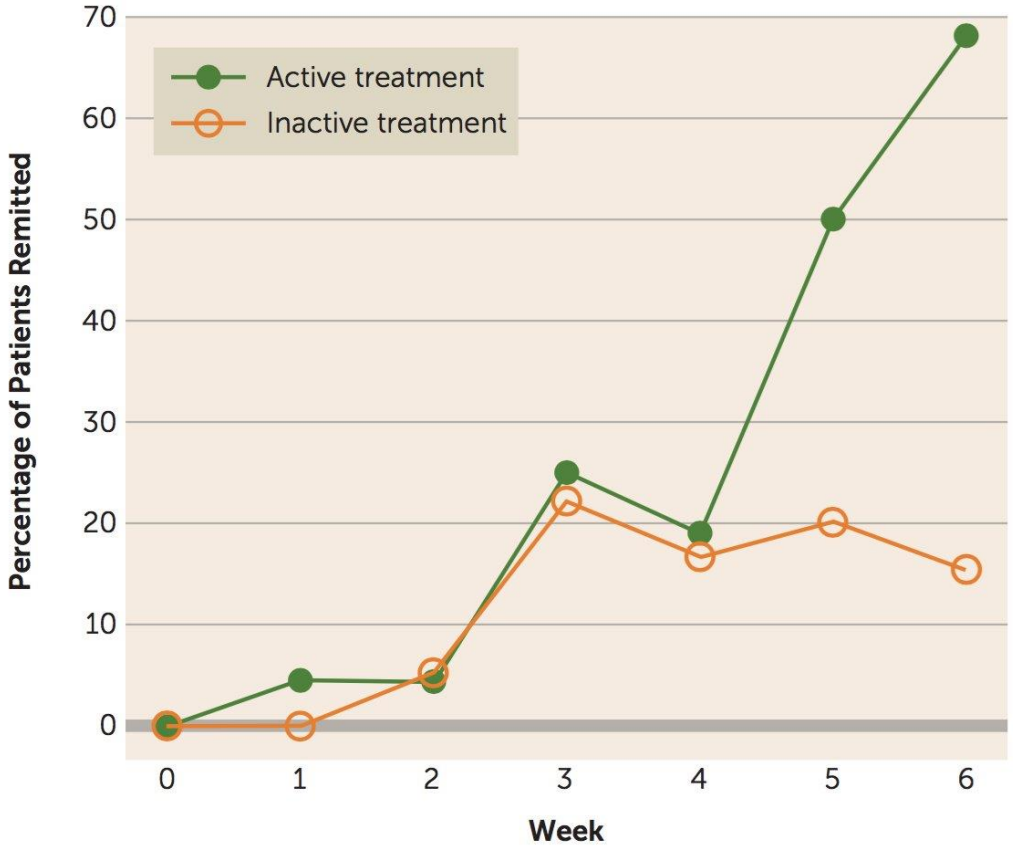
Treatment of a Rapidly Cycling Bipolar Patient by Using Extended Bed Rest and Darkness to Stabilize the Timing and Duration of Sleep

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

14 hrs then 10 hrs
In bed after dark



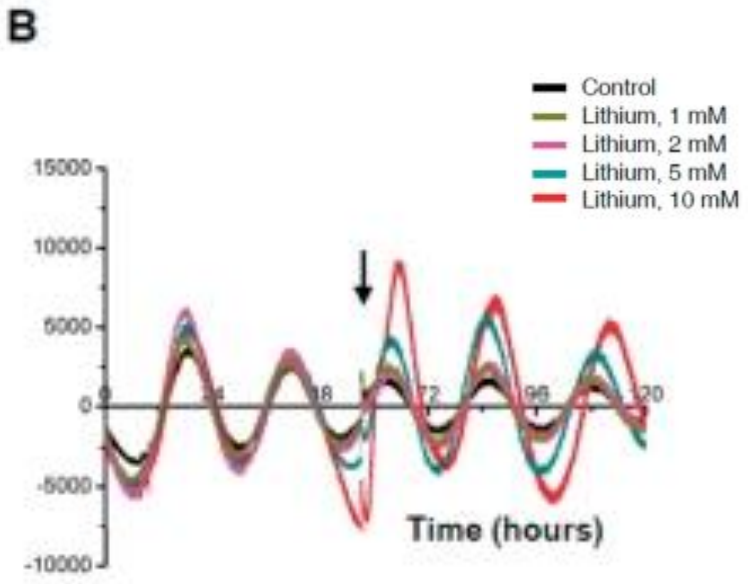
Daily bright light therapy at midday (12-2:30pm) helps people with bipolar depression



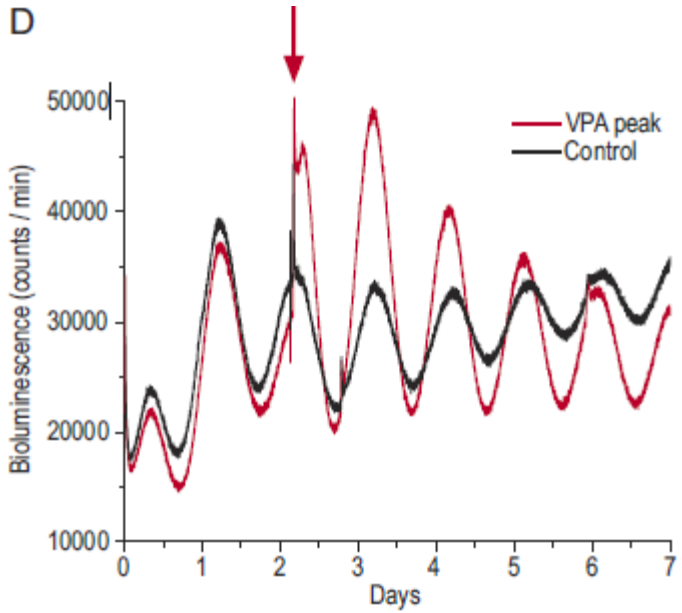
[a] Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004).

Sit et al., Am J Psychiatry 2018

Lithium and VPA increase molecular rhythm amplitude

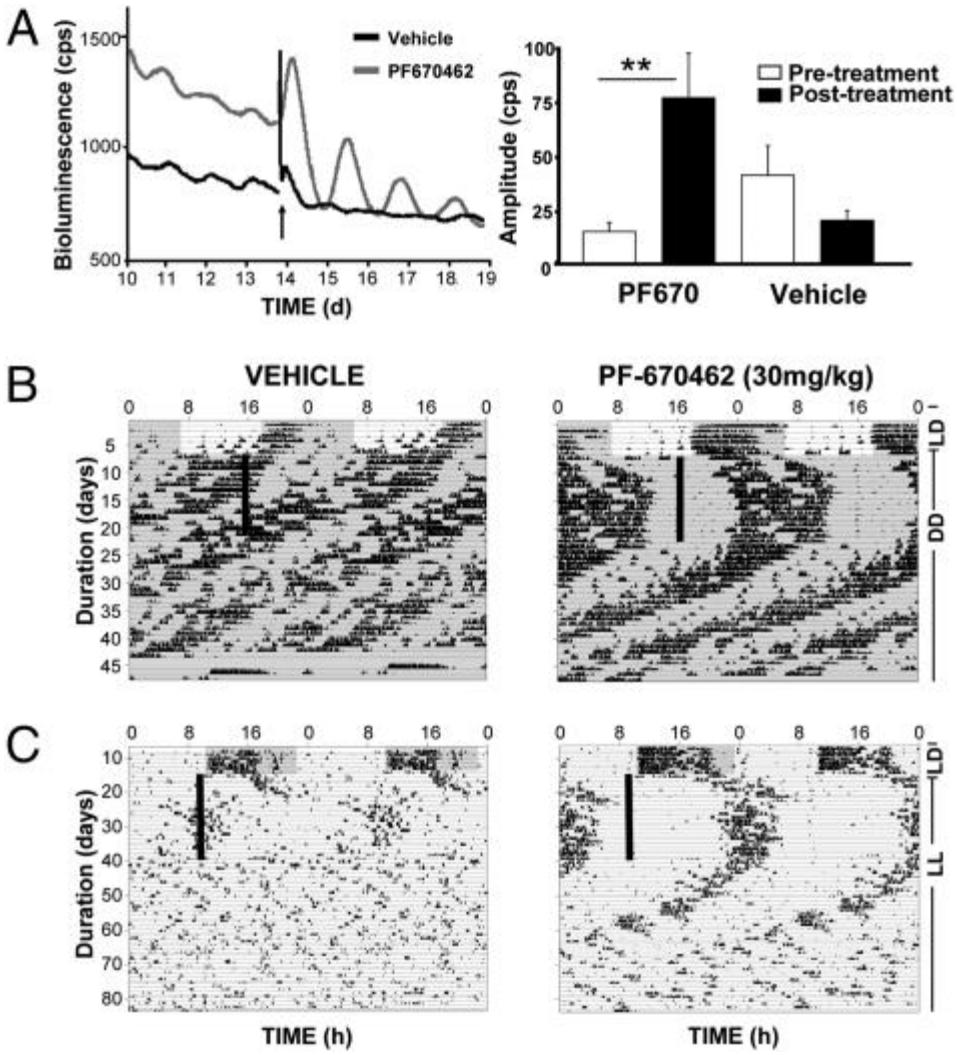


Li et al., 2012



Johansson et. al 2011

CK1 ε/δ inhibitors increase rhythm amplitude under compromised conditions

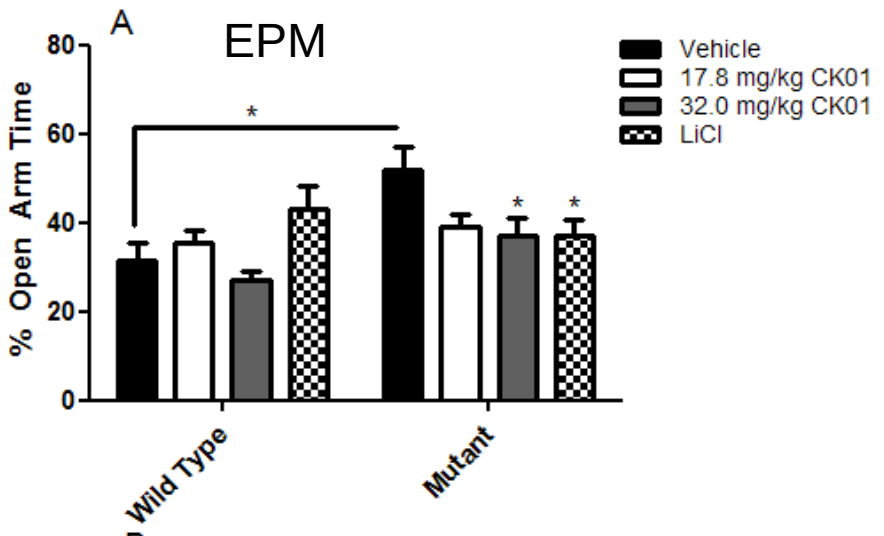


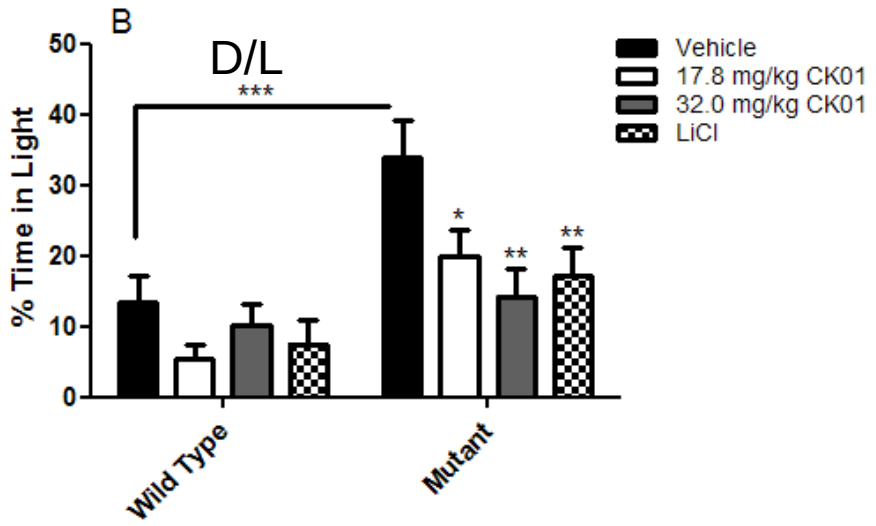
Vipr2 -/-

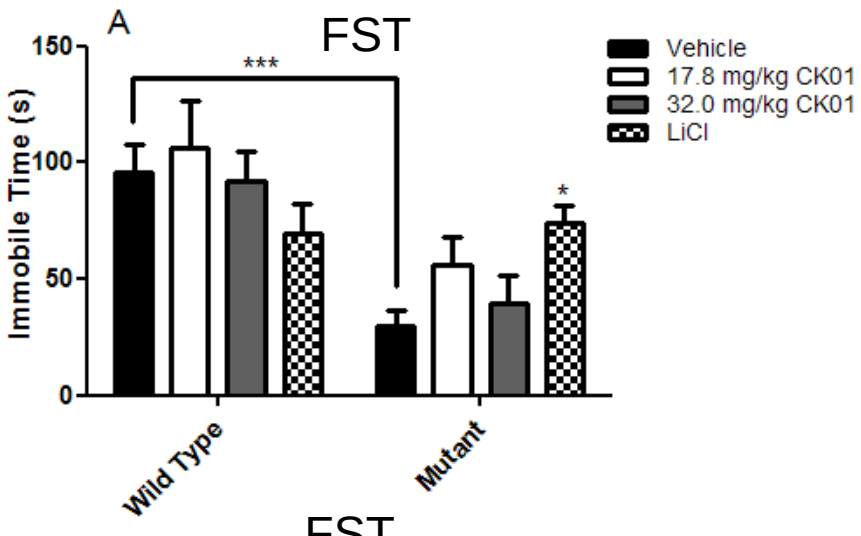
Constant light

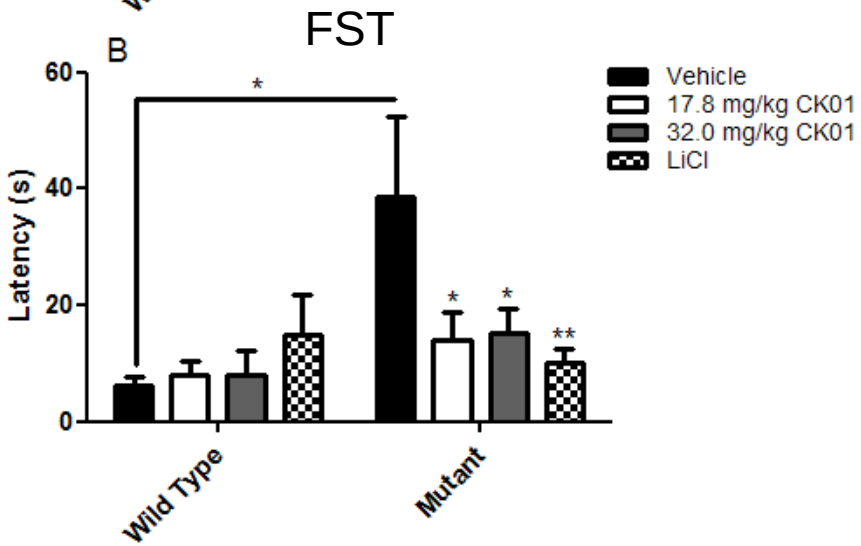
Meng et al., 2010

CK01 normalizes anxiety-related behavior and partially Normalizes depression-like behavior in the *Clock*Δ19 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

Collaborators at Pitt

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

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

Past members

Angela Ozburn
Rachel Arey
Michelle Sidor
Kole Roybal
Shibani Mukherjee

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

Funding

NIDA, NIMH, NINDS, **NARSAD (The Brain and Behavior Foundation)** The McKnight Fund for Neuroscience, Autifony Ltd., The Blue Gator Foundation, IMHRO, University of Pittsburgh Center for Clinical and Translation Studies, Hillman Foundation (UPBI), Pfizer, Janssen Pharmaceuticals

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