THE ADOLESCENT BRAIN AND MOOD DISORDER RISK

Carrie E. Bearden, PhD

Departments of Psychiatry and Biobehavioral Sciences and Psychology
Semel Institute for Neuroscience and Human Behavior

University of California, Los Angeles

cbearden@mednet.ucla.edu

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Disclosure

Carrie E. Bearden, PhD

I have no relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

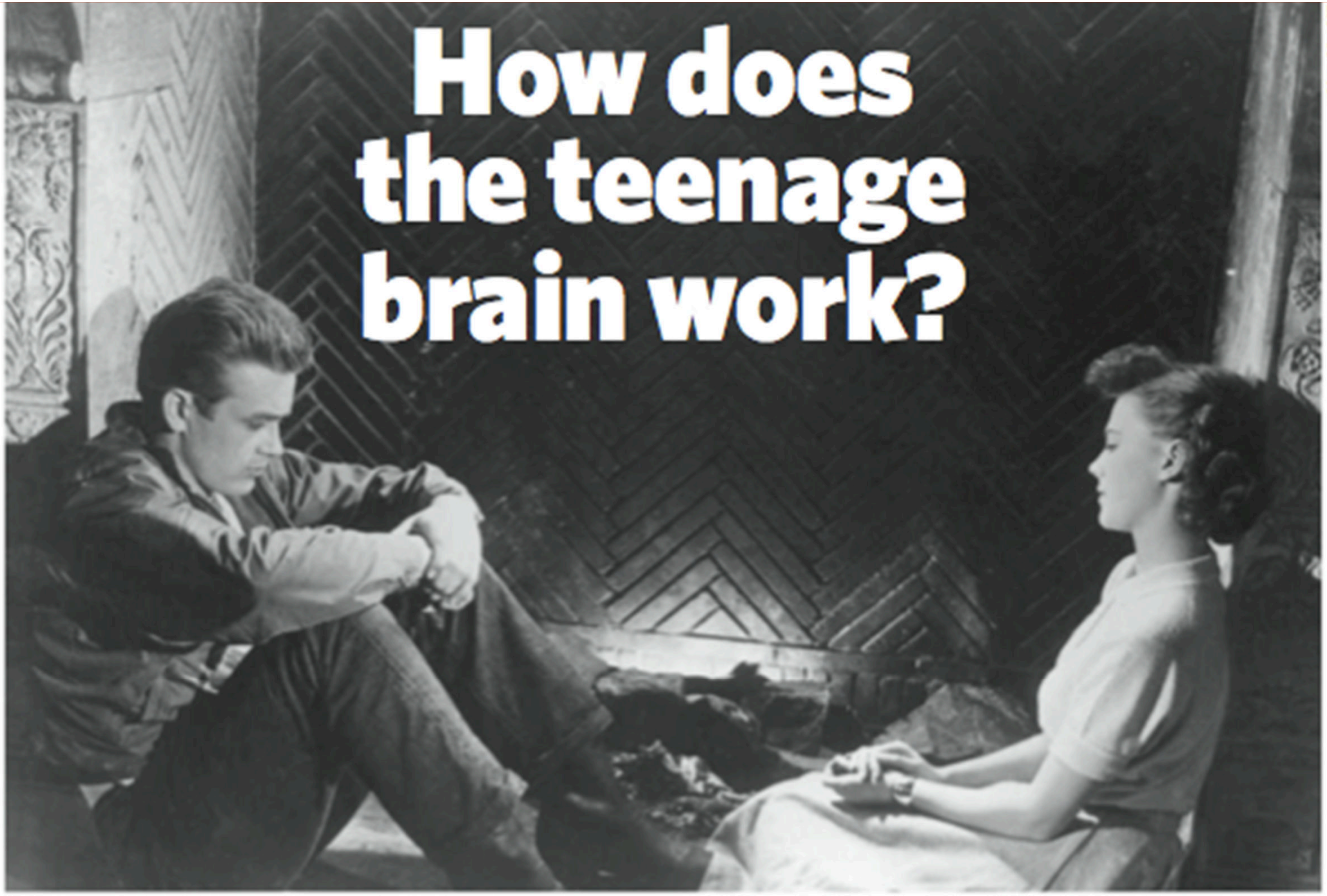
Outline of Presentation

Brain plasticity and vulnerability in adolescence

Sleep and circadian changes in adolescence

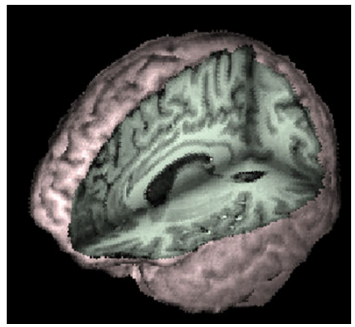
The Costa Rica-Colombia Bipolar project

- Bipolar-associated phenotypes in adults
- Pilot adolescent study

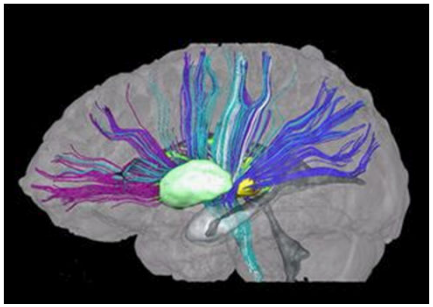


Teenage brain "remodeling" analogous to the developmental window of increased plasticity seen in infancy

The Adolescent Brain and Risk for Psychopathology:
What Goes Wrong?

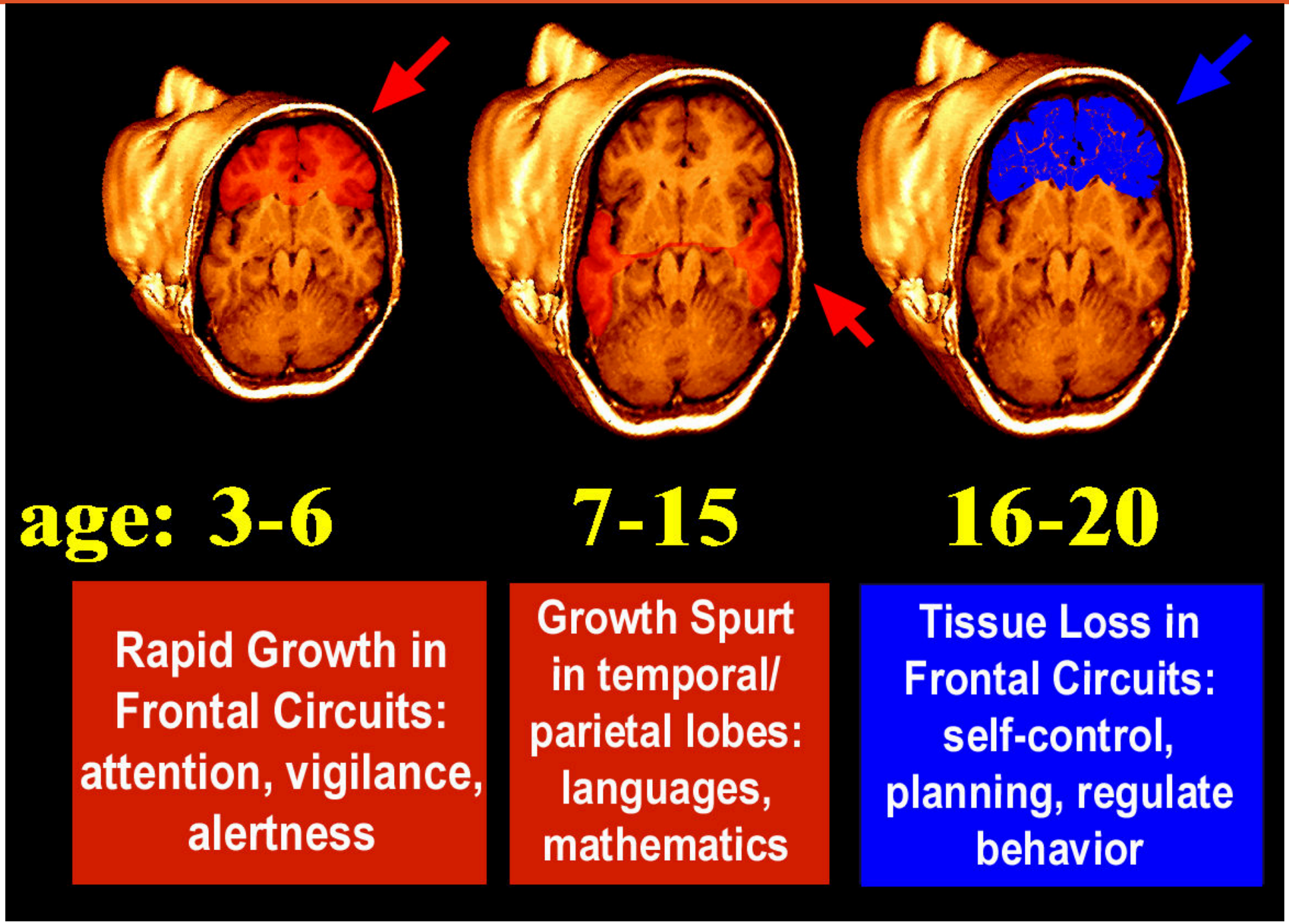


- Adolescent Neurodevelopment:
- Gray matter changes
  - Typical Development
    - Synapses overproduced early in development
    - Across development and during adolescence, normal pruning processes eliminate 40% of cortical synapses **(Huttenlocher PR, et al. *J Comp Neurol*. 1997;387(2):167-178.)**



- White matter changes
  - Typical Development
    - Hippocampus and frontal lobe undergo majority of myelination in adolescence and into early adulthood **(Gogtay N, et al. *Proc Natl Acad Sci*. 2004:101(21):8174-8179.)**
    - During adolescence while gray matter decreases (pruning), white matter increases **(Lenroot RK, et al. *Neurosci Biobehav Rev*. 2006;30(6):718:729.)**

- Brain plasticity: Much of the potential and many vulnerabilities of the brain may depend on the first 2 decades of life **(Lenroot RK, et al. 2006)**

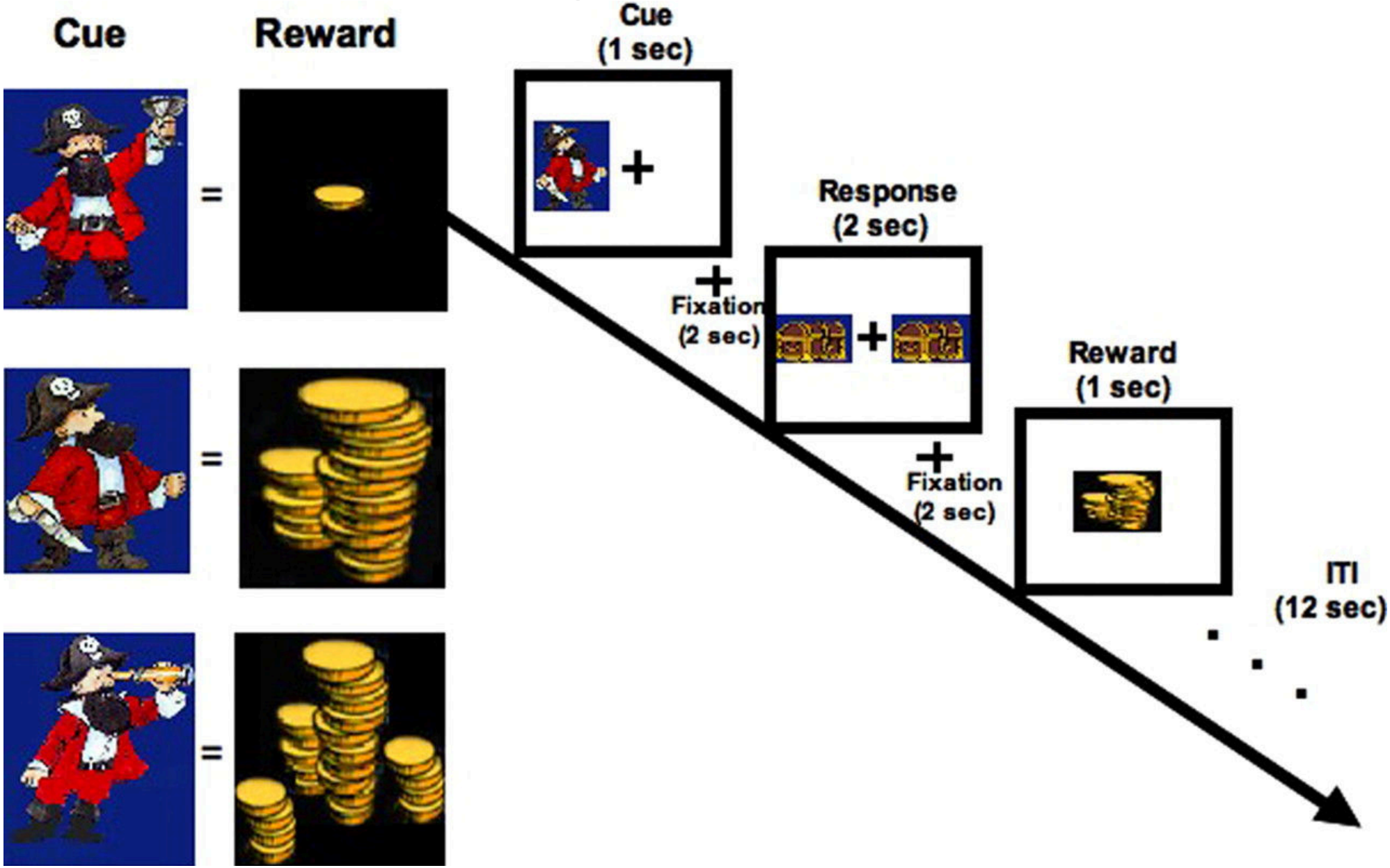


Casey BJ, et al. *Curr Opin Neurobiol*. 2005;15(2):239-244.

Adolescence as a Health Paradox?

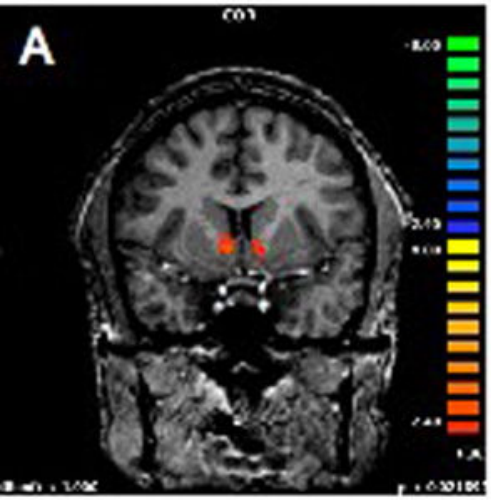
- A time of extensive increases in physical and mental capabilities, yet increased overall mortality/morbidity
- Asynchrony in developmental time courses between affective/approach and cognitive control brain systems may lead to increased vulnerability for risk taking in adolescence **(Willoughby T, et al. *Brain Cogn*. 2013;83(3):315-323.)**
- Prefrontal cortical maturation (dorsolateral and orbito- frontal regions) assumed to correspond to development of higher-level cognitive processes
- Maturing subcortical systems (eg, nucleus accumbens) disproportionately activated relative to top-down control systems in adolescence **(Galvan A, et al. *J Neurosci*. 2006;26(25):6885-6892.)**

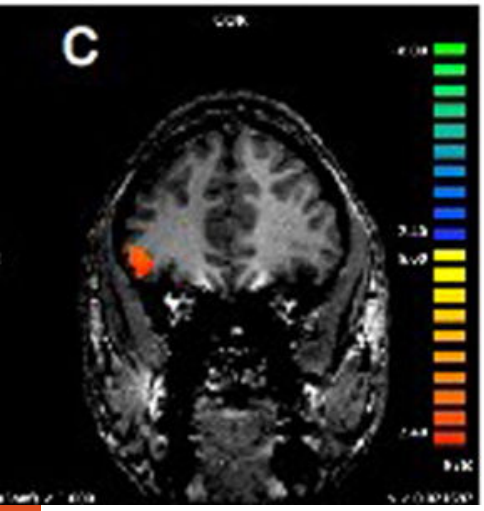
Neural Systems Implicated in Reward-Seeking Behaviors in Adolescents

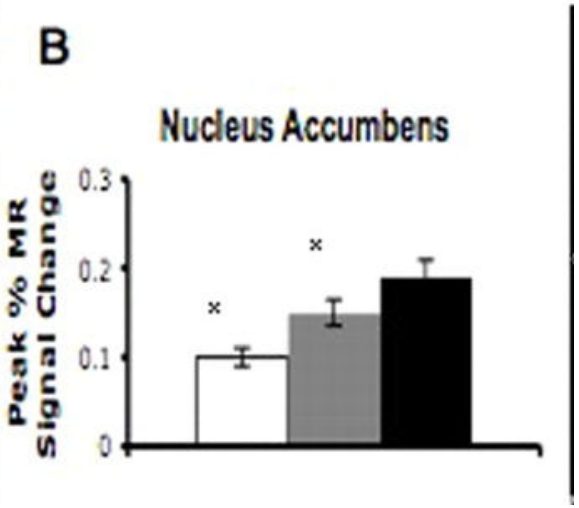


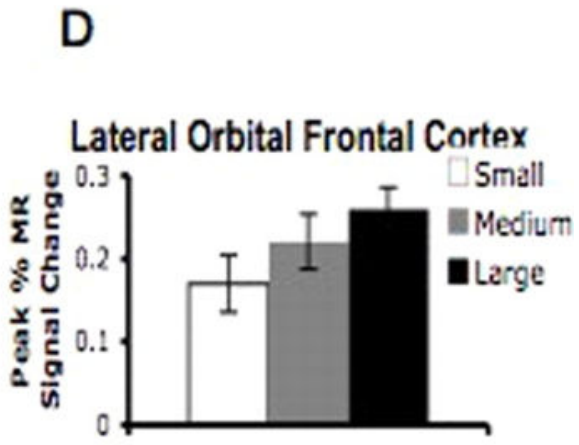
Galvan A, et al. *J Neurosci*. 2006;26(25):6885-6892.

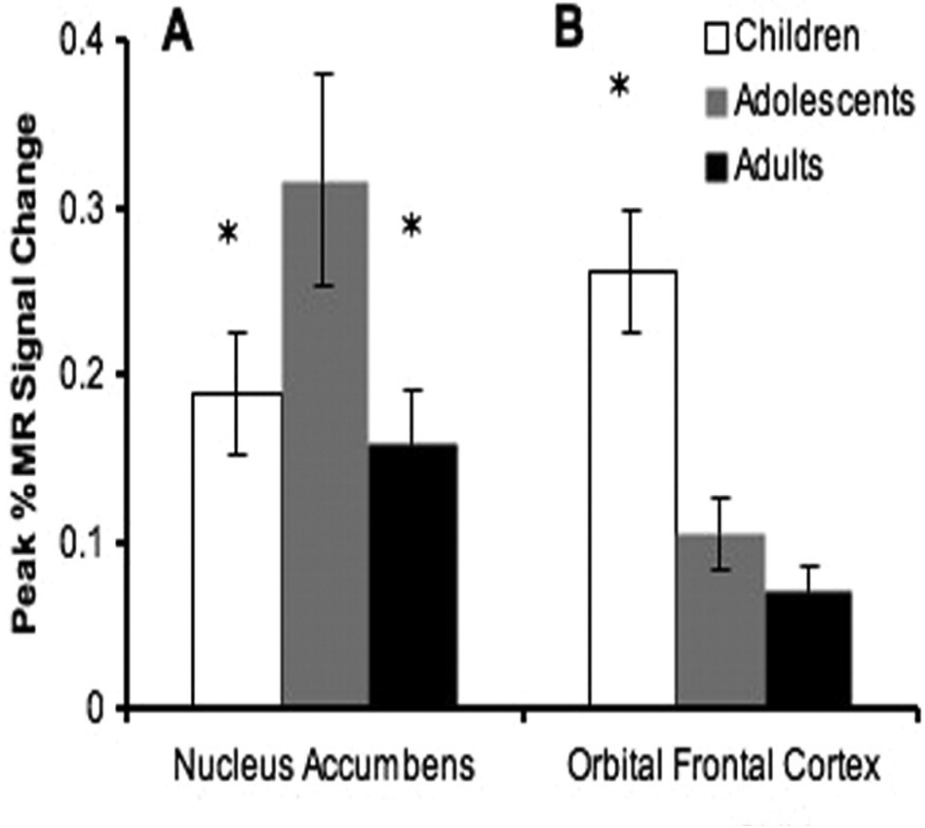
More Nucleus Accumbens Activity with Greater Reward Value







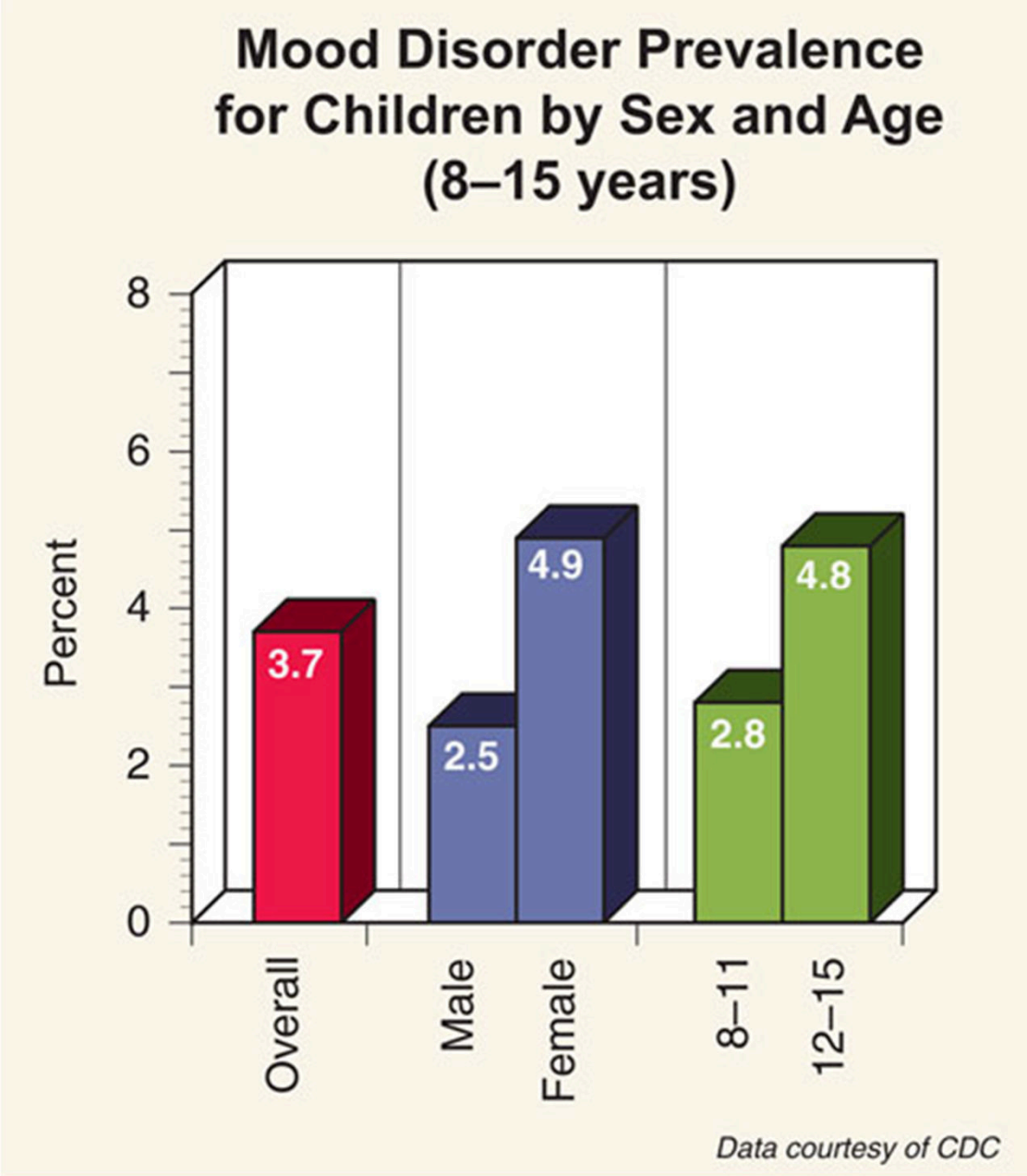




Galvan A, et al. *J Neurosci*. 2006;26(25):6885-6892.

Different developmental trajectories for frontal/subcortical regions may relate to increased impulsivity/risky behavior during adolescence

Also Related to Increased Mood Lability and Risk for Mood Disorders during This Time Period?



www.cdc.gov

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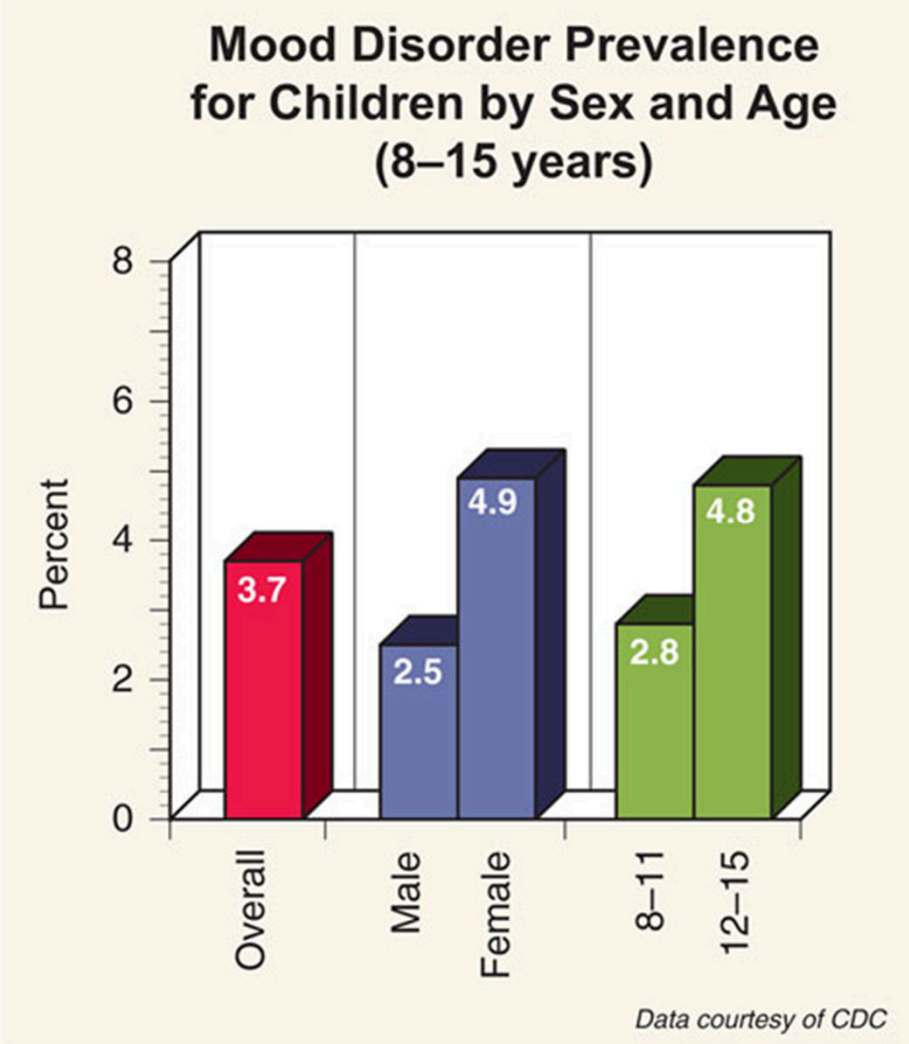
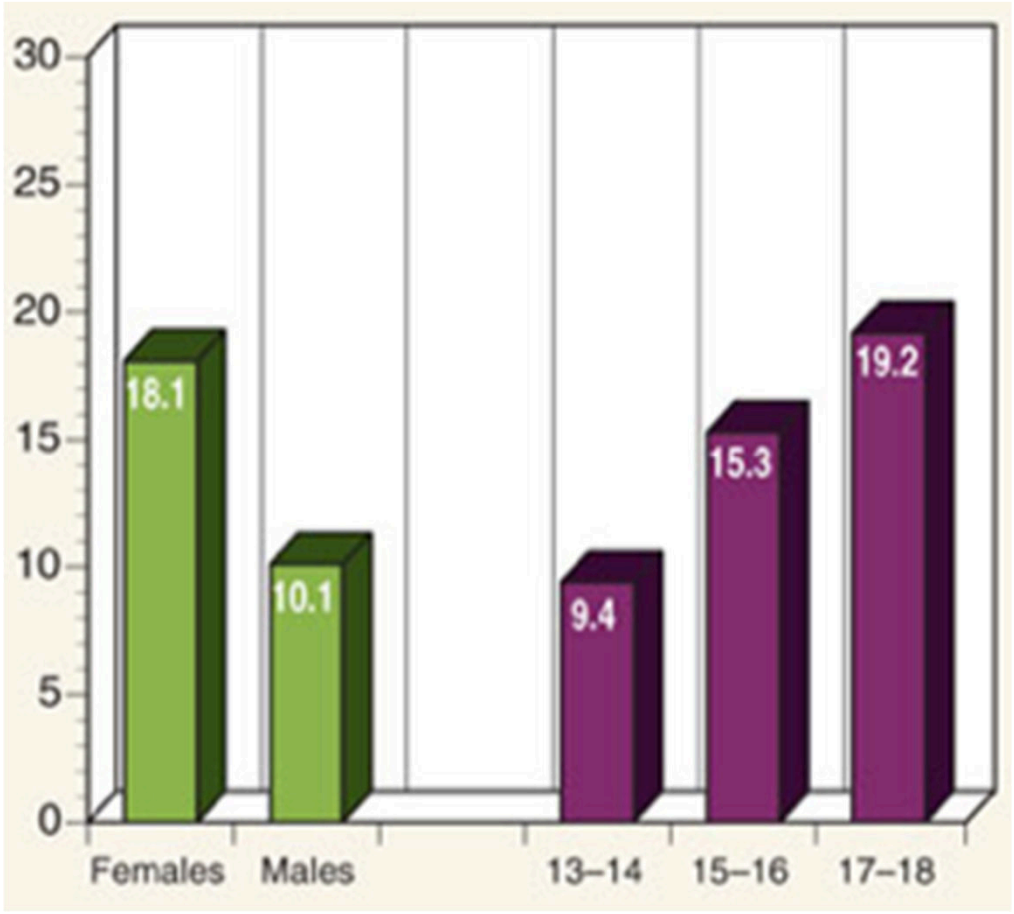
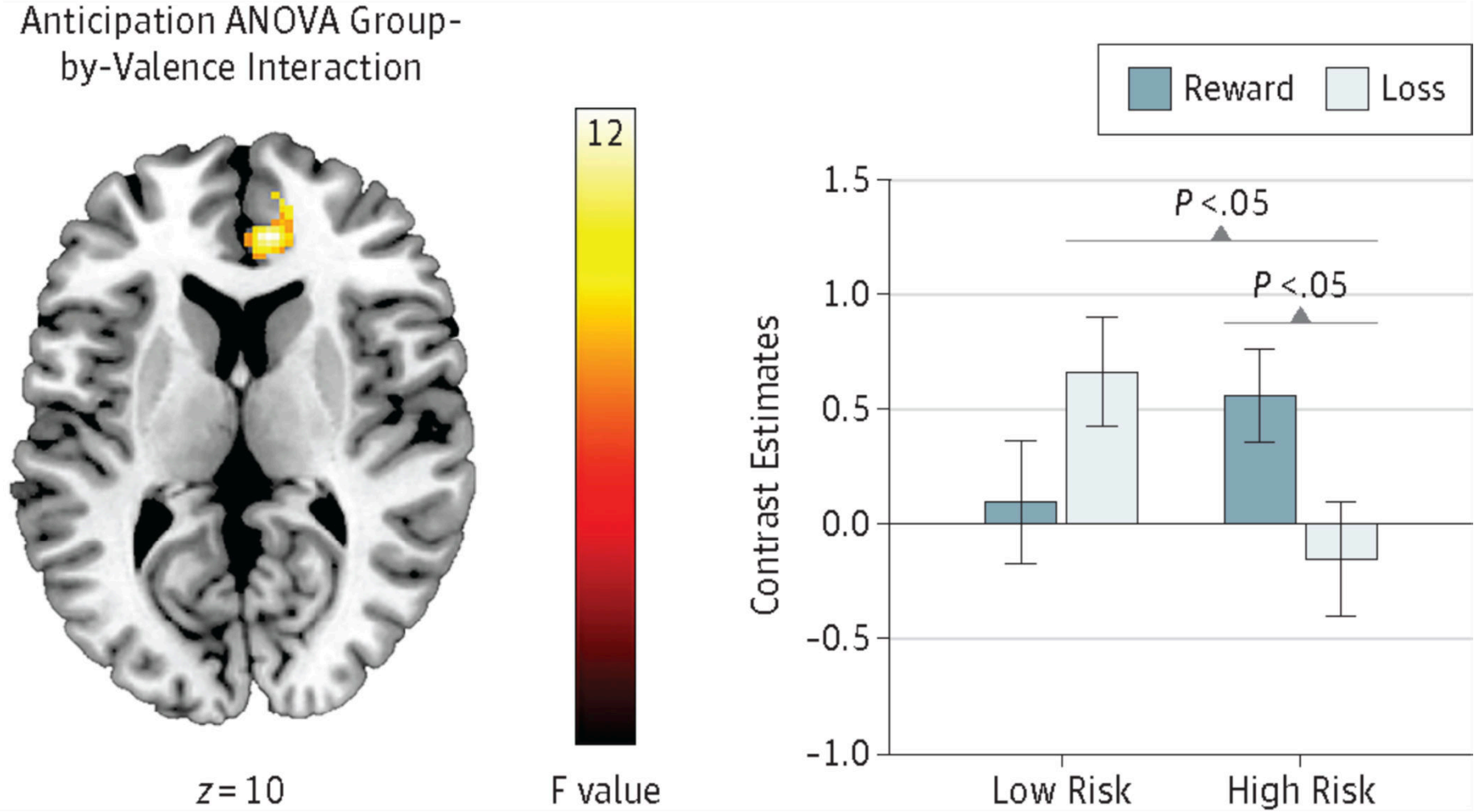




Impaired Reward Processing as a Risk Factor for Bipolar Disorder in Adolescence?



- Decreased activation in the pregenual cingulate during loss anticipation
- Novelty seeking and impulsivity associated with increased striatal and amygdalar activation

Singh MK, et al. *JAMA Psychiatry*. 2014;71(10):1148-1156.

Other Key Developmental Changes in Adolescence:

Newborns sleep 16 to 18 hours (in 3 to 4 hour periods)

Average sleep at age 5 = 11.1 hours

Adolescence: Nighttime sleep reduces from ~9 hours at age 13 to 7.9 hours at age 16
(Hoban TF. *Semin Neurol*. 2004;24(3):327-340.)

Circadian changes in adolescence: delay in circadian phase and sleep onset, often shifting past midnight

(Carskadon MA, et al. *Sleep*. 2002;25(6):453-460. Tate J, et al. *Nursing*. 2002;32(8):46-49.)

Increased biological need for sleep associated with pubertal development

(Dornbusch SA. In: Carskadon MA, Ed. *Adolescent Sleep Patterns: Biological, Social, and Psychological Influences*. Cambridge University Press; 2002)

Inadequate Sleep "Epidemic" in Adolescents

	Insufficient (<=7h)		Borderline (8h)		Optimal (>=9h)	
	%	95% CI	%	95% CI	%	95% CI
Overall	68.9	(66.9-70.9)	23.5	(21.8-25.3)	7.6	6.8-8.4)

- Nationwide, almost 70% of students reported insufficient sleep on average school night **(Eaton DK, et al. *J Adolesc Health*. 2010;46(4):399-401.)**
- Poor sleep associated with poor academic performance for adolescents from middle school through college **(Wolfson AR, et al. *Sleep Med Rev*. 2003;7(6):491-506.)**
- Insufficient sleep associated with higher odds of current substance use, risky behavior, sadness, suicidal ideation **(McKnight-Eily LR, et al. *Prev Med*. 2011;53(4-5):271-273.)**


the worst thing after waking up?
everything until i go to bed again

“Eveningness”/Sleep Variability as Risk Factors for Mood Dysregulation

- 6631 adolescents, aged 14.1 to 18.6 years: “Eveningness” associated with more daytime sleepiness, attention problems, poor school achievement, more injuries, more “emotional upset”, more sleep disturbance **(Gianotti F, et al. *J Sleep Res*. 2002;11(3):191-199.)**
- Sleep Habits Survey administered to 3120 high school students: Students who slept < 6 hr 45 min on school nights and/or had > 2 hour weekend bedtime delay reported increased daytime sleepiness, depressive mood, and sleep/wake behavior problems **(Wolfson AR, et al. *Child Dev*. 1998;69(4):875-887.)**

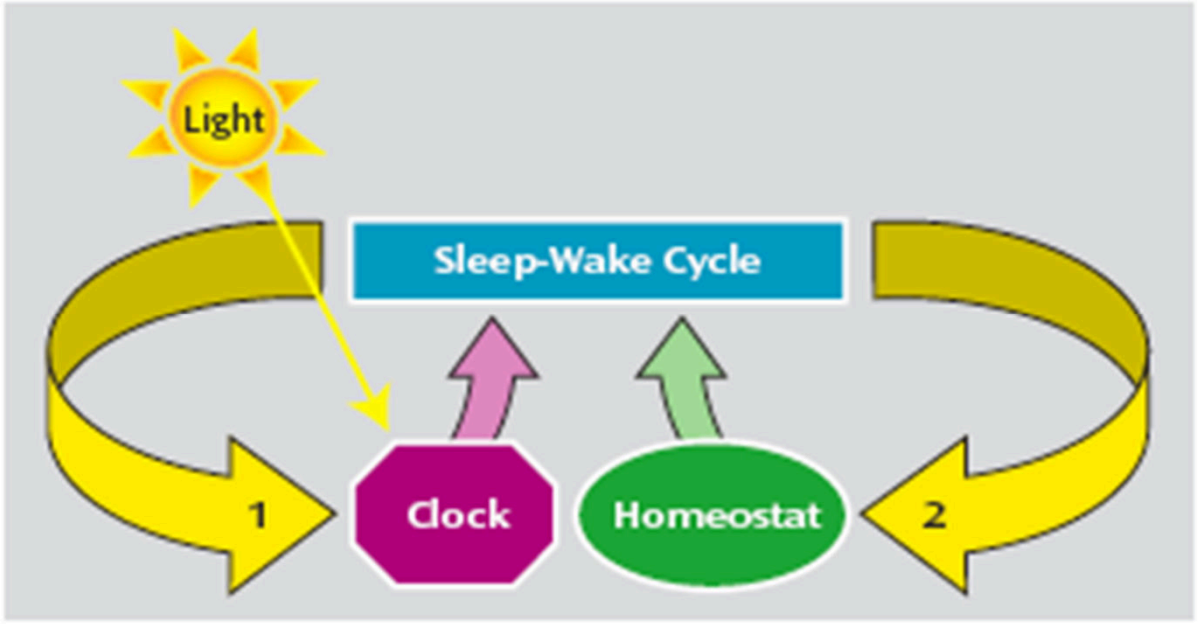
Sleep Indicators are Related to Daily Mood in Adolescents

	r			
	Anxiety	*Depression*	*Fatigue*	*Happiness*
Daily sleep	– .21***	– .17***	– .21***	.13***
School night sleep	– .23***	– .16***	– .20***	.15**
Nonschool night sleep	– .11**	– .13***	– .10**	.06
Sleep deviation	.23***	.16**	.20***	– .09*

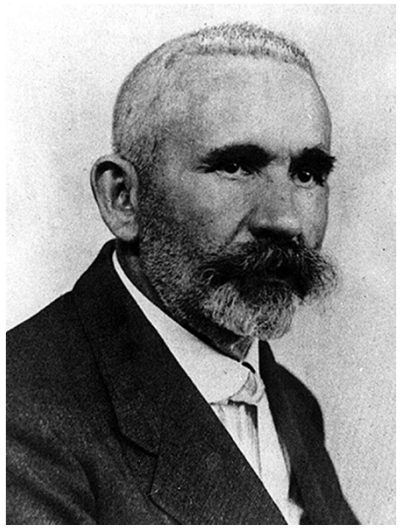
Fuligni AJ, et al. *J Res Adolesc*. 2006;16(3):353-378.

Sleep-Wake Cycle is Regulated by Interaction between:

- Circadian Rhythm, driven by SCN in hypothalamus
- Homeostatic Process, determined by prior sleep and wakefulness
- Maintain wakefulness during the day and promote sleep at night



SCN = suprachiasmatic nucleus. Dijk DJ, et al. *J Appl Physiol*. 2002;92(2):852-862.



"…The attacks of manic-depressive insanity are invariably accompanied by all kinds of bodily changes. By far the most striking are the disorders of sleep and general nourishment. In mania …sometimes there is even almost complete sleeplessness, at most interrupted for a few hours, which may last for weeks, even months… In the states of depression in spite of great need for sleep, the patients lie for hours, sleepless in bed, although even in bed they find no refreshment."

—Emil Kraepelin, *Manic-Depressive Insanity and Paranoia*

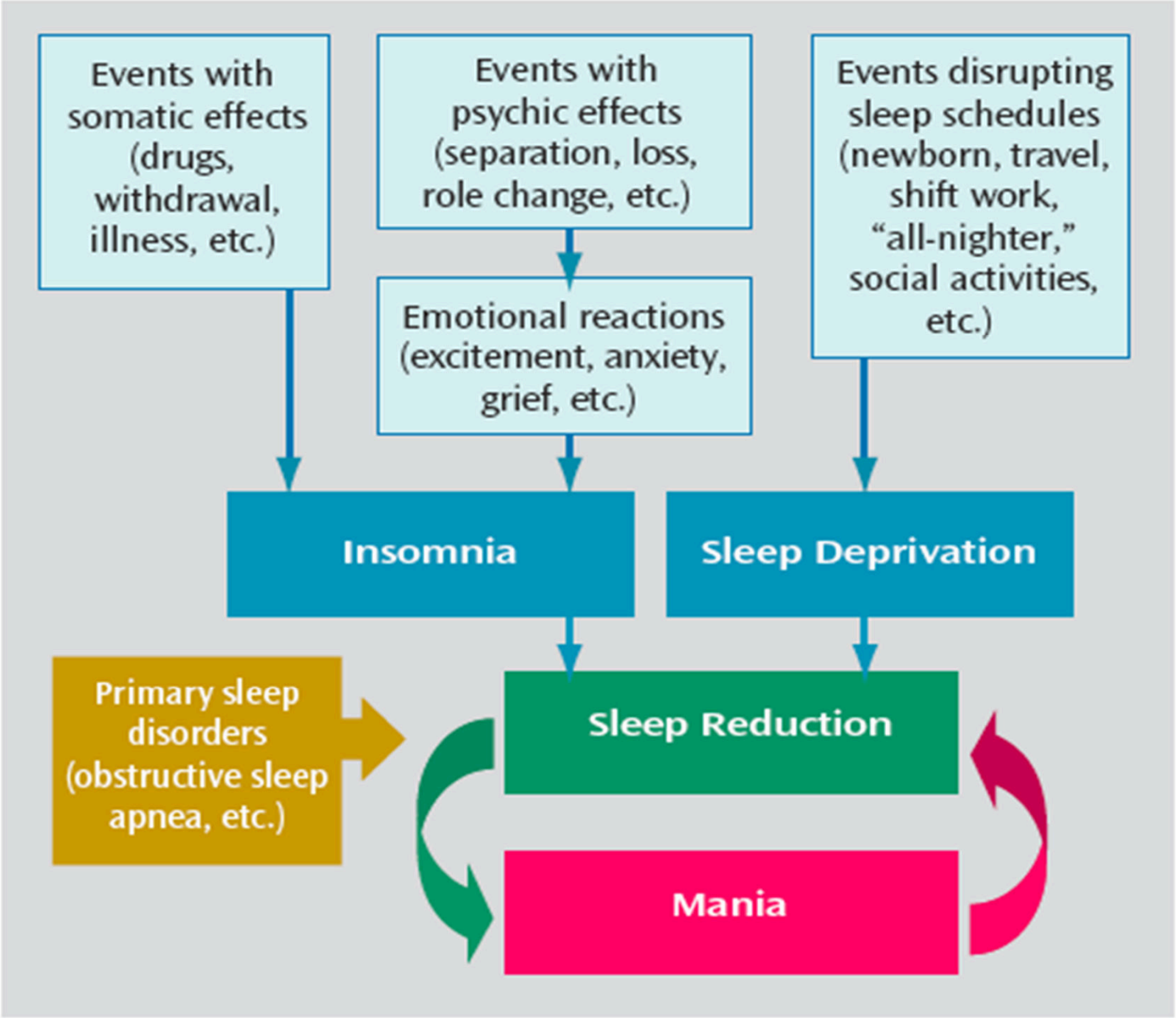
Fatal Consequences of Long-Term Sleep Deprivation

Bell (1849) documented several cases of florid mania characterized by almost no sleep that typically ended fatally	Animal models of sleep deprivation – death is outcome of prolonged sleep deprivation, despite increased food intake **(Rechtschaffen A, et al. *Sleep*. 1989;12(1):68-87.)**	Sleep deprivation and/or deprivation of NREM sleep produced a reliable syndrome: debilitated appearance, skin lesions, weight loss, increased energy expenditure, body temperature (late stages), plasma norepinephrine and thyroxine, death **(Rechtschaffen A, et al. *Sleep*. 2002;25(1):68-87.)**

Lines of Evidence for Central Role of Sleep/Circadian Disturbance in Bipolar Disorder

- Sleep disturbances are among the most prominent correlates of mood episodes and inadequate recovery in bipolar patients **(Harvey AG, et al. *Am J Psychiatry*. 2008;165(7):820-829.)**
- Impaired sleep can induce and predict manic episodes **(Plante DT, et al. *Am J Psychiatry*. 2008;830-843.)**
- Cyclicity of manic and depressed states; diurnal mood variation
- CLOCK (circadian protein) knockout mouse exhibit “manic”-like behaviors; reversed with lithium Tx **(Roybal K, et al. *Proc Natl Acad Sci U S A*. 2007;104(15):6406-6411.)**; CLOCK involved in regulation of dopamine activity

Sleep Deprivation as a Proximal Cause of Mania



Wehr TA, et al. *Am J Psychiatry*. 1987;144(2):201-204. Plante DT, et al. *Am J Psychiatry*. 2008;830-843.

Multi-Generational Bipolar Pedigrees in Latin American Founder Populations

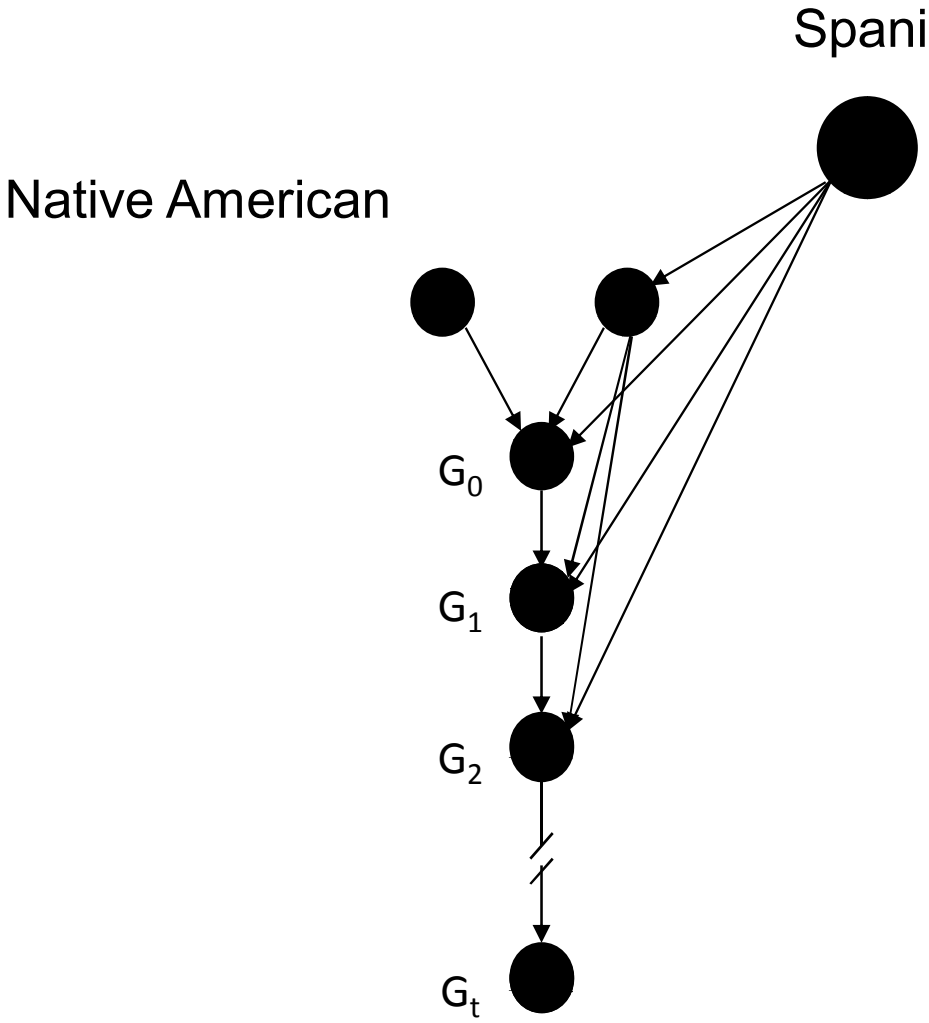
History

- Population isolates established in 16th and 17th centuries
- Admixture of a genetically similar founder populations of Amerindian and Spanish immigrants
- Exponential growth from small number of founders:

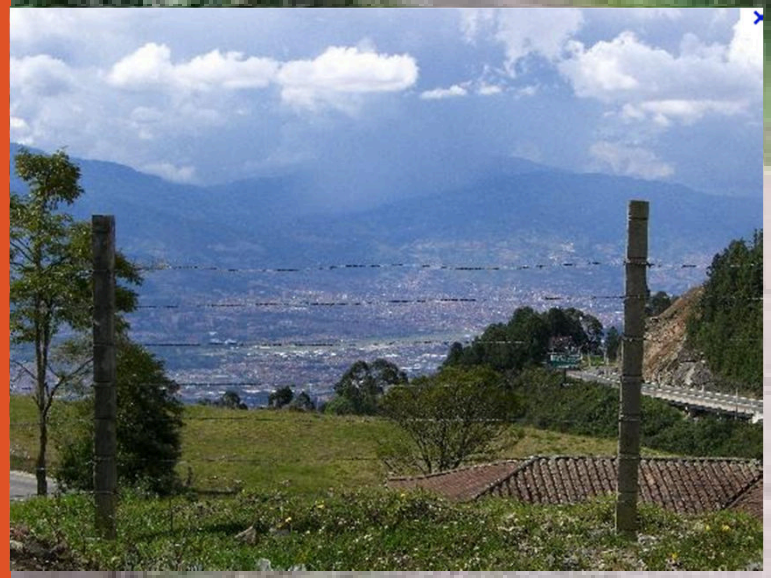
Sample

- 26 families heavily loaded for severe bipolar
- 750 sampled for clinical and behavioral traits
- 530 with MRIs

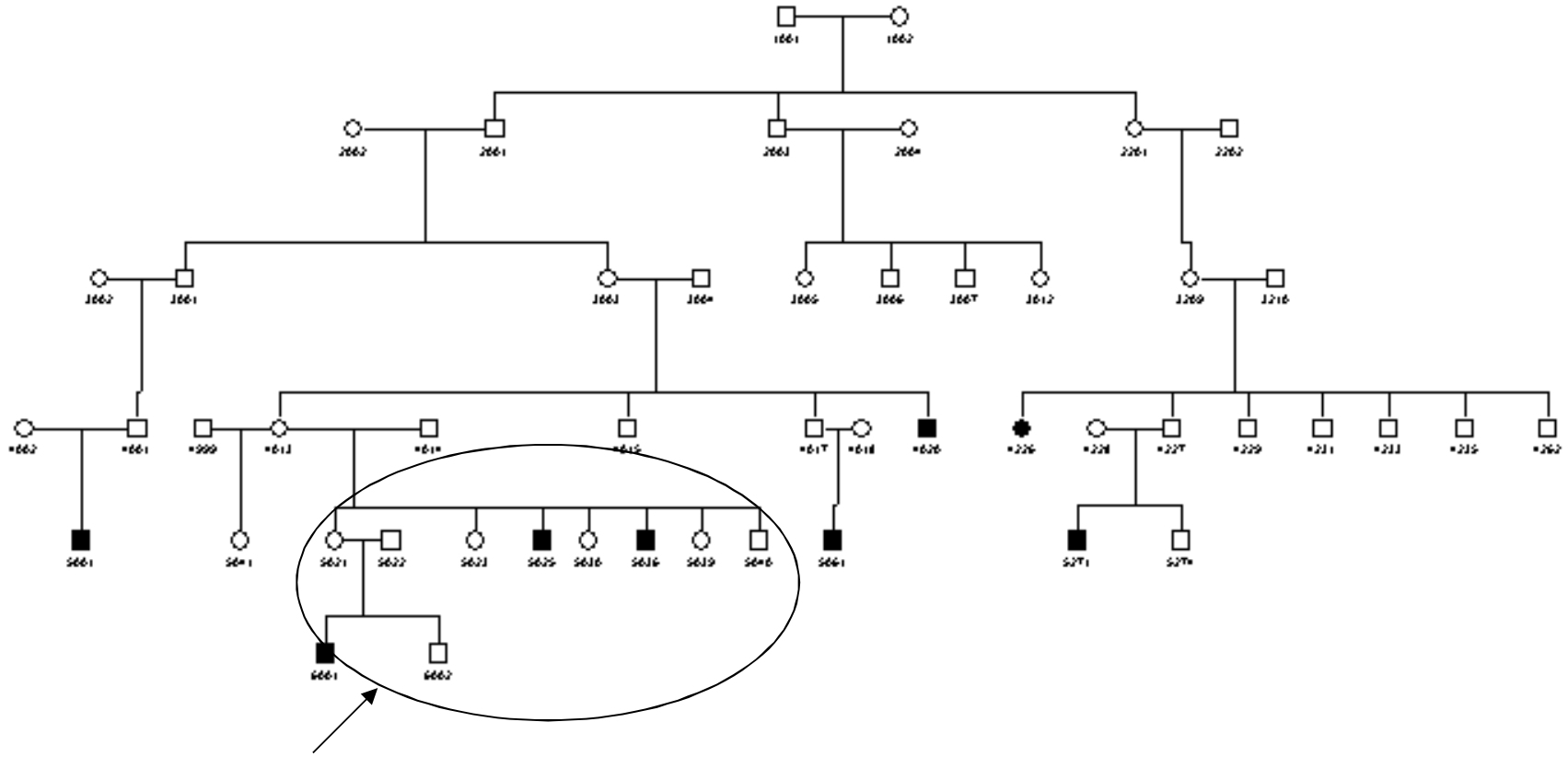
CO and CR Populations: Similar processes of admixture



Acosta, Costa Rica



Study of Multi-Generational Pedigrees Genetically Enriched for Bipolar Disorder



Prioritize most informative pedigree branches

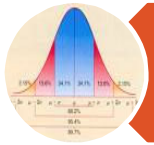
Sample Characteristics by Country

Total Sample		Sample Assessed for Component Phenotypes				
Family	**n (BP-I cases)**	**n (BP-I cases)**	**MRI (DTI)**	**Female**	**Mean Age (SD) <range>**	**Mean Years of Education (SD) <range>**
ANT All	512 (96)	353 (86)	242 (225)	58%	47.7 (17.7) <18-85>	8.3 (4.7) <0-23>
CVCR All	918 (128)	386 (95)	285 (0)	55%	49.1 (15.6) <18-87>	7.8 (4.9) <0-24>

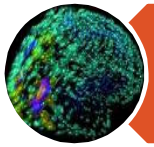
Can We Advance Understanding of Disease States by Elucidating the Biology Beneath the Syndrome?

Syndrome

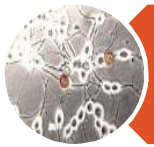
Symptoms



Quantitative Biobehavioral Variables

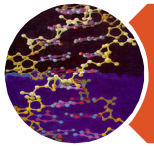


Neural Circuit



Cellular Systems/Signaling Pathways (Circadian Biology)

Functional Genome

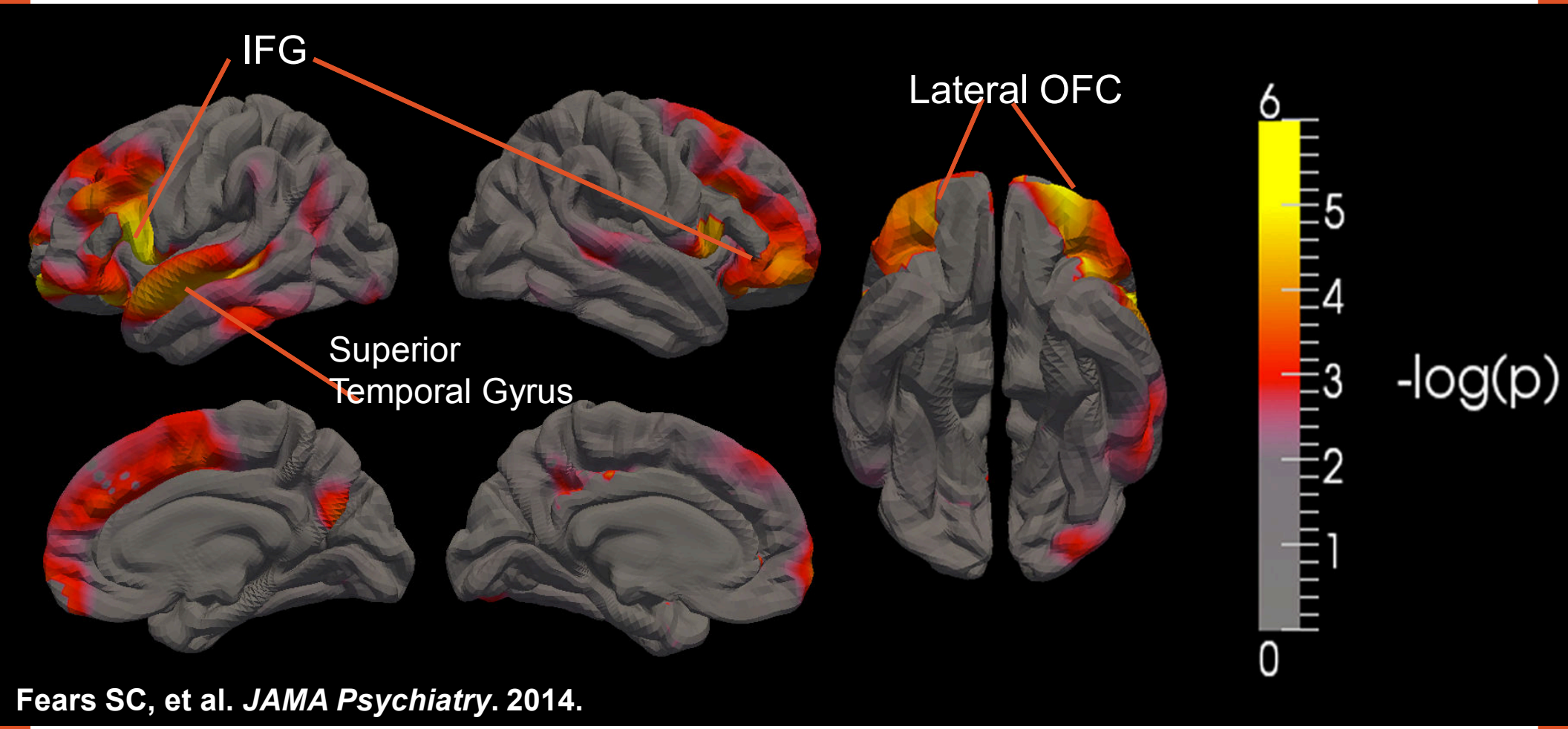


Structural Genome

Phenotypes Investigated in Costa Rica and Colombia Bipolar Pedigrees

Domain	Type
Psychiatric diagnosis	Interview (DIGS)
Temperament, delusion-proneness, creativity, sensation seeking, and impulsivity	Self-report questionnaire
Structural neuroanatomy	MRI
White matter microstructure	MRI (Diffusion tensor imaging)
Neurocognition	Neuropsychological assessment
Sleep and circadian rhythm	Self report, actigraphy, molecular phenotype in fibroblasts
Gene expression (blood cells/fibroblasts)	Microarray

Cortical Thickness in Inferior and Middle Frontal, Orbitofrontal and Left Superior Temporal Regions is Significantly Heritable and Associated with BP-1

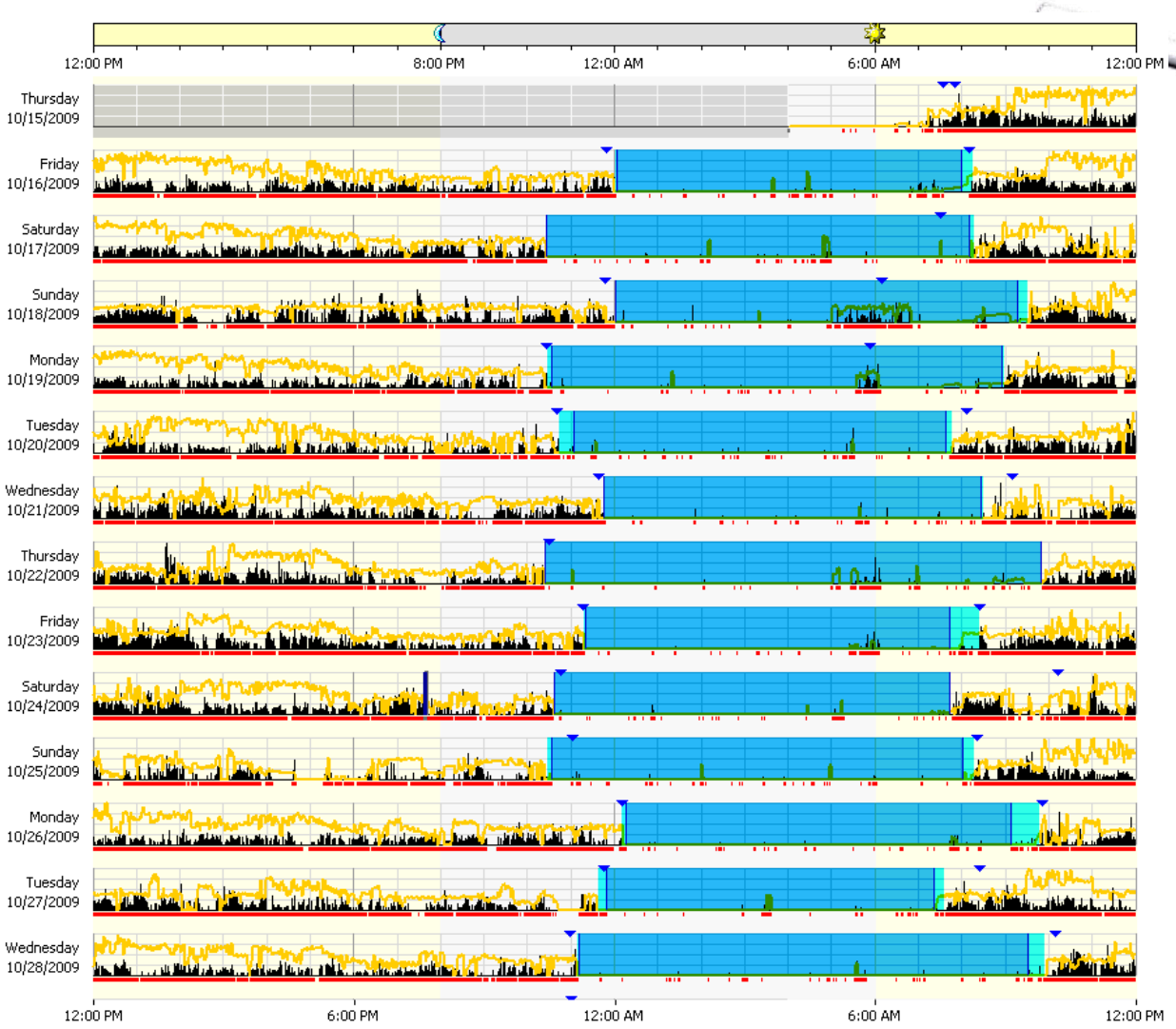


Fears SC, et al. *JAMA Psychiatry*. 2014.

Compared to non-BP family members, BP subjects showed:

- Decreased global gray and white matter , increased ventricular volume.
- Decreased subcortical volume in hippocampus and ventral diencephalon (trend in amygdala).
- Decreased WM integrity (FA) of corpus callosum.

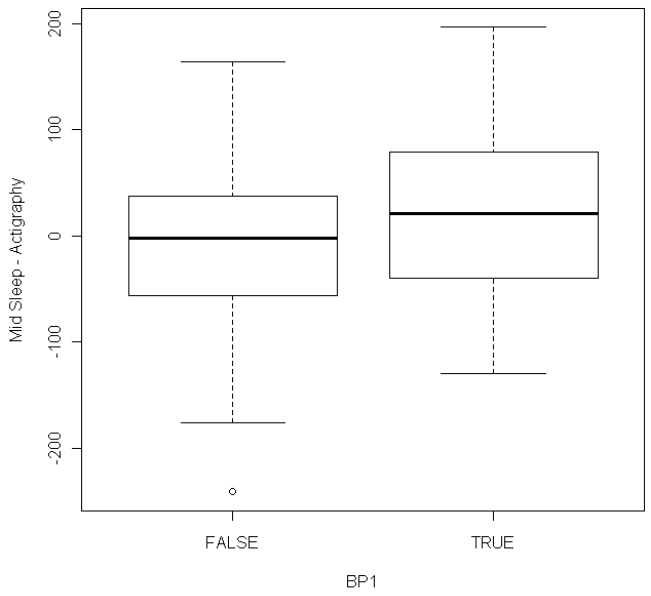
Activity and Circadian Rhythm Endophenotypes in Bipolar Families



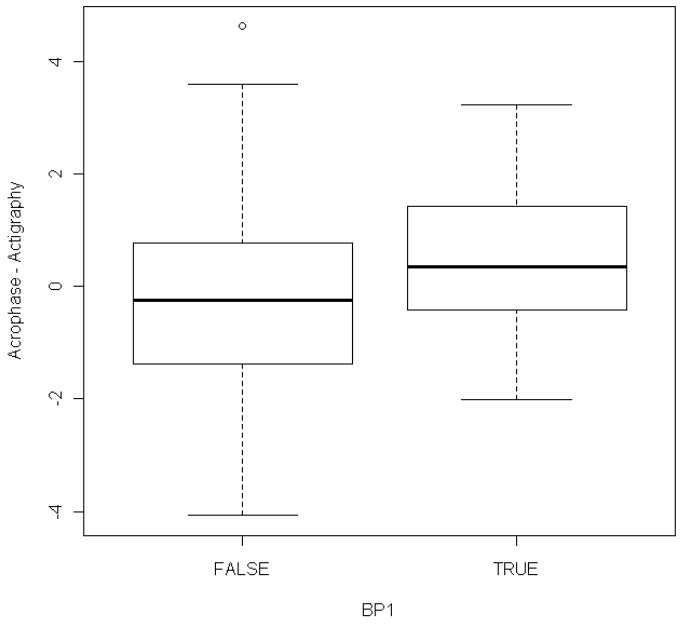
Adult BP-I participants tend toward later timing for peak activity and mid-sleep behavior

Phenotype	Covariates	SOLAR		
		H2r	SE	Pval
Acrophase (Actigraphy)	Age	0.800	0.145	1.00E-07
Mid-Sleep (Actigraphy)	Age	0.962	0.129	1.00E-07
Mid-Sleep (MCTQ)	Country, Age	0.188	0.138	5.06E-02
Chronotype (MCTQ)	Usual days worked per week	0.259	0.121	4.27E-03
Extremely Early (Chronotype = 0)	None	0.681	0.294	5.88E-03

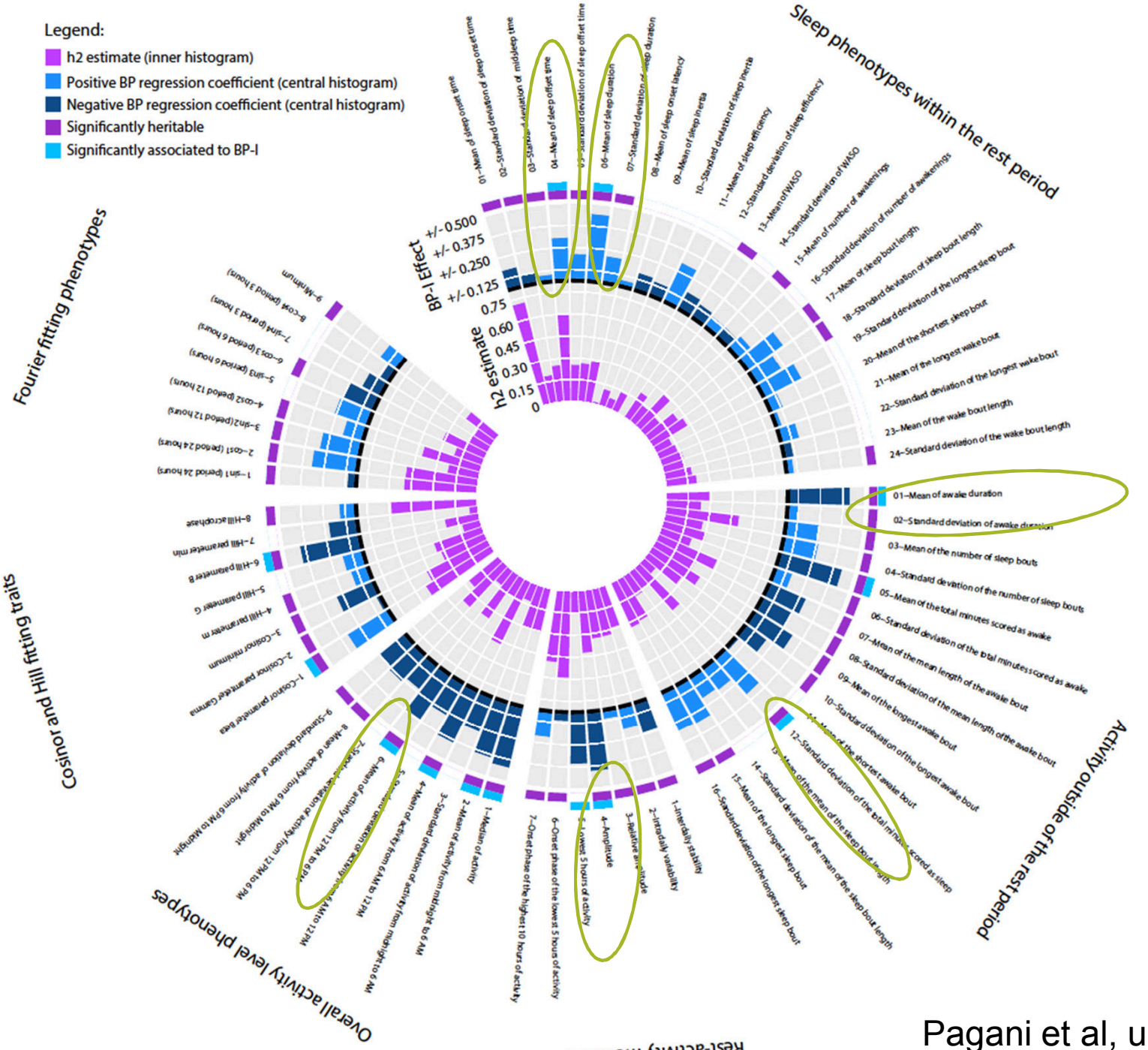
Actigraphic Mid-Sleep



Acrophase (Peak Activity)



Circadian heritable and disease-associated traits in CR and CO pedigrees



Pagani et al, under revision

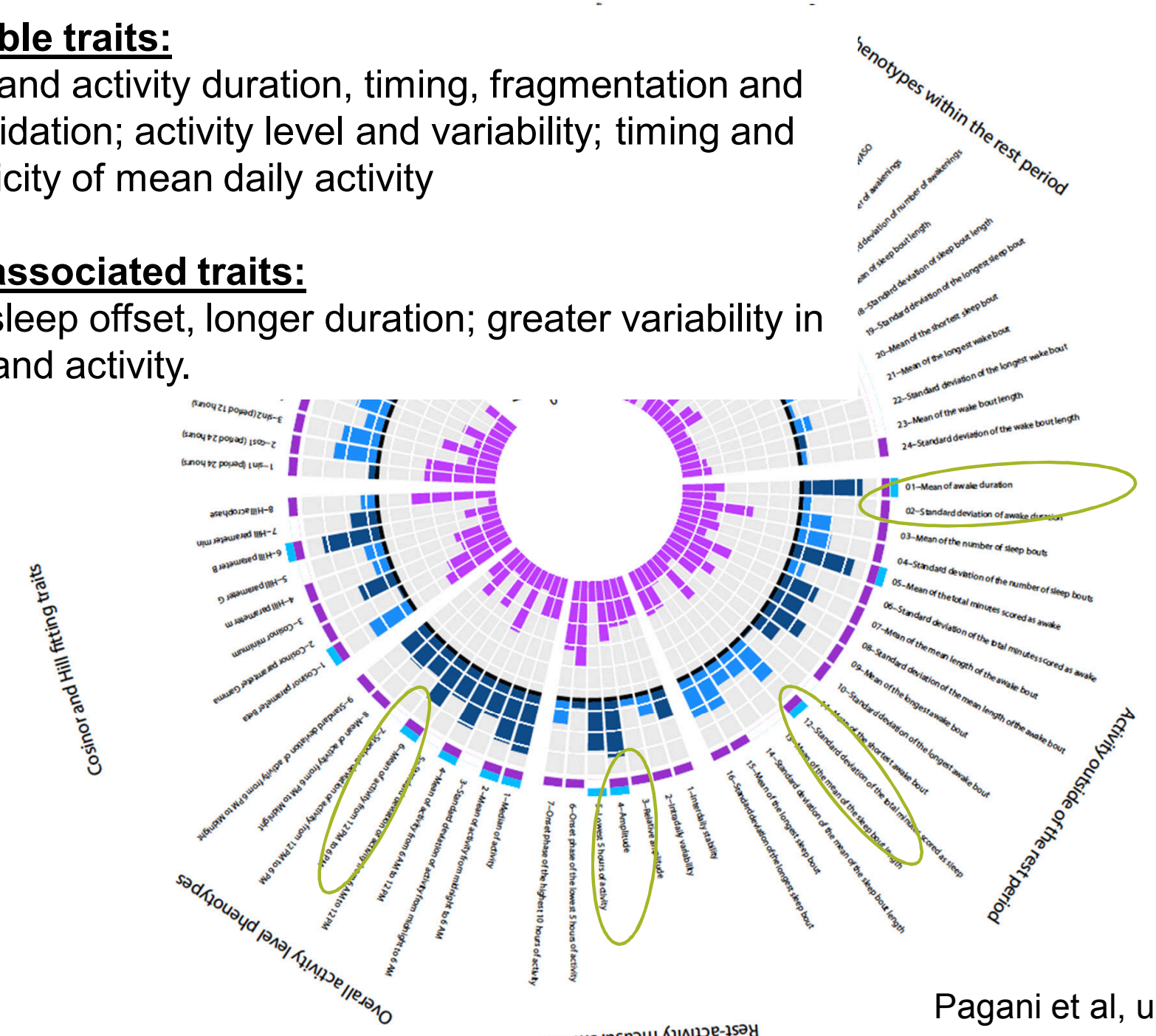
Circadian heritable and disease-associated traits in CR and CO pedigrees

Heritable traits:

Sleep and activity duration, timing, fragmentation and consolidation; activity level and variability; timing and periodicity of mean daily activity

BP-1 associated traits:

Later sleep offset, longer duration; greater variability in sleep and activity.



Pagani et al, under revision

Can we investigate these genetically mediated phenotypes earlier in development?

- Adolescence is a time of extensive increases in physical and mental capabilities, yet increased overall mortality/ morbidity
- Asynchrony in developmental time courses between affective/approach and cognitive control brain systems may lead to increased vulnerability for risk taking in adolescence (Willoughby et al. 2013)
- Prefrontal cortical maturation (dorsolateral and orbito- frontal regions) assumed to correspond to development of higher-level cognitive processes
- Maturing subcortical systems (e.g. nucleus accumbens) disproportionately activated relative to top-down control systems in adolescence (Galvan et al 2006)
- Major shifts in sleep/circadian rhythms: Night-time sleep reduces from ~9 hrs at age 13 to <8 hours at age 16 (Hoban 2004); Delay in circadian phase and sleep onset, often shifting past midnight (Carskadon 2002; Tate 2002).

Phenomenology of Initial Mania Prodrome

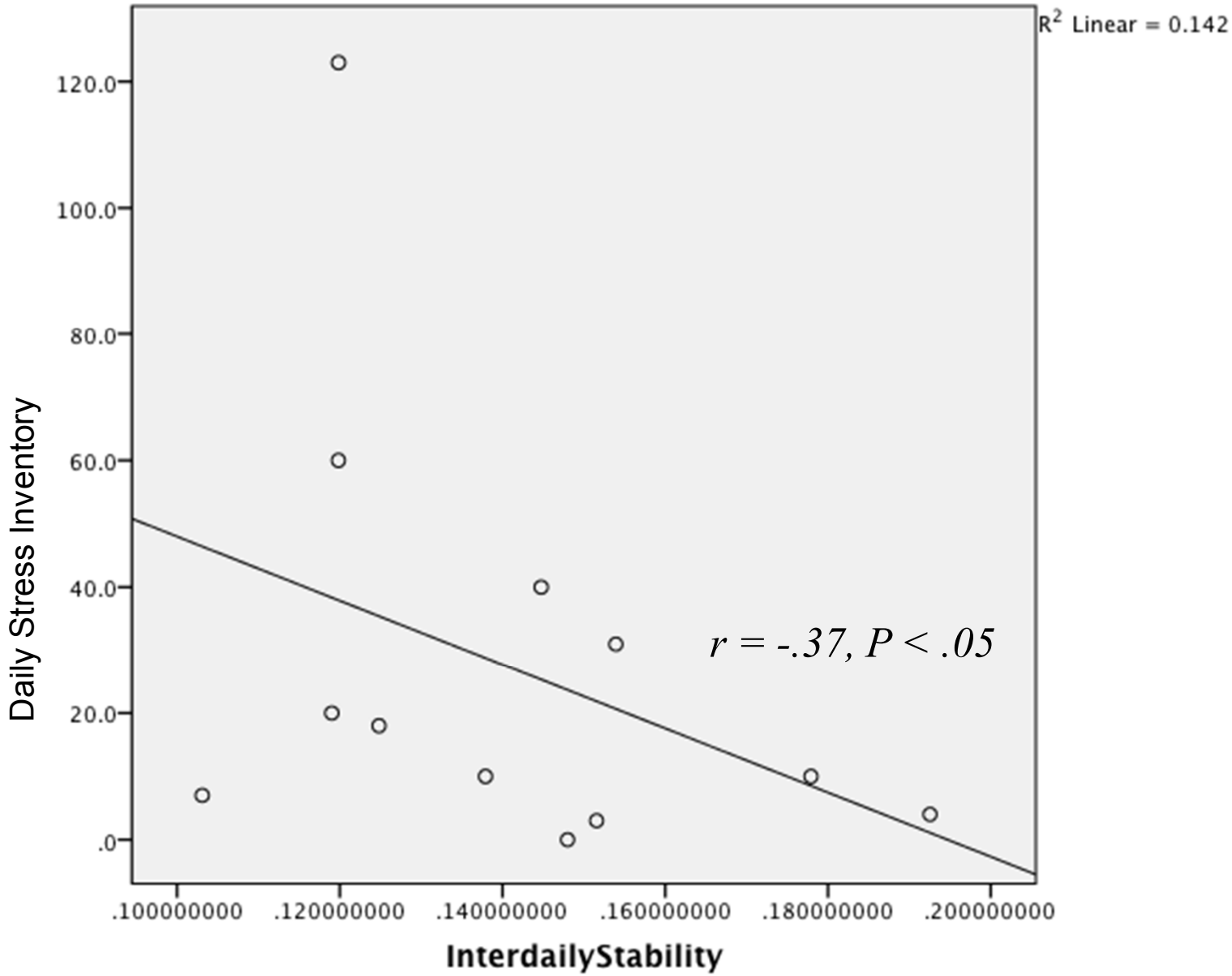
Distal Prodrome	Mood Symptoms	Sleep changes	Behavior/Other Symptoms
Lish et al., 1994 n = 500	Depression, hopelessness, mania/hyperactivity, mood swings	Sleep reduction	Functional impairment, anger, irritability
Egeland et al., 2012 n = 58	Episodic mood change, depressed mood	Decreased need for sleep	Anger dyscontrol, irritability, changed energy level
Kowatch et al., 2005; n = 400	Episodic mood change, elevated mood	Decreased need for sleep	Anger dyscontrol, irritability, changed energy level, conduct problems
<u>Proximal Prodrome</u> Bechdolf et al., 2012; n = 8	Elevated mood	Sleep disturbances	Anger/irritability, increased energy/activity, anxiety, decreased functioning
Thompson et al 2003; n = 3	Mood Swings	Sleep disturbances	Increased energy/activity, racing thoughts, percpetual changes

DSM Diagnoses in Adolescent High Risk Offspring in Colombia (N = 17)	Age 14.7+/ 2.3 years; 50% Female
Anxiety Disorder	11 (66%)
ADHD	7 (40%)
Major Depression	1 (6%)
Dysthymia	2 (12%)
Conduct Disorder	1 (6%)

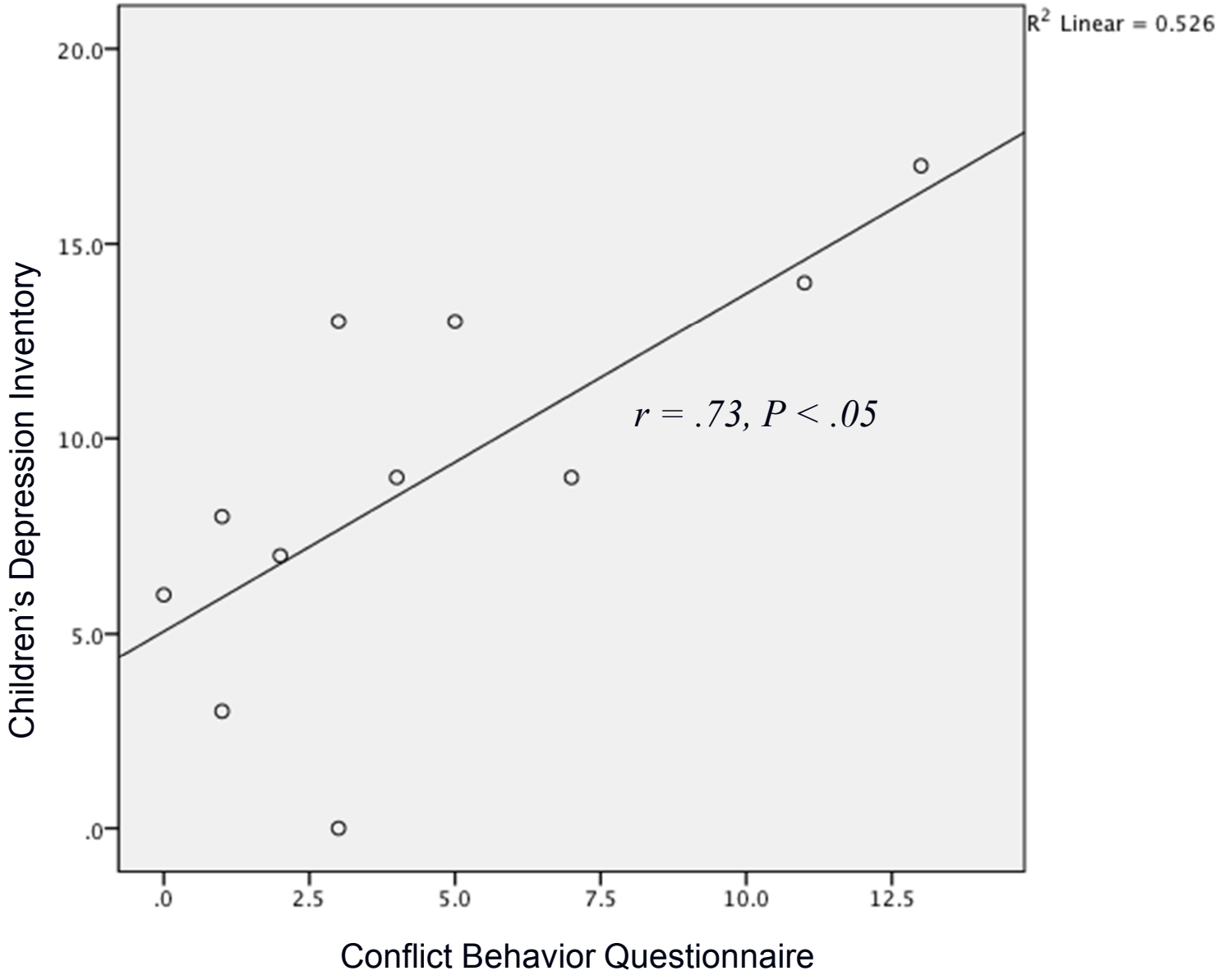
Consistent with other high risk studies, indicating greatly elevated rates of psychiatric disorders in high risk youth, especially anxiety/attentional disorders

Carlson GA, et al. *J Affect Disord*. 1993;28(3):143-153. Chang KD, et al. *J Am Acad Child Adolesc Psychiatry*. 2000;39(4):453-460. Chang KD, et al. *J Affect Disord*. 2003;77(1):11-19. Wals M, et al. *J Affect Disord*. 2005;87(2-3):253-263.

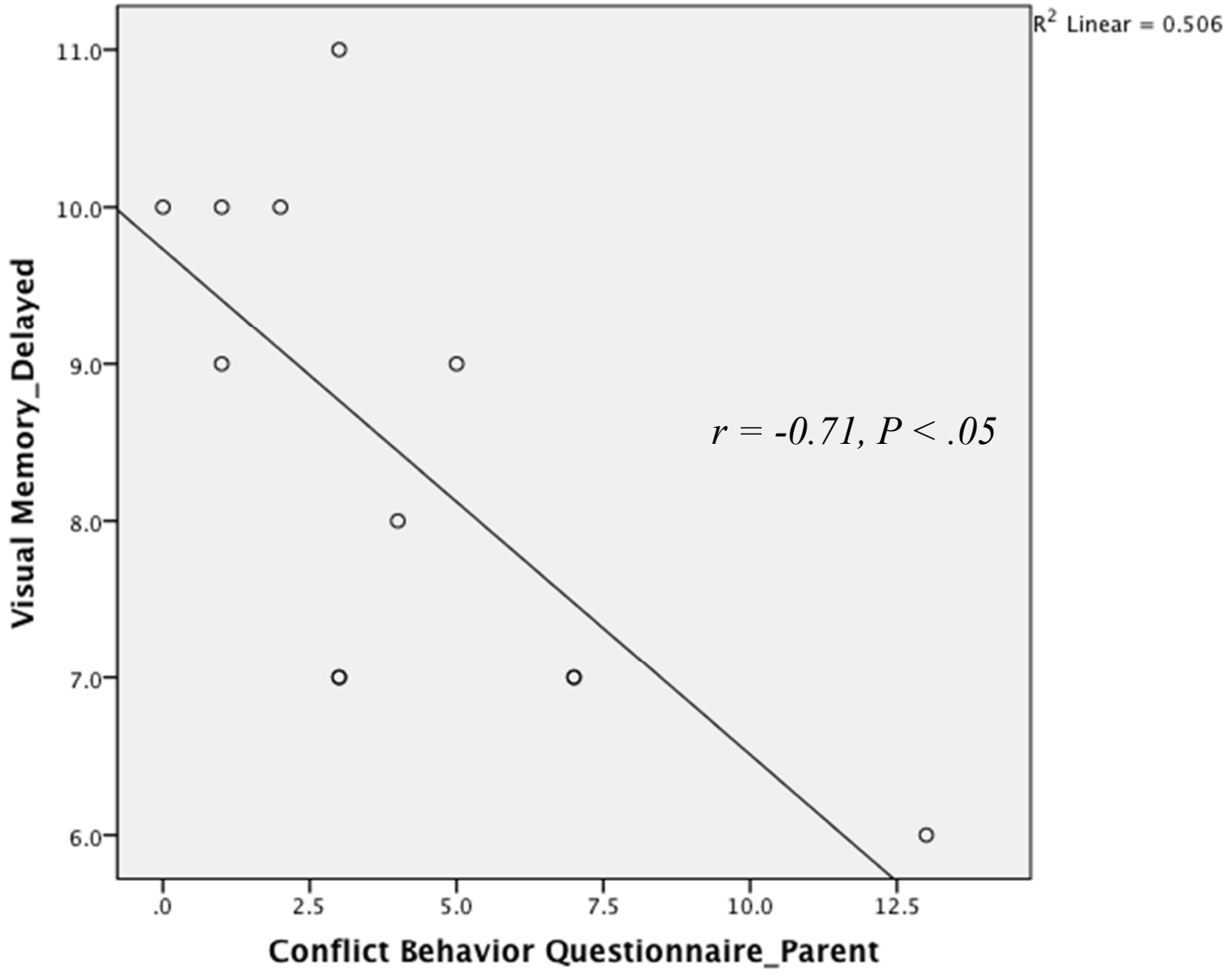
Greater Stability of Daily Rhythms Associated with Lower Self-Reported Stress in High Risk Adolescents



Greater Family Conflict Associated with Mood and Anxiety Symptoms in High Risk Adolescents

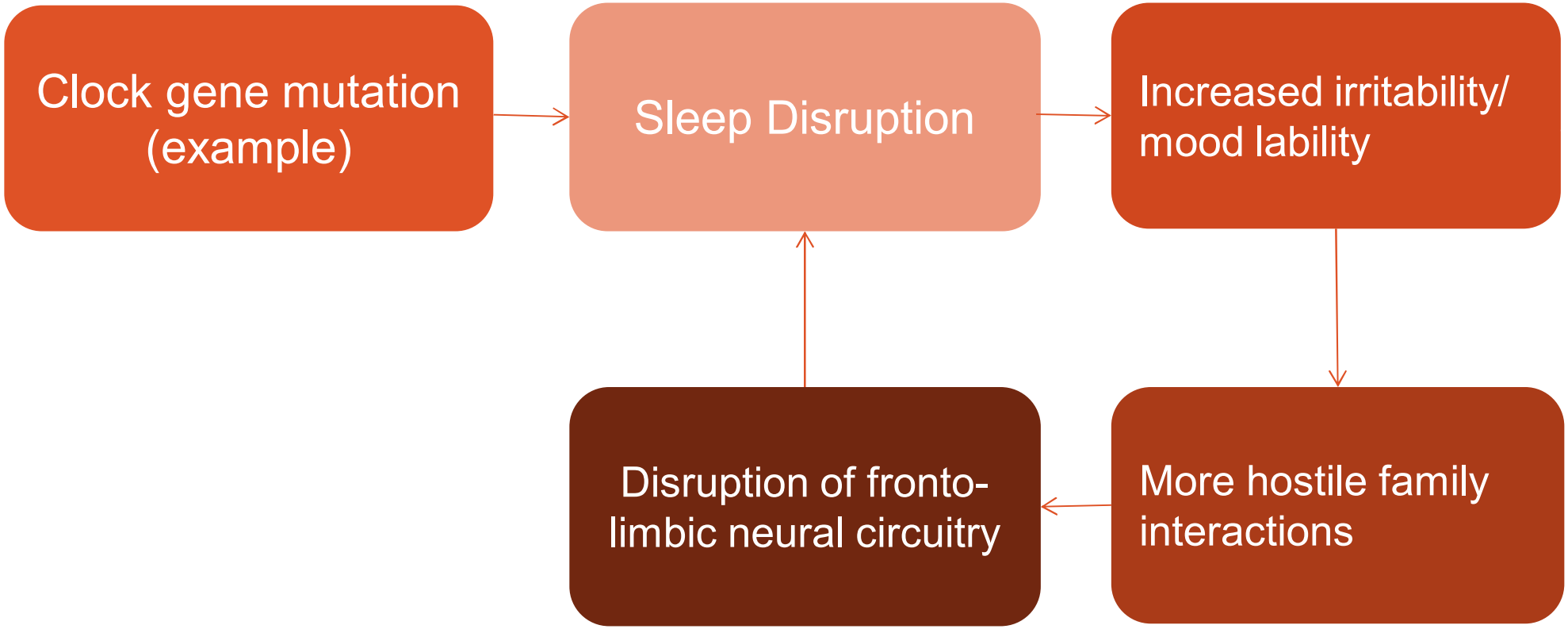


Greater Family Conflict Associated with Poorer Memory in High Risk Adolescents

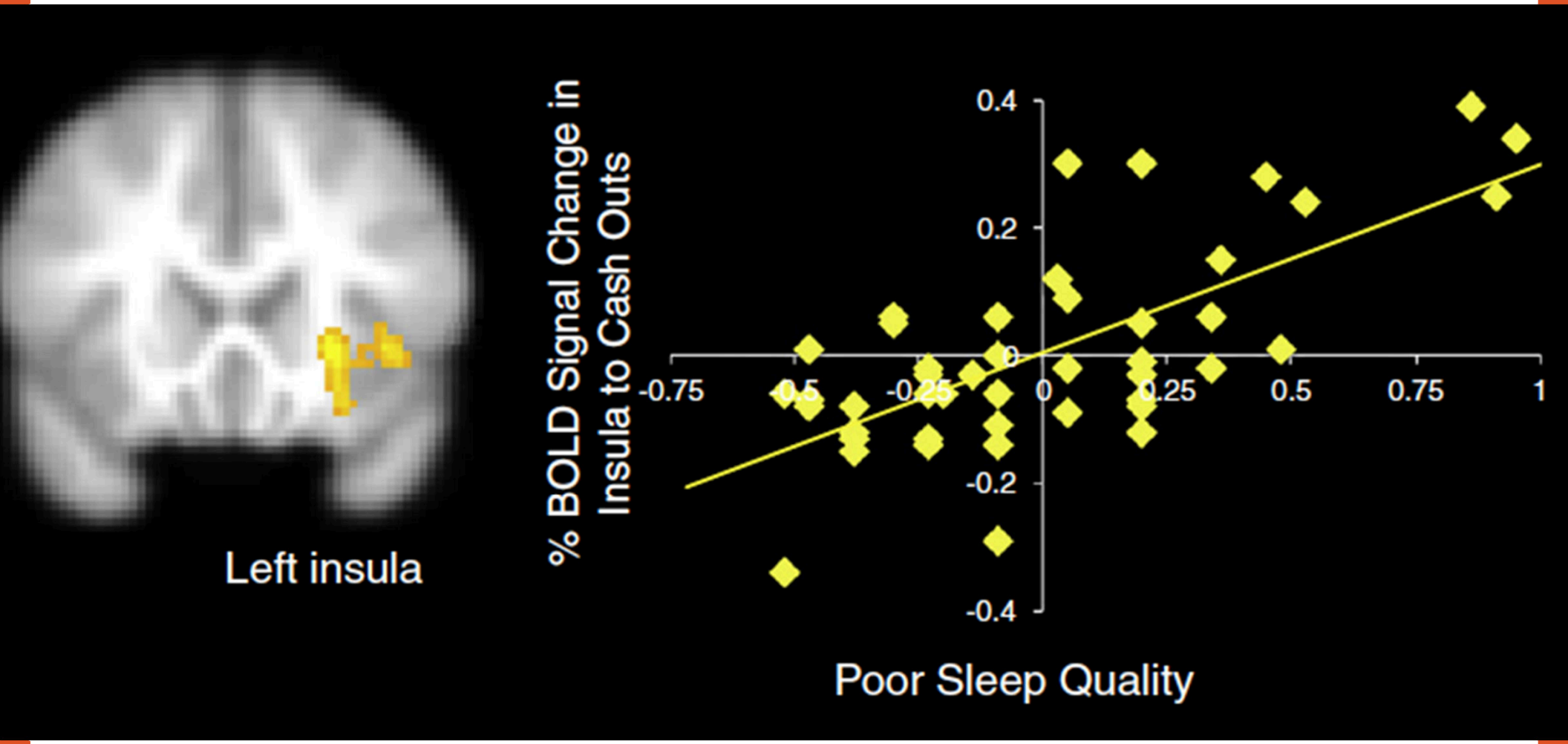


Direction of Causality…?

What is the Causal Pathway?



Poor Sleep Quality Associated with Greater Risk Taking, Increased Insula Activity, and Reduced Fronto-limbic Coupling during Reward Processing, Reduced Cognitive Control



- Poor sleep may exaggerate imbalance between affective and cognitive control systems, leading to increased risk-taking

Telzer EH, et al. *Neuroimage*. 2013;71:275-283.

Summary and Implications

Adolescence is a period of brain plasticity and structural reorganization; asynchrony in developmental time courses between frontal-subcortical structures

Sleep disruption is a risk factor for development of mood disorders in adolescence; may exaggerate normative imbalance between affective and cognitive control systems

Based on findings in adult pedigree members, brain abnormalities in regions involved in inhibitory control and emotion regulation, as well as circadian rhythm disruption, are key heritable endophenotypes that may index disease risk

Initial data in high risk adolescents suggest robust links between daily rhythm stability/stress, family conflict/mood and cognition

Clinical Implications: Lifestyle Interventions

In older adults with major depressive disorder, increasing evidence for effectiveness of complementary/ alternative therapies

(eg, yoga, tai chi, exercise)

"Social rhythm" therapy effective for adult bipolar disorder

(eg, **Frank E, et al. *Biol Psychiatry*. 1997;41(12):1165-1173. Frank E, et al. *Biol Psychiatry*. 2000;48(6):593-604. Frank E, et al. *Dialogues Clin Neurosci*. 2007;9(3):325-332.**);

regularize daily routines, diminish interpersonal problems

For adolescents:

Regular sleep schedule; avoid over-scheduling

Limit caffeine intake and screen time

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