BMC Youth Model Seminar #7

Circadian-based Mood Disorders:
Bipolar and Atypical Depression

Presented by

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THE UNIVERSITY OF SYDNEY

Acknowledgements

- Of country
- Of lived experience

Overview

1. Light-dark cycle
2. Role of clinical trajectories
3. Circadian-based mood disorders
4. Clinical staging
5. Case example

Light-Dark Cycle as the principle driver of rhythms

The 24-hour light-dark cycle is the primary environmental time cue that entrains the circadian system

we have adapted (almost) to live on a 24-hour planet
(actually humans have 24.2 hr cycle)_

Light as the central regulator: Direct and Indirect

Light as a central modulator of circadian rhythms, sleep and affect

Tara A. LeGates[1,2], Diego C. Fernandez[1] and Samer Hattar[1,3]

Abstract | Light has profoundly influenced the evolution of life on earth. As widely appreciated, light enables us to generate images of our environment. However, light — through intrinsically photosensitive retinal ganglion cells (ipRGCs) — also influences behaviours that are essential for our health and quality of life but are independent of image formation. These include the synchronization of the circadian clock to the solar day, tracking of seasonal changes and the regulation of sleep. Irregular light environments lead to problems in circadian rhythms and sleep, which eventually cause mood and learning deficits. Recently, it was found that irregular light can also directly affect mood and learning without producing major disruptions in circadian rhythms and sleep. In this Review, we discuss the indirect and direct influence of light on mood and learning, and provide a model for how light, the circadian clock and sleep interact to influence mood and cognitive functions.

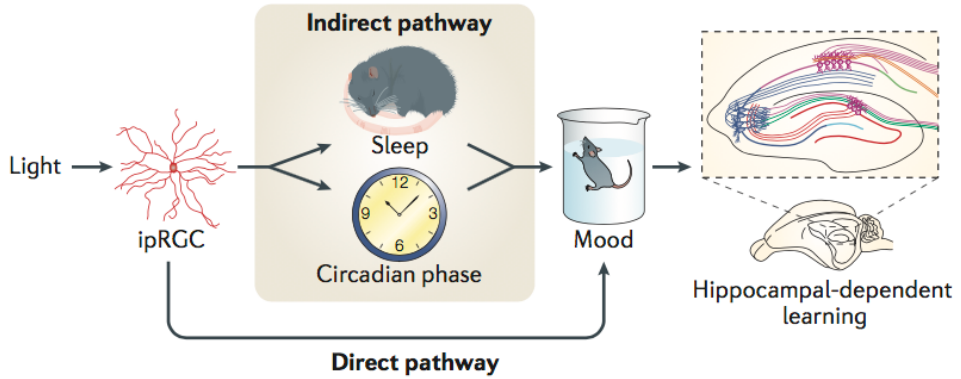
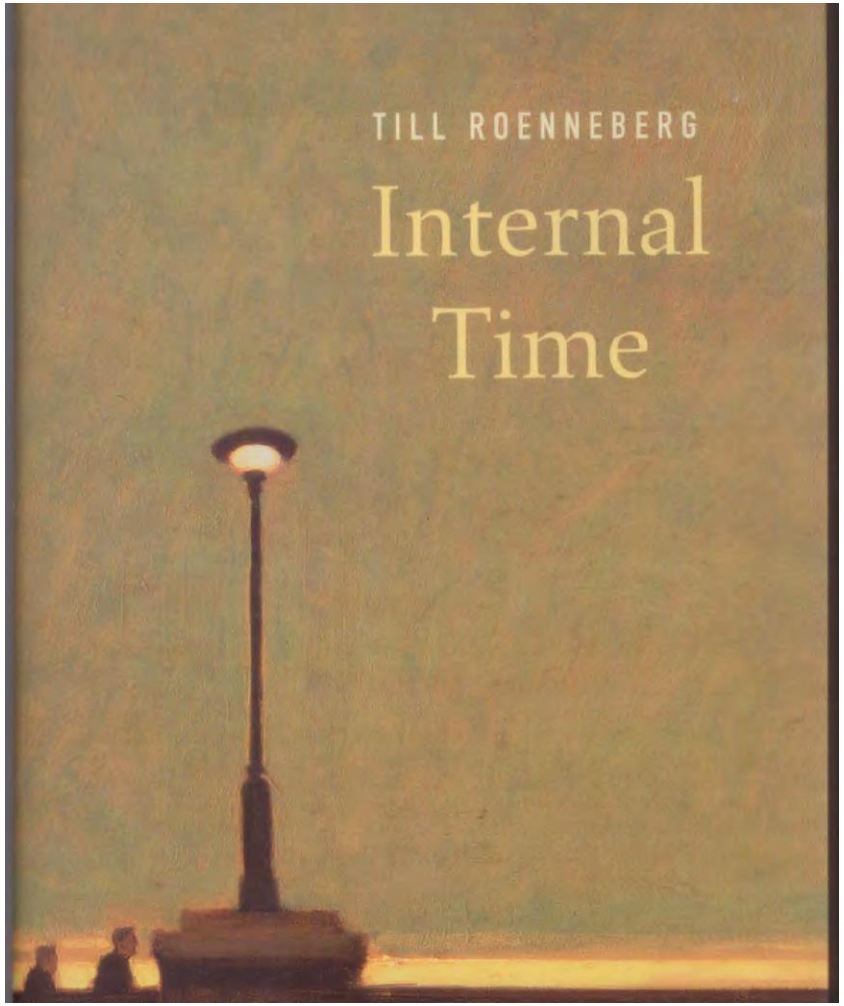


Figure 1 | **Model of the direct and indirect influences of light on mood and cognition.** Light can regulate mood and learning by first modulating sleep and circadian rhythms (indirect pathway), or it can directly affect mood without disrupting sleep or causing circadian arrhythmicity (direct pathway). These pathways have also been shown to mediate the effects of light on hippocampal-dependent learning in rodents. The effects of light on circadian rhythms, sleep and mood are mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs). Figure from REF. 85, Nature Publishing Group.

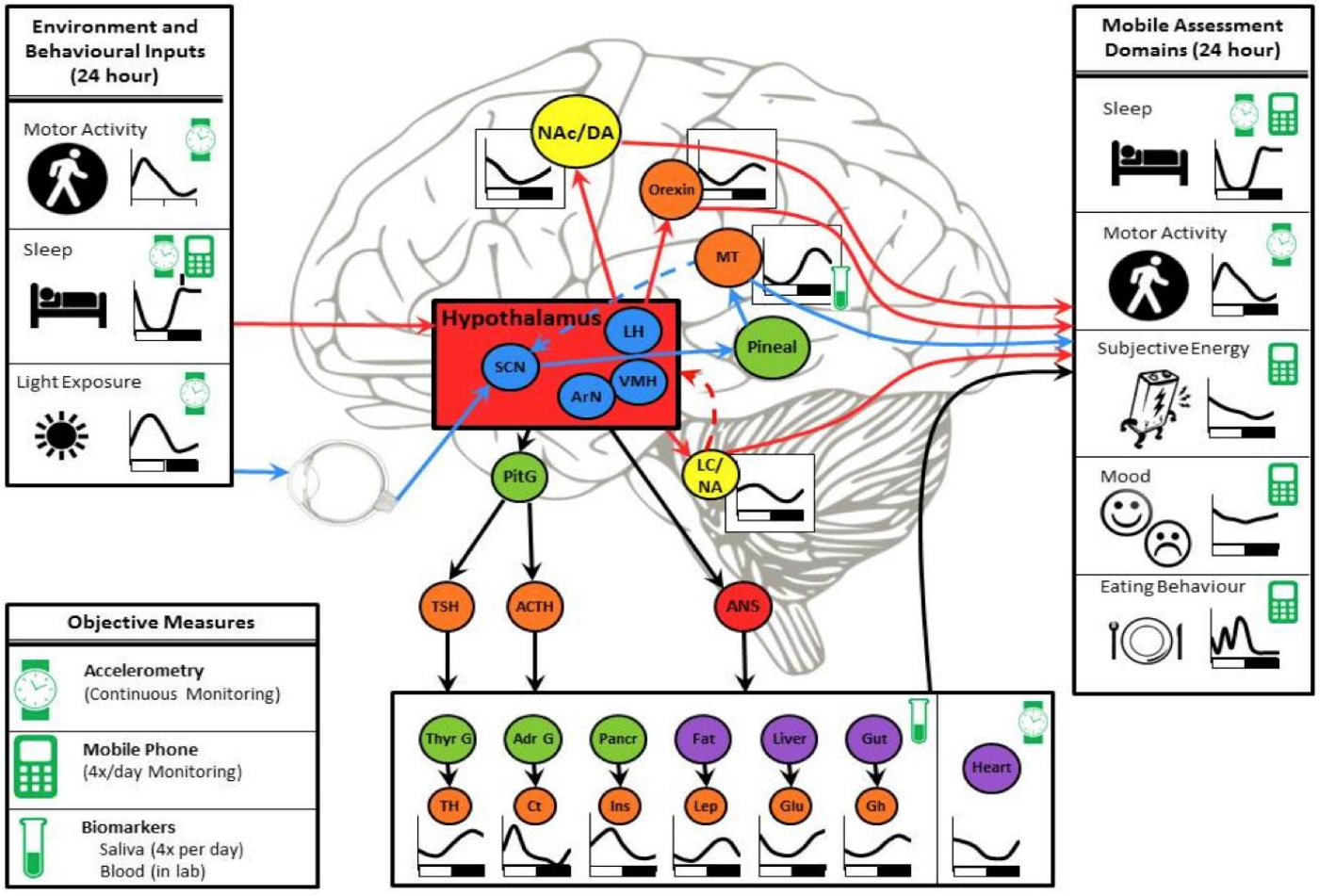
Characteristics of a functioning clock

Till Roenneberg 'Internal Time' 2012

- 1. Our body's internal day is controlled by its own biological clock;
- 2. Since the biological clock is not 24 hours in length it must be periodically re-set to match the external world;
- 3. The biological clock varies from individual to individual (AND BY DISEASE STATE)!;
- 4. We feel best when all of our bodily functions oscillate in synchrony.

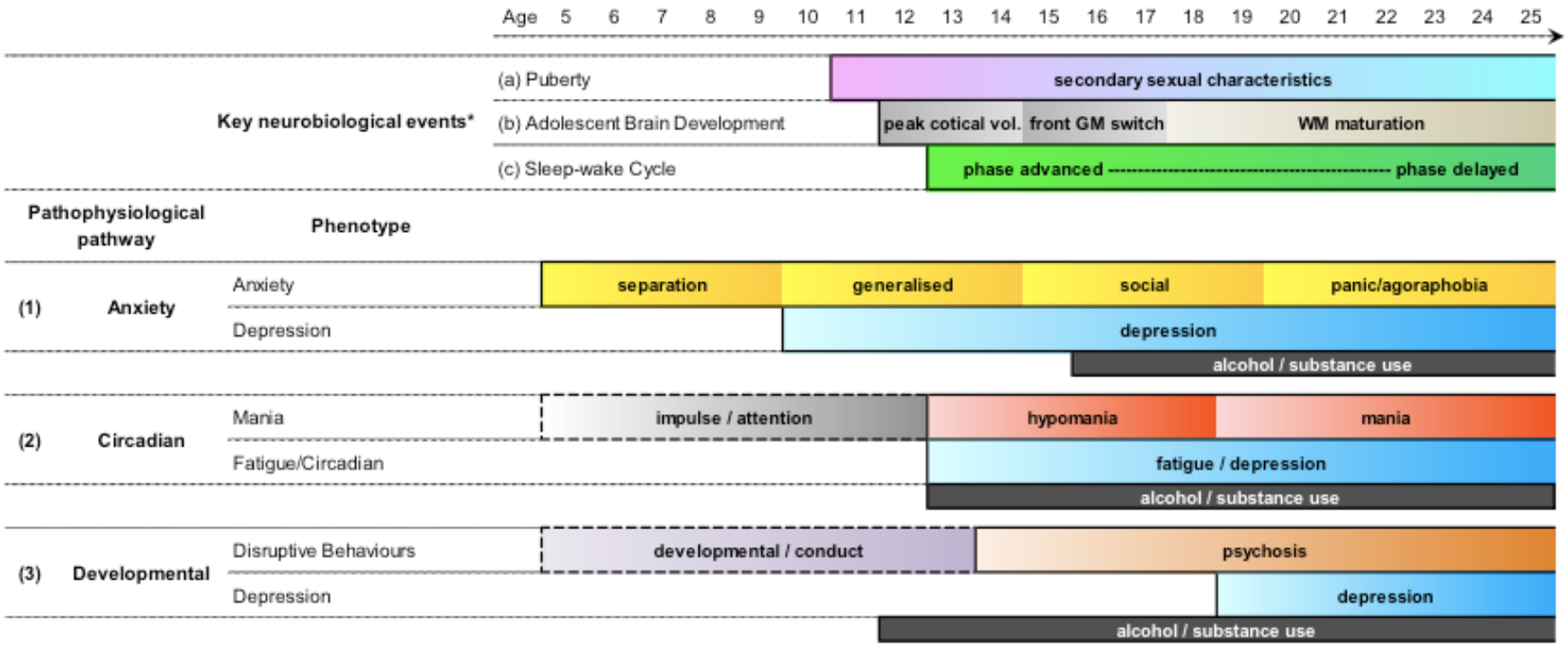


Environmental processes associated with regulation of the circadian system

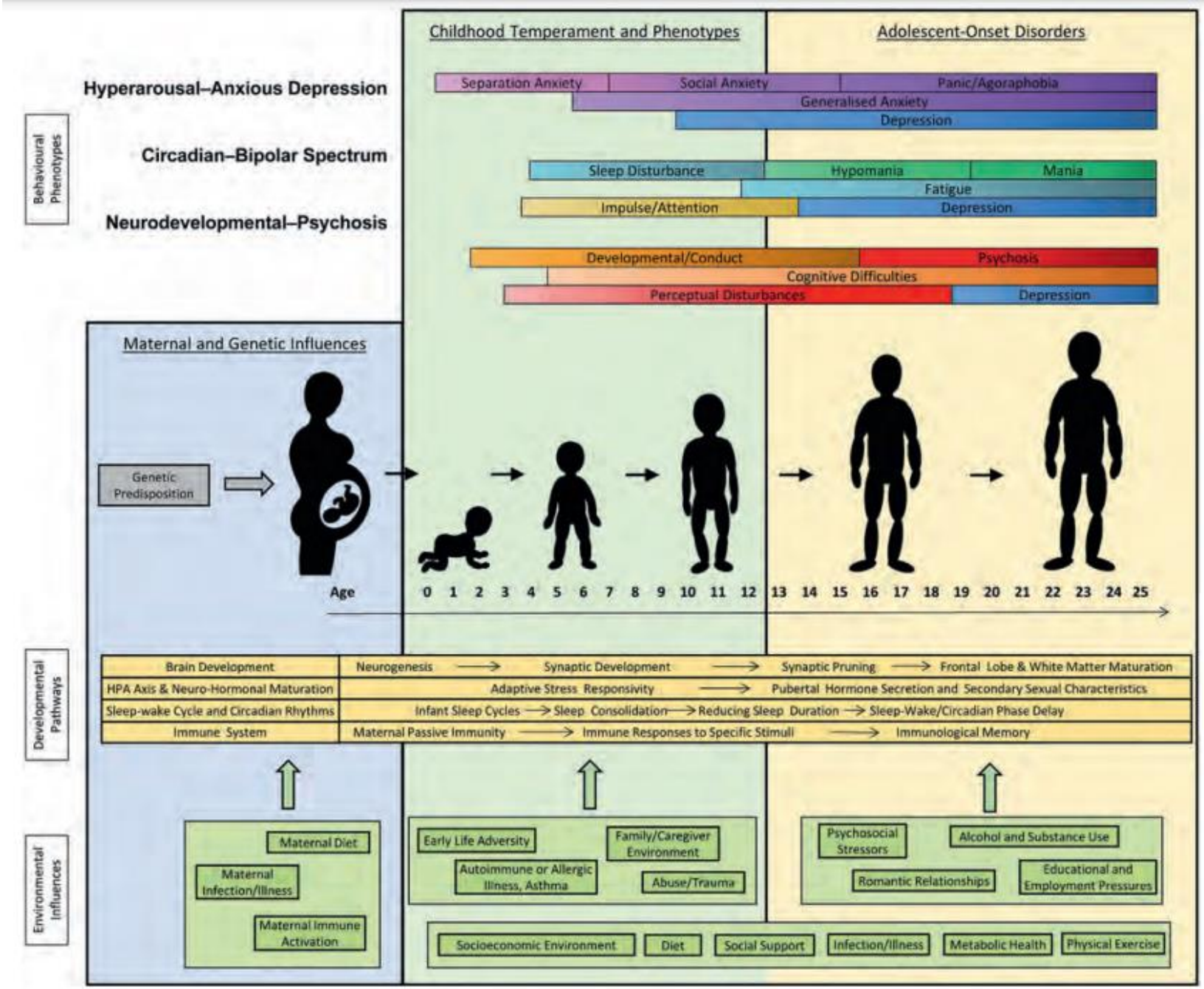


Hypothetical Trajectories/Pathways to Adolescent-Onset Depressive Disorders

1. Highlighting Circadian-based Pathways to Adult Mood Disorders
2. Enhancing anxiety-driven and developmental pathways



Age-dependent mood disorder phenotypes in the context of developmental and environmental influences

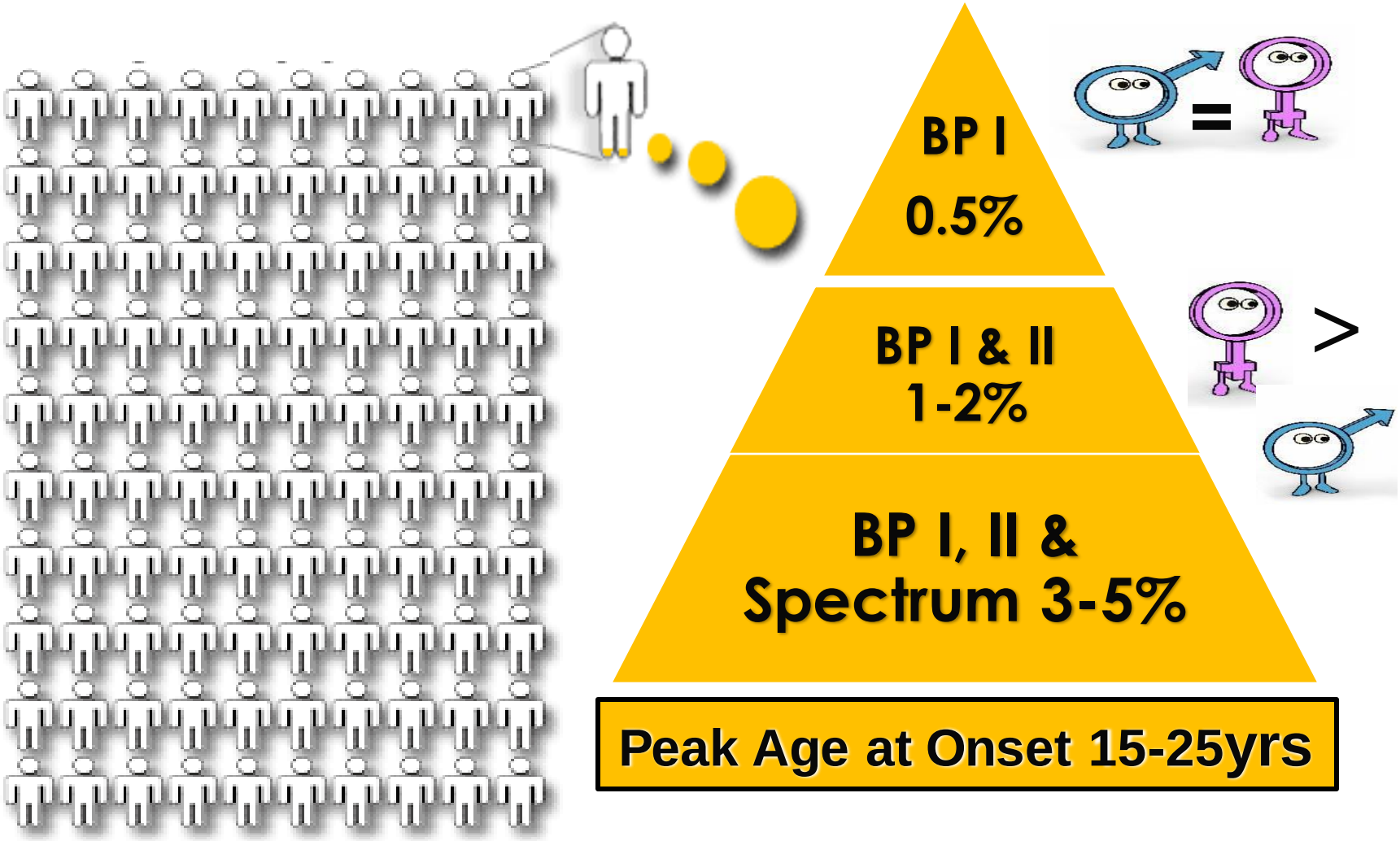


Carpenter et al., 2019

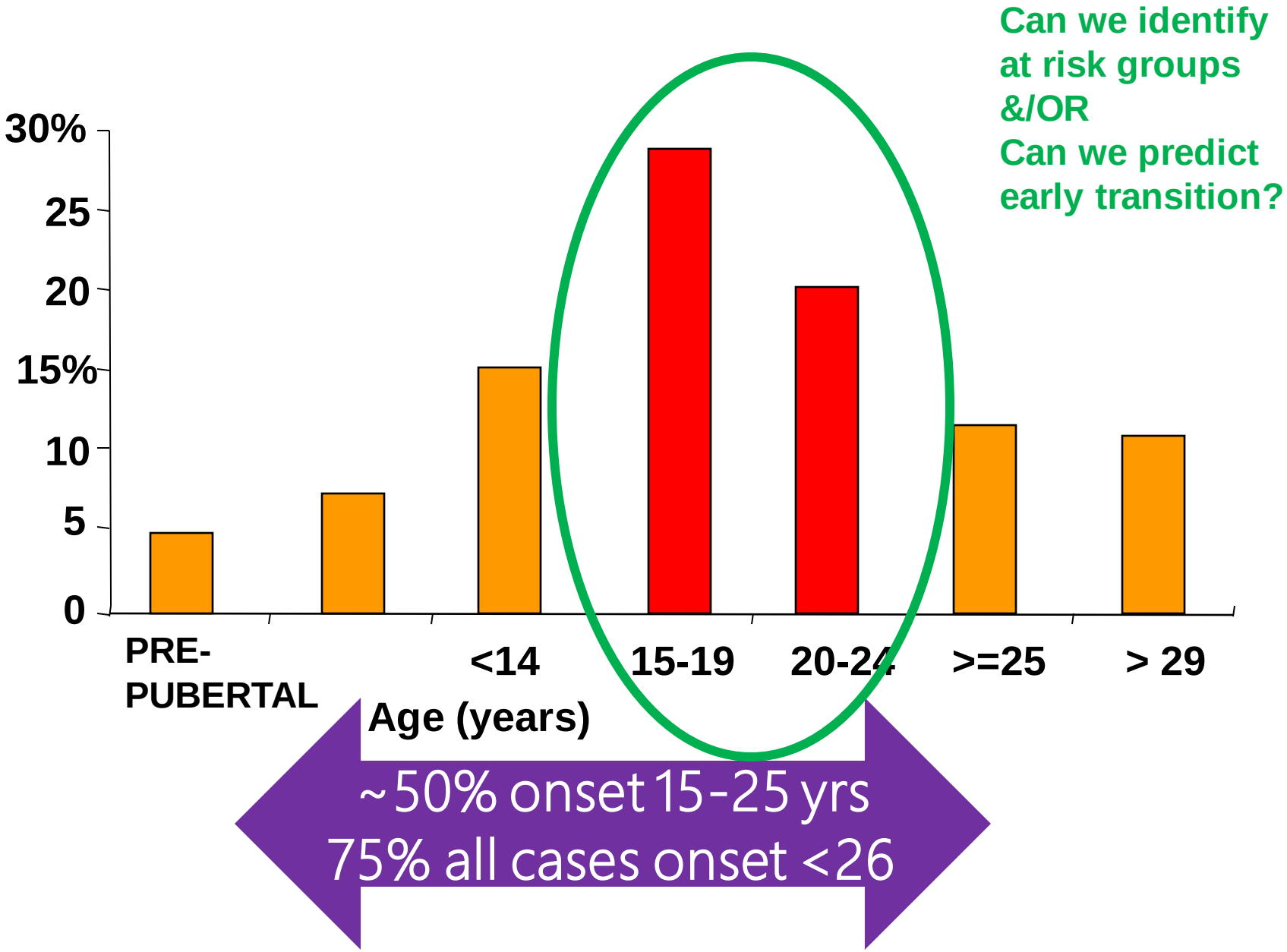
Circadian-based mood disorders:
Bipolar Disorder, Atypical Depression, Seasonal Affective Disorder

1. Disruption of the 24-hour sleep-wake and circadian systems as the fundamental biology
2. Atypical depression - 25-30% of clinical cases in young people
3. Novel Assessment Techniques – actigraphy, melatonin-onset assays
4. Targeted interventions for depression – behaviourally on sleep-wake and pharmacologically on melatonin-analogues or arousal systems
5. Relevance of traditional medications – notably lithium (lengthens the circadian period)
6. Exploration of effects of other modalities on circadian periods (anticonvulsants and other mood stabilizers, modafinil etc)

Bipolar Disorders-
A Short History of Everything

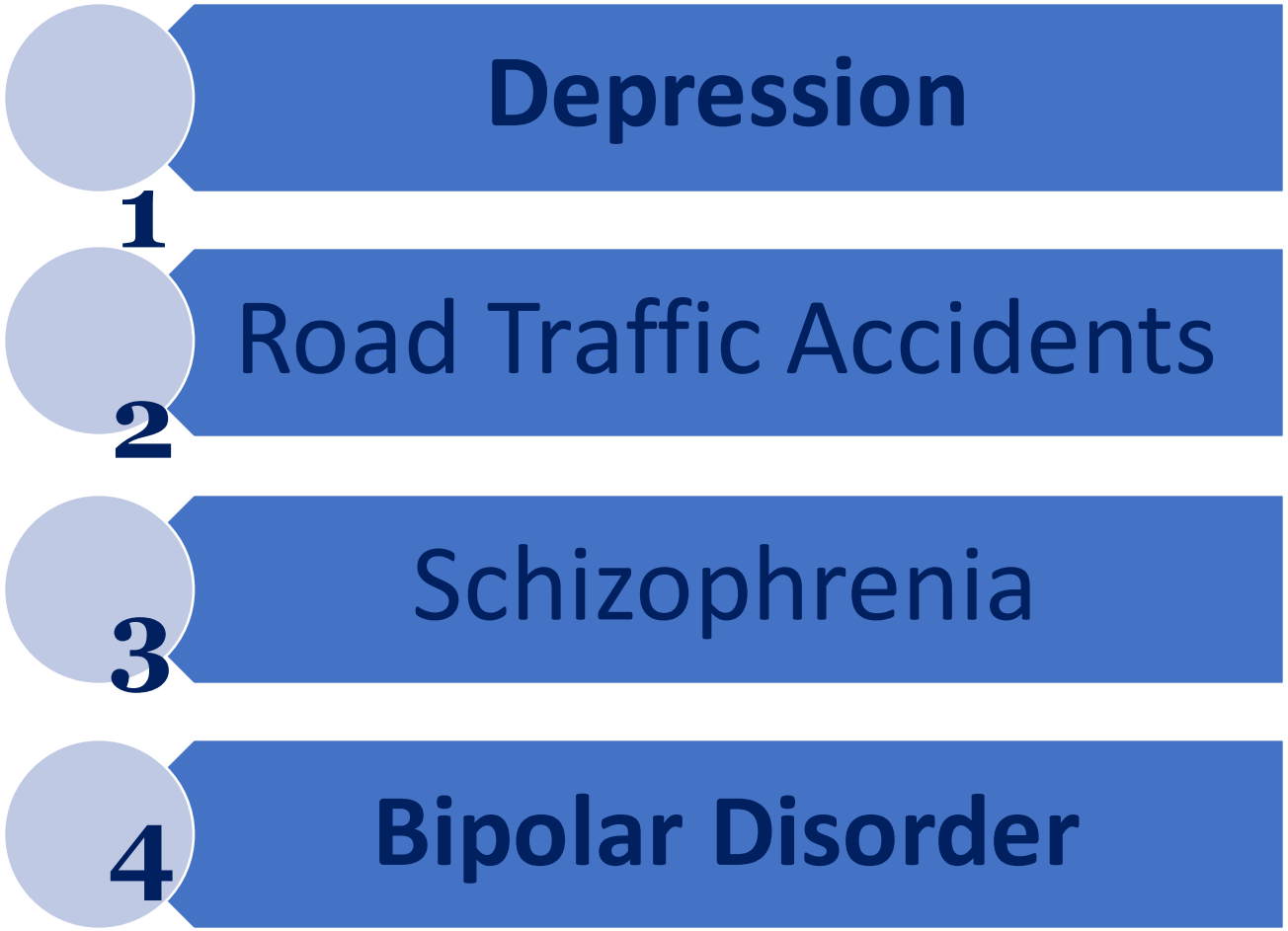


Age of Onset of Bipolar Disorders

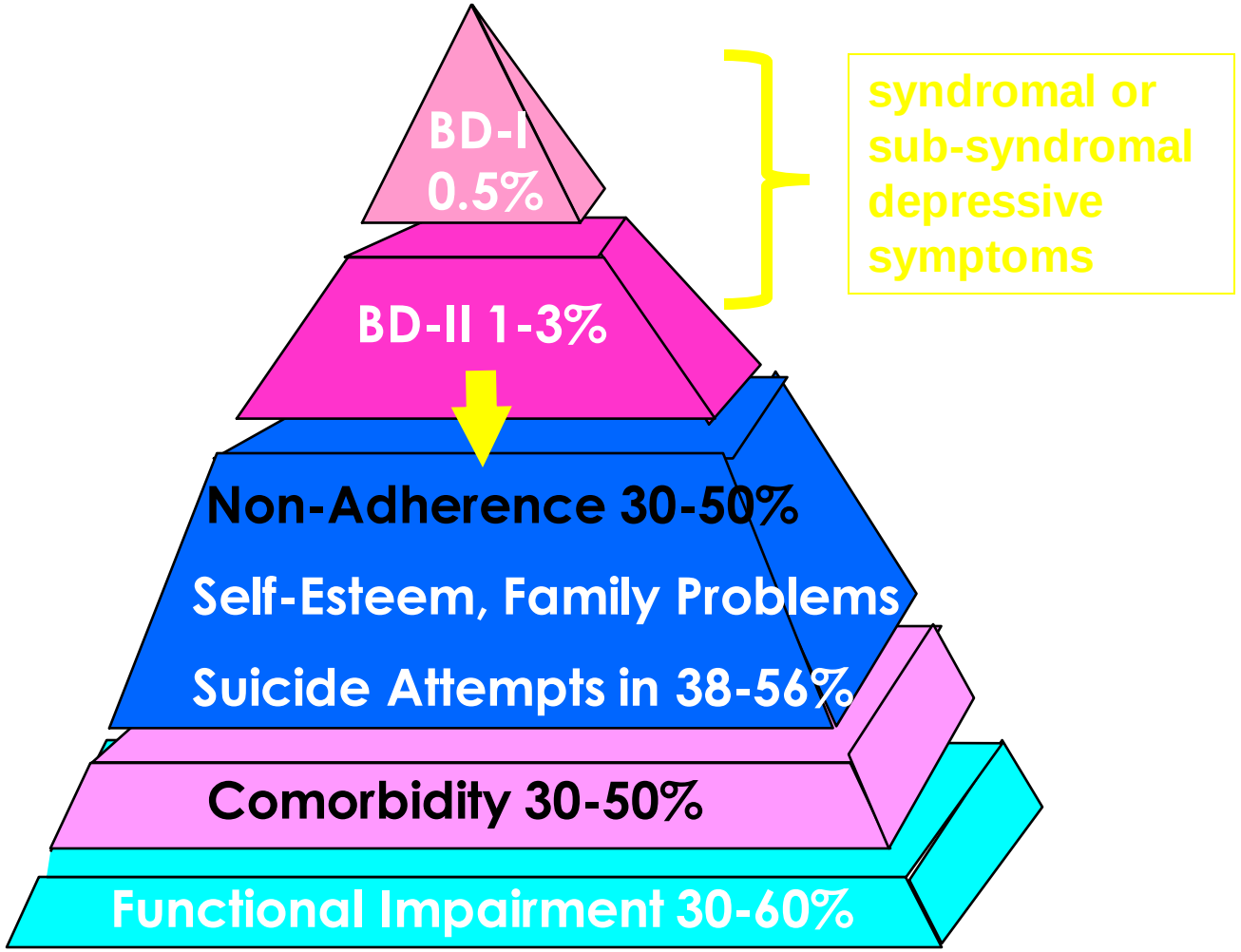


Global burden of disease in individuals under 24

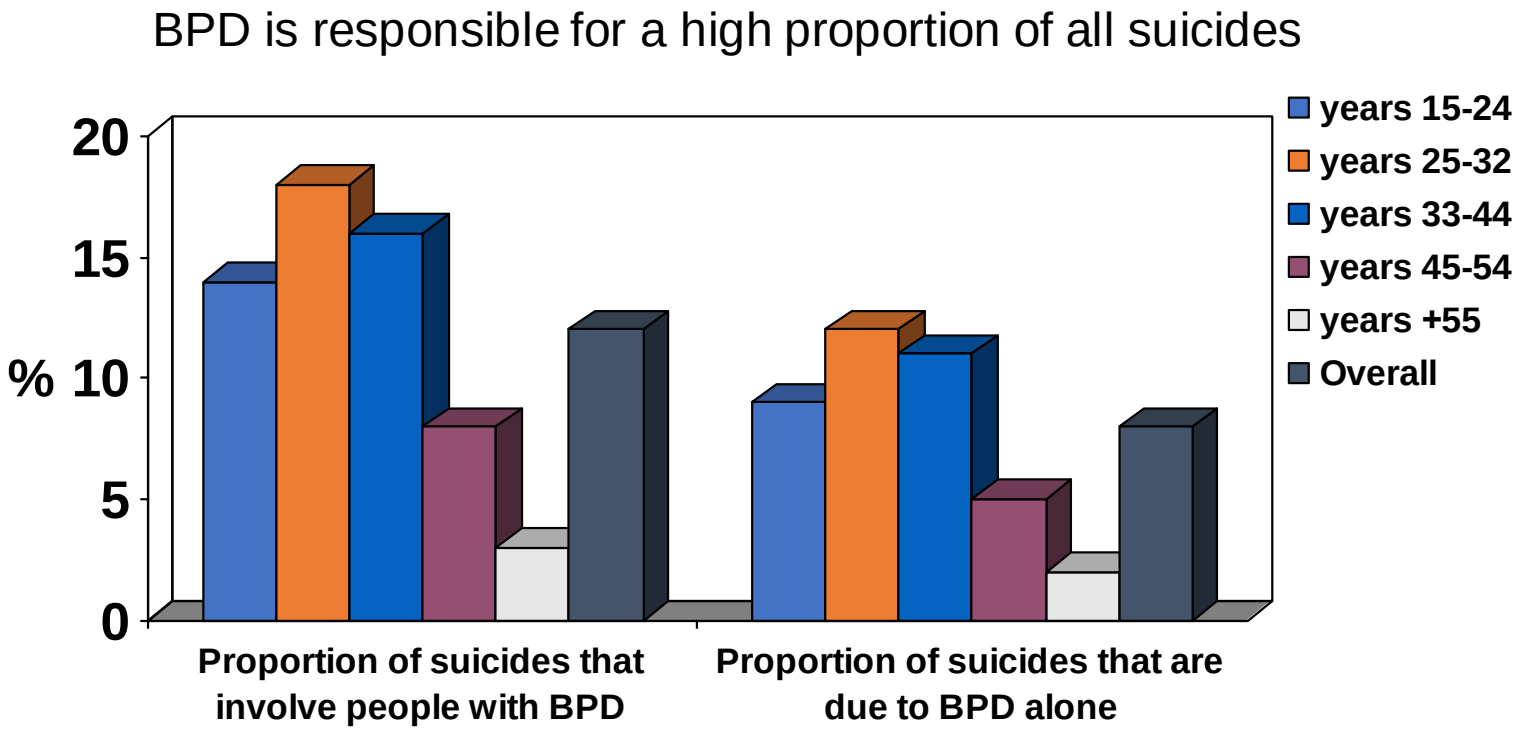
(Gore et al,2011)



The Problem of Bipolar Disorders



Bipolar disorder is a major burden…



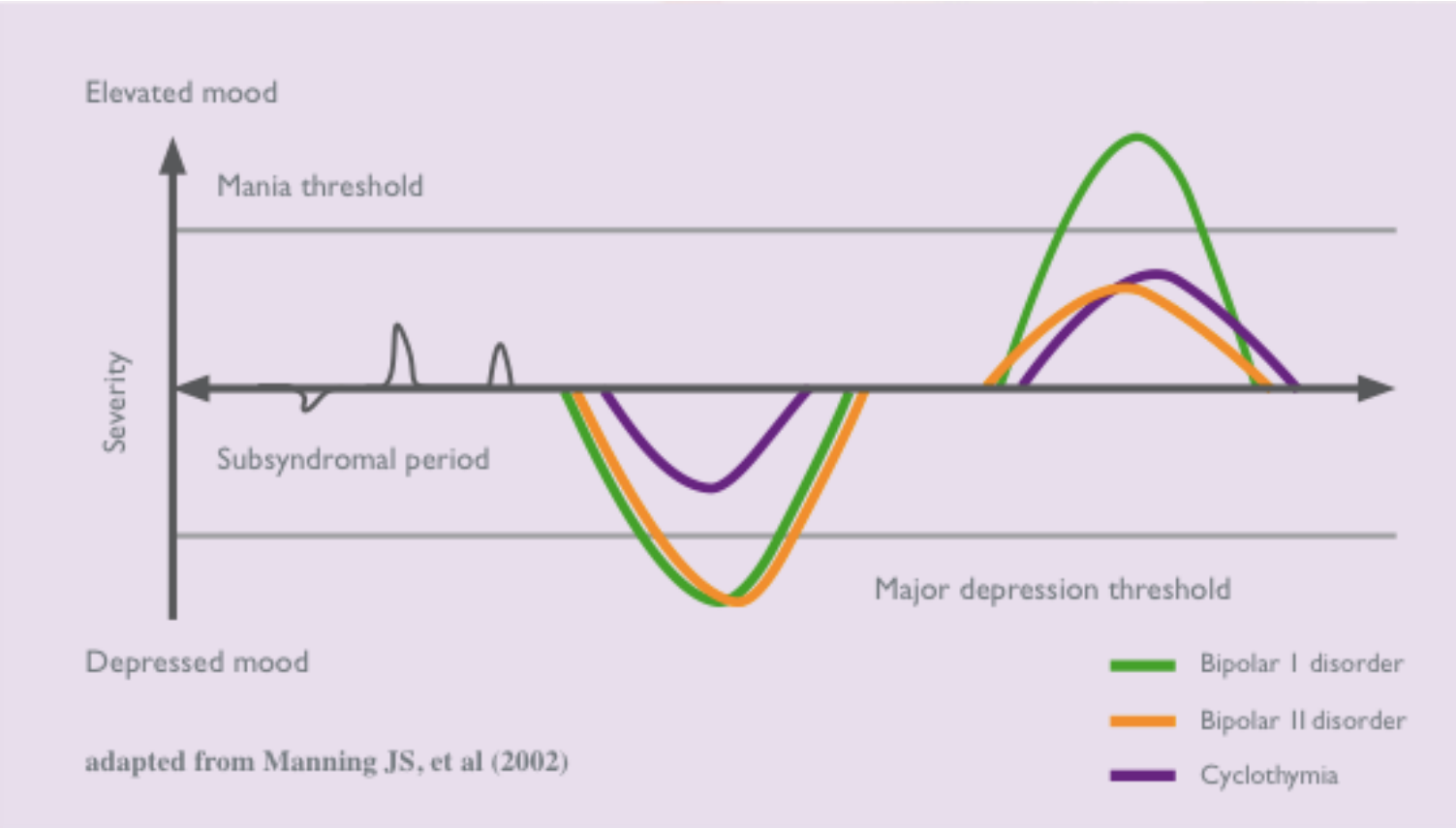
Note:

More than 25% of people with BPD attempt suicide, which is nearly twice the rate observed among patients with depression.[13]

The lifetime risk of suicide for people with BPD is approx. 15%

Access Economics; SANE Australia (2003)

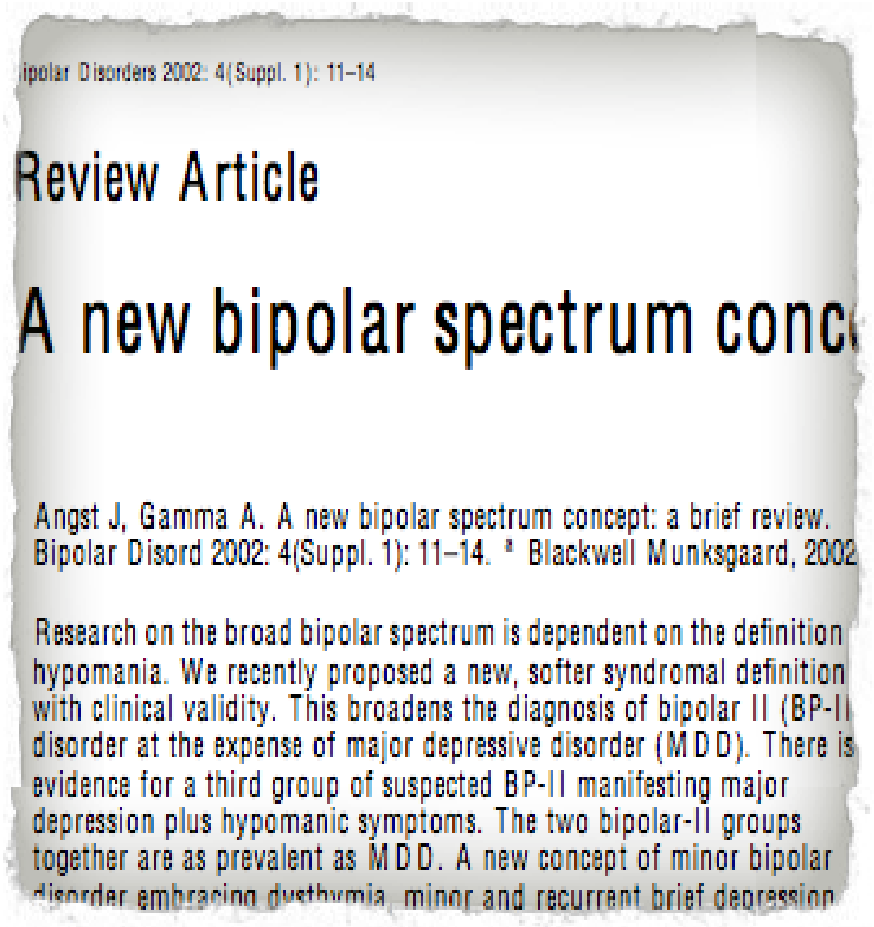
The bipolar spectrum



- Lifetime prevalence rate of 1.6% for bipolar disorder in the general population
- The prevalence rate is over 6% if subthreshold or atypical forms of the disorder are included (eg bipolar II, BD NOS, cyclothymic disorder)

Manning JS (2005) Burden of Illness in Bipolar Depression. Prim Care Companion J Clin Psychiatry 7(6):260-267

What is the bipolar spectrum?



ipolar Disorders 2002: 4(Suppl. 1): 11–14

Review Article

A new bipolar spectrum conc

Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord 2002: 4(Suppl. 1): 11–14. © Blackwell Munksgaard, 2002

Research on the broad bipolar spectrum is dependent on the definition hypomania. We recently proposed a new, softer syndromal definition with clinical validity. This broadens the diagnosis of bipolar II (BP-II disorder at the expense of major depressive disorder (MDD). There is evidence for a third group of suspected BP-II manifesting major depression plus hypomanic symptoms. The two bipolar-II groups together are as prevalent as MDD. A new concept of minor bipolar disorder embracing dysthymia, minor and recurrent brief depression

- "Hypomania: a syndrome (no minimum duration) characterised by the presence of
  - a) overactivity, euphoria or irritability plus
  - b) three of seven DSM-IV criteria symptoms leading to subjective or social consequences"
- BP-II disorders are defined as major depressive episodes with hypomania

Angst J and Gamma A (2002) A new bipolar spectrum concept: a brief review. Bipolar Disorders 4:11-14

What is the bipolar spectrum?

A spectrum of disorders characterised by:

- Episodic changes in activation and drive
- Mood disturbance
- Cognitive symptoms
- Hormonal/endocrine abnormalities
- Disrupted circadian system
- Metabolic impairment
- Altered immunoregulation
- Autonomic dysregulation

Circadian-based Mood Disorder Phenotypes

1. *MANIA – HYPOMANIA: HIGH ACTIVITY STATE*

Secondary phenomena :

↑ ELEVATED MOOD ↓ DECREASED SLEEP – ↓ WEIGHT LOSS

2. *FATIGUE – DEPRESSION; LOW ACTIVITY STATE*

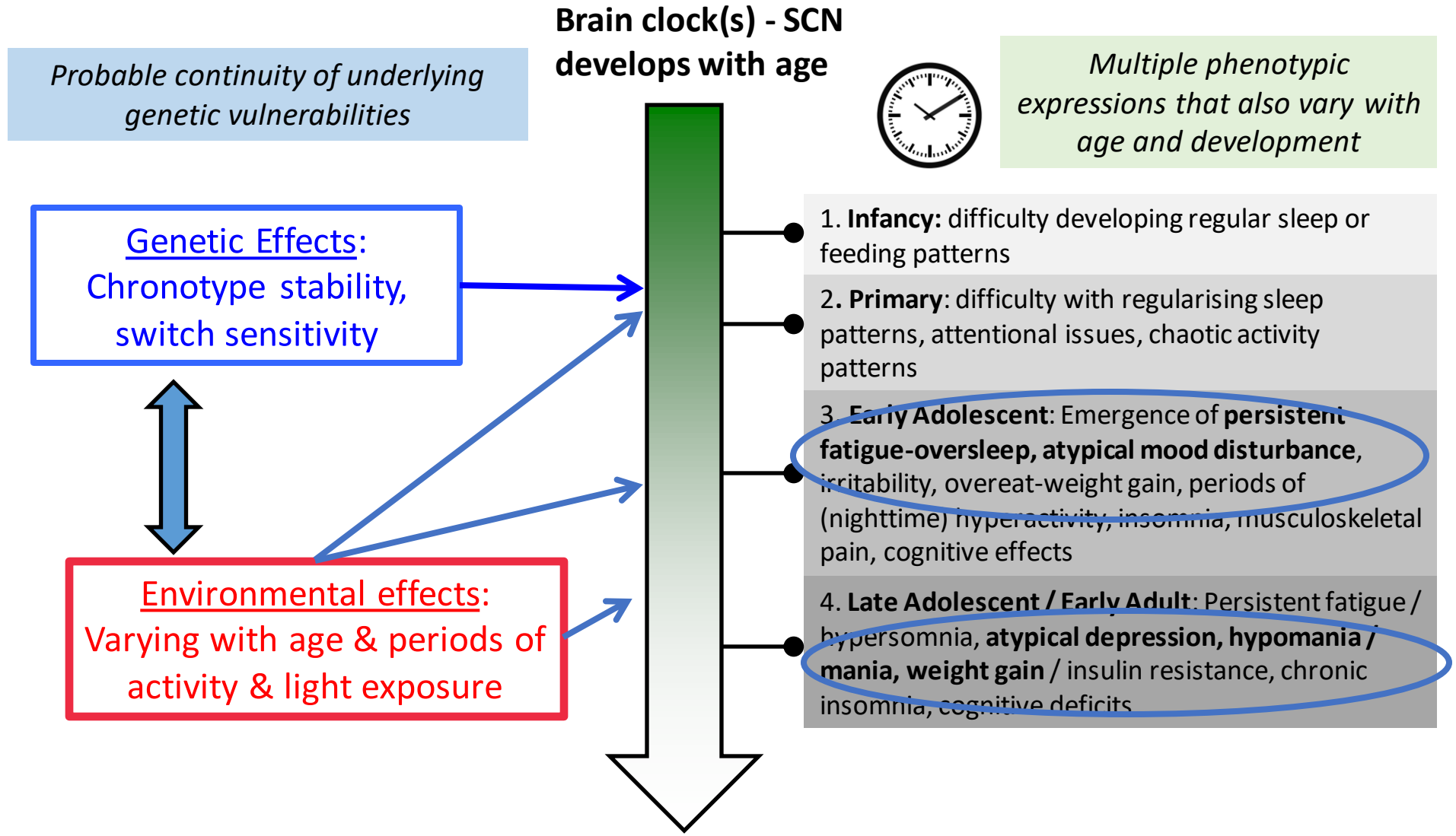
Secondary Phenomena:

↓ LOW MOOD/FATIGUE ↑SLEEP ↑WEIGHT GAIN

SWITCHING FROM ONE STATE TO ANOTHER UNDER A VARIETY OF CIRCUMSTANCES:

- 1. SEASONAL (LIGHT PERIODS)
- 2. MEDICATION (STIMULANTS, ANTIDEPRESSANTS)
- 3. OTHER CIRCADIAN OR SLEEP DISRUPTING STRESSORS (INFECTION, SLEEP DEPRIVATION, SHIFT WORK, TRANSMERIDIEN TRAVEL)

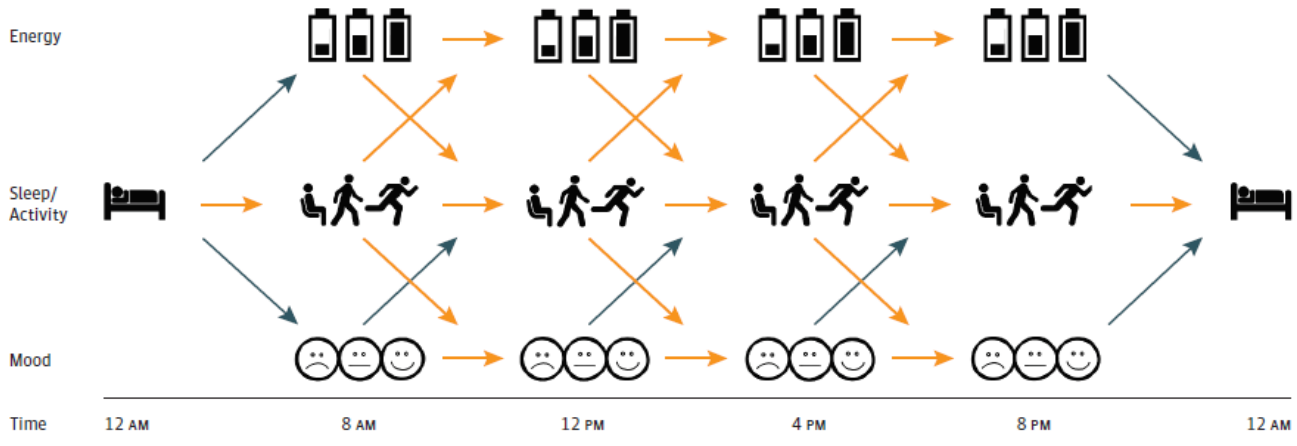
A circadian-dysfunction model of age-dependent phenotypes leading to adolescent-onset mood disorders



Activity and Energy are bidirectional:
low mood is a consequence of low activity

- Circadian disturbance may reflect bipolar as a disorder of activation.
  - Potential treatment and monitoring implications

Figure. Summary of Within- and Across-Domain Associations of Subjective Mood and Energy, Motor Activity, and Sleep Duration



Subjective energy and mood were assessed by ecologic momentary sampling and motor activity, and sleep duration was assessed by actigraphy across 2 weeks. Yellow (thicker) arrows indicate statistically significant associations; blue arrows indicate nonsignificant associations.

Scott, J., Murray, G., Henry, C., Morken, G., Scott, E., Angst, J., . . . Hickie, I. B. (2017). Activation in bipolar disorders: A systematic review. *JAMA Psychiatry, 74*(2), 189-196

Merikangas, K.R., et al., *Real-time Mobile Monitoring of the Dynamic Associations Among Motor Activity, Energy, Mood, and Sleep in Adults With Bipolar Disorder.* JAMA Psychiatry, 2018.

Rohani, D.A., et al., *Correlations Between Objective Behavioral Features Collected From Mobile and Wearable Devices and Depressive Mood Symptoms in Patients With Affective Disorders: Systematic Review.* JMIR Mhealth Uhealth, 2018. **6**(8): p. e165.

Distinguishing emerging bipolar disorders from unipolar depression

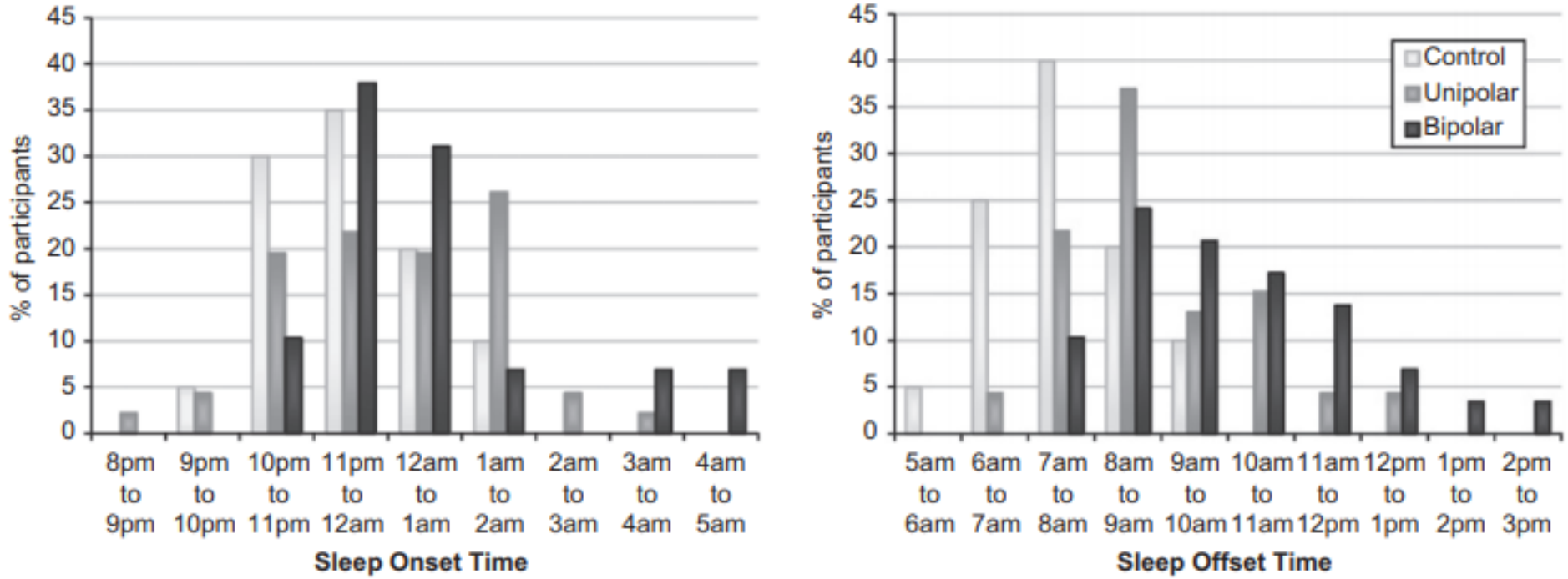
Prevalence of comorbid diagnoses (top panel) and positive family history (bottom panel) in the bipolar versus unipolar-type syndrome groups.

	All (*n*/*N*)	Bipolar (*n*/*N*)	Unipolar (*n*/*N*)	$\chi 2$ (*df*=305) [*p*]
Comorbidity				
Nil	27% (83/305)	30% (27/89)	26% (56/216)	0.6 [.431]
Anxiety	20% (61/305)	13% (12/89)	23% (49/216)	3.3 [.068]
Psychosis	13% (41/305)	15% (13/89)	13% (28/216)	0.1 [.702]
Beh/Dev	22% (68/305)	21% (19/89)	23% (49/216)	0.1 [.799]
Substance misuse	11% (33/305)	11% (10/89)	11% (23/216)	0.0 [.881]
Other	6% (19/305)	9% (8/89)	5% (11/216)	1.6 [.201]
Family history				
Depression	52% (132/254)	48% (38/77)	53% (94/177)	0.3 [.582]
Anxiety	28% (70/254)	34% (26/77)	25% (44/177)	2.1 [.144]
Bipolar	14% (36/254)	21% (16/77)	11% (20/177)	4.0 [.046]*
Schizophrenia	12% (31/254)	19% (15/77)	9% (16/177)	5.5 [.019]*
Substance misuse	27% (68/254)	35% (27/77)	23% (41/177)	3.9 [.049]*
Suicide	5% (14/254)	5% (4/77)	6% (10/177)	0.0 [.884]

- Young persons with bipolar disorders are best discriminated from those with unipolar depression by a family history of bipolar, psychotic or substance use disorders.
- Early in the course of illness, clinical features of depression, or neuropsychological function, do not readily differentiate the two illness trajectories.

Scott et al., 2013

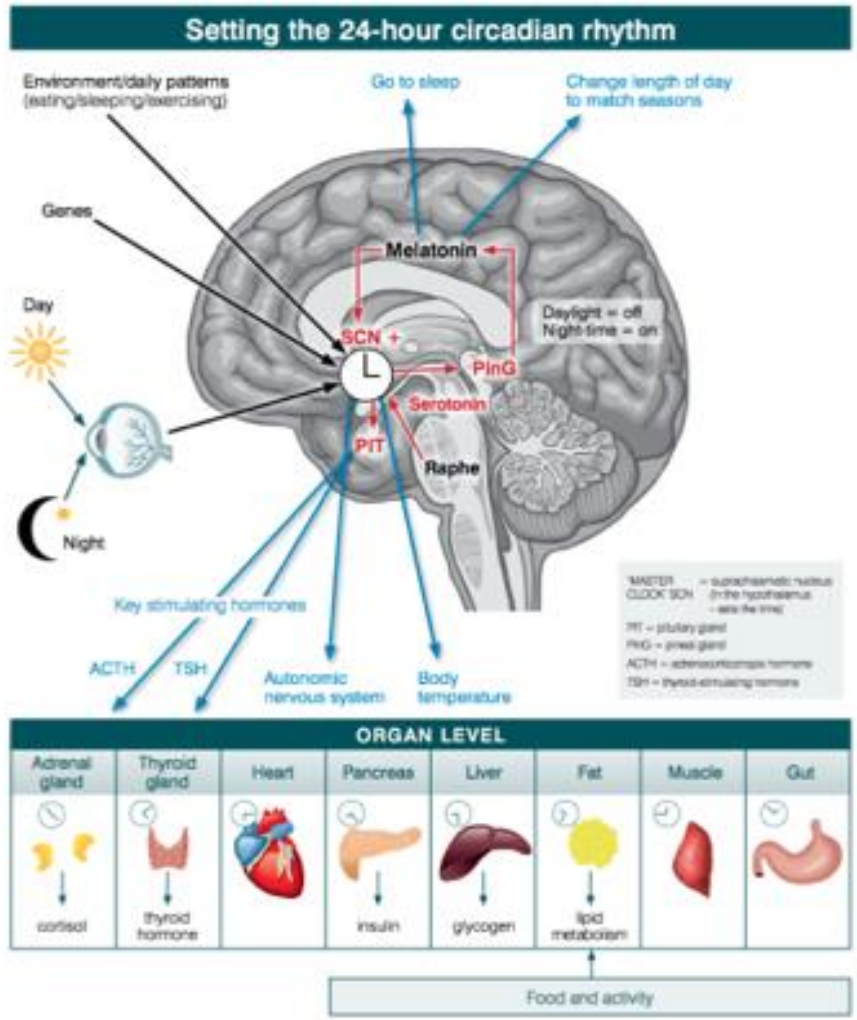
Delayed sleep phase in young persons with unipolar and bipolar affective disorders



- Sleep phase of young persons in the depressed phase is delayed
- The phase delay is more pronounced in those with bipolar as opposed to unipolar depression
- Highlights a pathophysiological pathway for targeted treatment

Robillard et al., 2013

24 hour sleep-wake and circadian system: studying mood and metabolic outcomes



Atypical depression- Silverstein & Angst 2015

- Low mood
- Low energy
- Disordered eating
- Hypersomnia (phase delay)
- Fatigue
- Pain
- Irritability
- Social anxiety/avoidance

- Earlier age of onset
- F>M
- Obesity
- Chronic pain/headache
- Metabolic syndrome
- PCOS/thyroid disease
- Raised inflammatory markers (IL6, CRP)
- Autoimmune/inflammatory disease

What should be the focus for mental health care?

Stakeholder perspectives

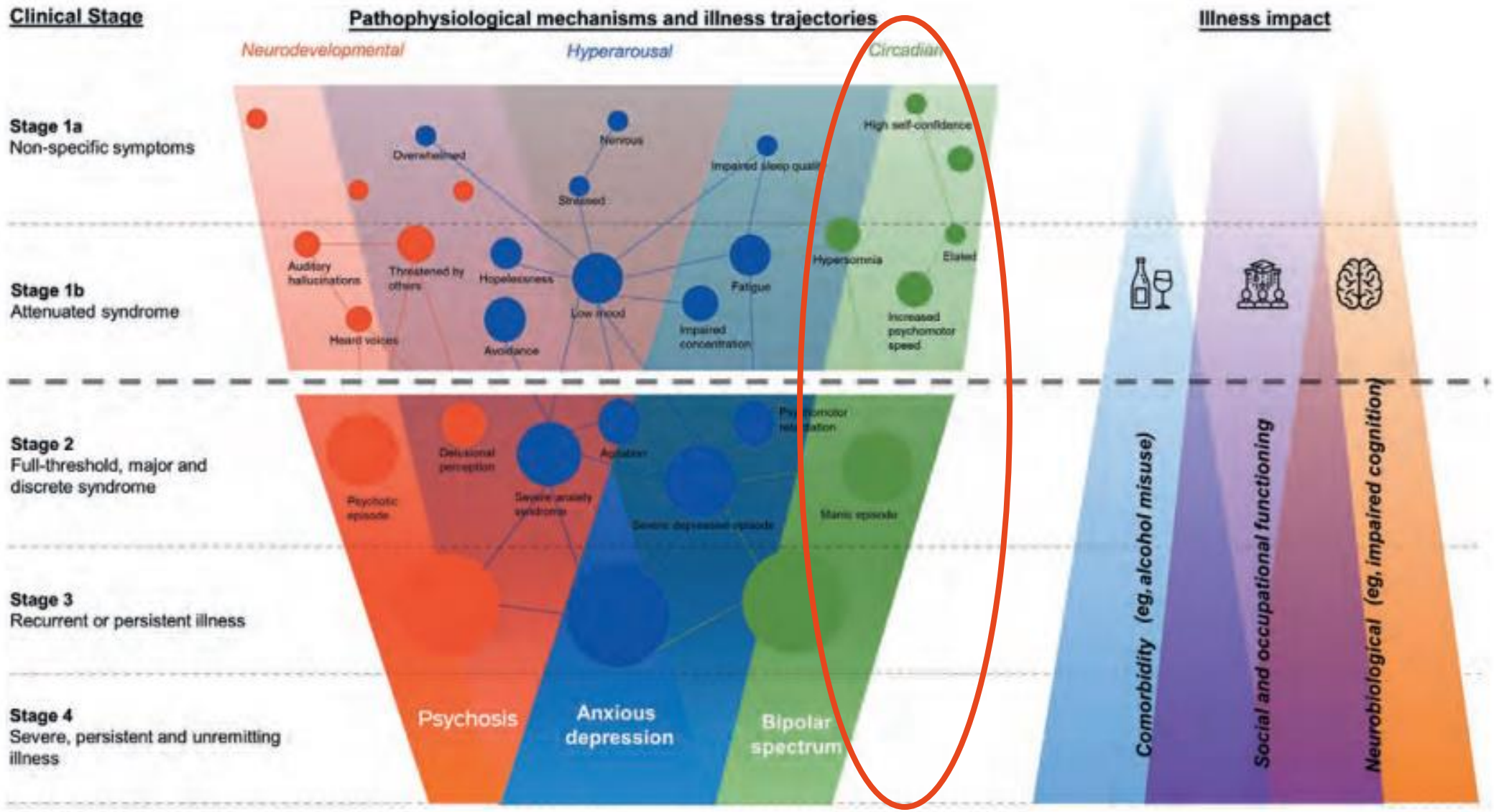
Various stakeholder perspectives of what should be the focus for mental health care across multidimensional domains

	Young people	Families and carers	Mental health professionals and service providers	Policy makers and funders
Illness type, stage and trajectory	• Do not rate symptom reduction as highly as health professionals for quality of life[101] • Those with severe symptoms value symptom reduction higher[103] • Believe recovery should go beyond symptom control[104]	• Formal diagnostic processes are largely relevant to gaining access to care	• Rate symptom reduction for quality of life higher than young people[101] • Most outcome measures focus on symptoms[105] • Services are focused exclusively on group level symptom reduction[106]	• Social, existential, mental, substance misuse and somatic care should be integrated at the local level[106]

Iorfino et al., 2019

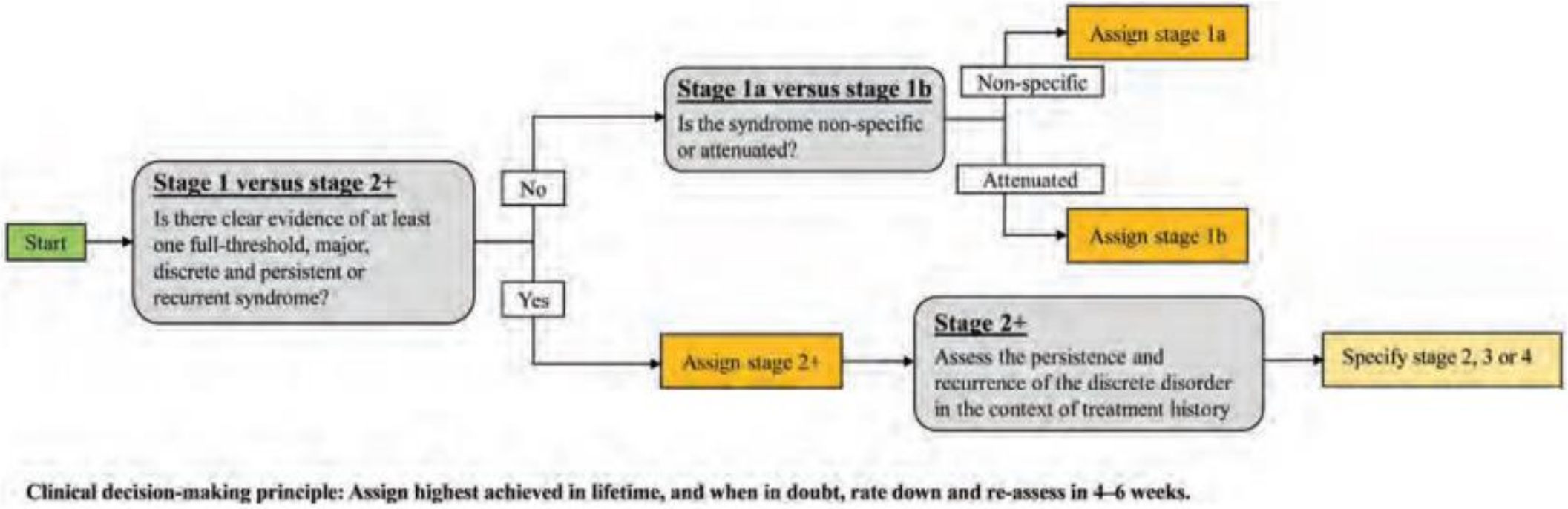
Model of illness trajectories and clinical stage

Disease progression and extension for the adolescent-onset of major mental disorders



Carpenter et al., 2019

Decision tree used to assign clinical stage



- Later stages are associated with greater distress, disability and functional impairment.
- Further, functional impairment persists longitudinally for those at later stages, emphasising the need for more intensive care.

Carpenter et al., 2019

Clinical staging and bipolar disorder

- Stage 0: identified by family history
- Stage 1: identified by family history and non-specific symptom (eg. anxiety) or due to subthreshold manic symptoms, mood instability or depressive episode
- Stage 2: typically defined by the first hypomanic, manic, or mixed episode, with or without psychotic symptoms
- Stage 3-4: typified by recurrent or chronic mood episodes and concurrent functional impairment.

**Implications for treatment planning will be discussed later.*

Vallarino et al., 2015

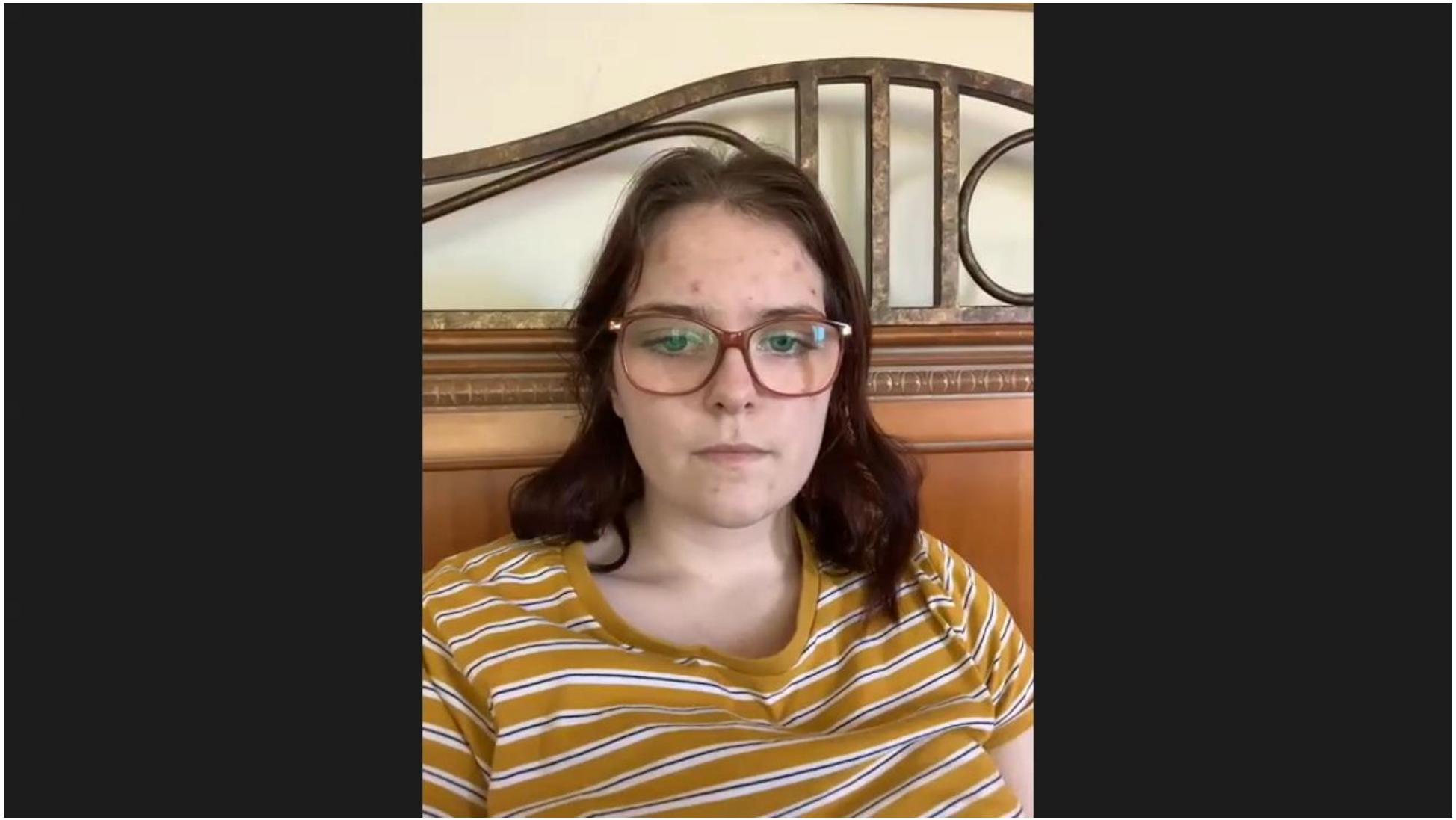
Clinical Staging and Atypical Depression

- Stage 0: identified by family history of bipolar spectrum disorder
- Stage 1: identified by family history and non-specific symptom (eg. anxiety) or due to subthreshold hypomanic symptoms, mood instability or depressive episode with circadian features
- Stage 2: typically defined by the first severe depressive episode associated with fatigue, hypersomnia, disordered eating, suicidal thoughts and behaviours with or without seasonal pattern
- Stage 3-4: typified by recurrent or chronic mood episodes and concurrent functional impairment.

**Implications for treatment planning will be discussed later.*

Vallarino et al., 2015

Case example – clinical presentation



Case example – atypical depression (stage 2)

- Early onset
- Anxiety/OCD
- Mood instability
- Low mood
- Low energy
- Hypersomnia, hyperphagia
- Pain, headache, fatigue, recurrent infection, GIT sx, autonomic dysregulation
- Hormonal dysregulation
- Suicidal thoughts and impulses

Summary…

- ‘Circadian-depression’ is particularly important in adolescents and young adults – in terms of likely prediction of illness progression to more severe adult phenotypes (including bipolar) and physical health complications.
- Are the childhood phenotypes that precede adolescent-onset depressed mood, fatigue and bipolar-type course more likely to be those of disrupted unstable sleep-wake cycles and inattention rather than anxiety?

Thank you!

CPD points can be claimed for psychologists, psychiatrists, social workers, occupational therapists, and mental health nurses.
Please contact ***tanya.jackson@sydney.edu.au*** *for more information.*

The Brain and Mind Centre would like to thank our research partners, such as

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