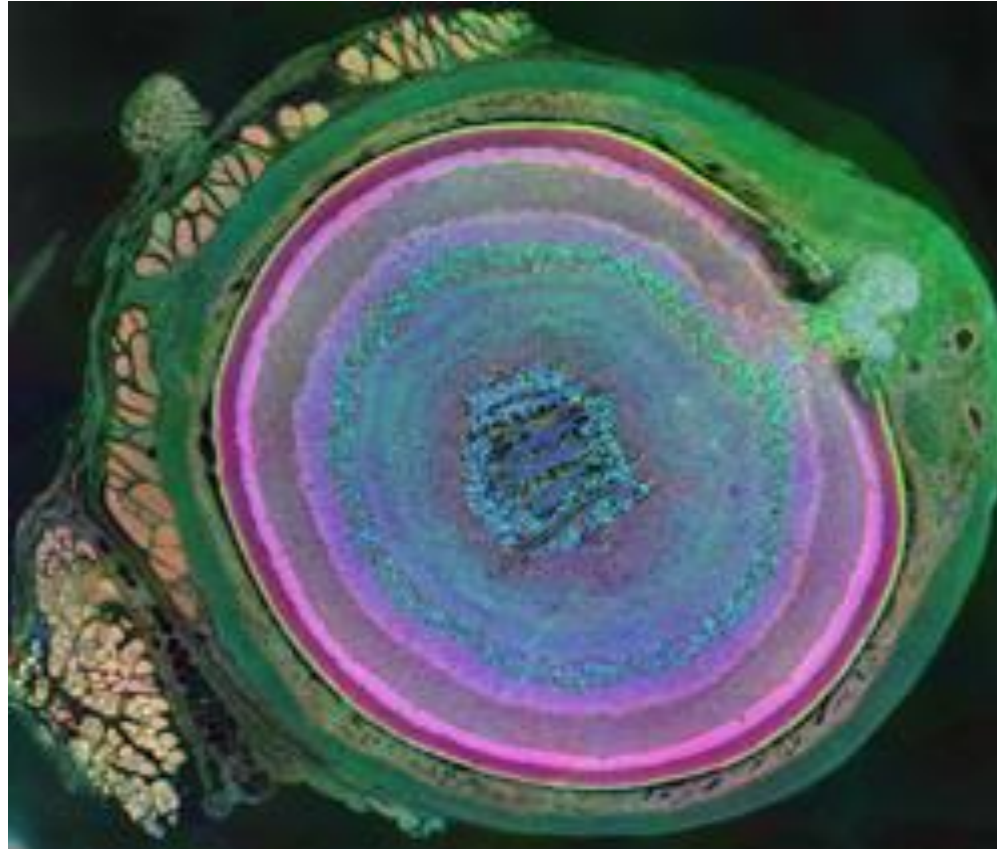


Is ADHD a Circadian Rhythm Sleep Disorder?

& relationship with health

ADANA, Barcelona, May10, 2019

J.J. Sandra Kooij, MD PhD



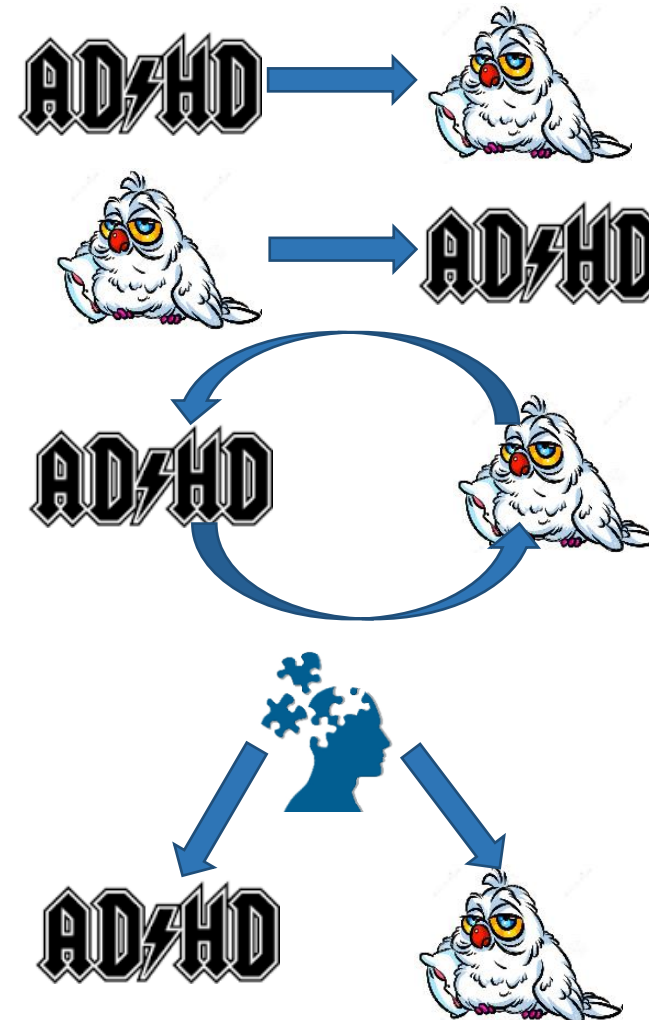
- Associate Professor of Psychiatry, VUMc Amsterdam, The Netherlands
- Head Expertise Center Adult ADHD, PsyQ, the Hague, The Netherlands

Conflict of interest JJS Kooij

None

ADHD and sleep: chicken or egg?

- ADHD causes sleep problems
- Sleep problems cause ADHD symptoms;
- ADHD and sleep problems interact, with reciprocal causation;
- ADHD and sleep problems have shared underlying etiology



ADHD & sleep in adults

Increased prevalence of:

- Delayed Circadian rhythm: **78%** ⁽¹⁾
- Longer sleep latency, shorter sleep ⁽²⁾
- Daytime fatigue: 62% ⁽³⁾
- Variability of sleep schedule ⁽³⁾
- Restless Legs Syndrome: 35-44% ^(4,5)
- Nightmares ⁽⁶⁾
- Sleep apnea

Circadian Rhythm Sleep-Wake disorders, Delayed Sleep Phase Type

DSPT is characterized by:

- A chronic pattern of (very) late sleep and preference for late rise
- Daytime sleepiness and/or sleep onset insomnia
- Compensated for by irregular sleep pattern
- Dysfunctioning due to increased inattentiveness and/or social problems



Nobelprijs gaat naar de biologische klok

NRC
2 okt 2017

De Nobelprijs voor medicijnen gaat naar de ontrafeling van moleculaire mechanisme van het dag-nachtritme bij dieren door drie Amerikaanse genetici. Zij vestigden het vakgebied van de 'circadiane biologie'.

Sander Voormolen 2 oktober 2017



Jeffrey C. Hall



Michael Rosbash



Michael W. Young



De Nobelprijs voor Geneeskunde en Fysiologie is maandag toegekend aan drie Amerikanen: Jeffrey Hall, Michael Rosbash en Michael Young voor hun ontdekkingen rond het moleculaire mechanisme dat biologische klok van mens en dier controleert. Dankzij

Advertentie

Onbeperkt vakantiedagen?



Hoe geeft u medewerkers vrijheid en regie over hun werklevens? Laat u inspireren door de succesverhalen van koplopers zoals scale-up Bynder.

Lees verder

Trending

Veel gedeeld



Hoe Oranje na het WK van 2014 een falende voetbalploeg werd

De implosie van Sebastian Vettel, en dus ook van de spanning

CATALONIE
Honderdduizenden demonstreren in Barcelona tegen afscheiding

Mister Ikea: 'Hoezo niet echt design? Omdat het een massaproduct is?'

Ze vragen zich ineens af: hoor ik er wel bij?

ADHD and circadian rhythm

Genetic basis

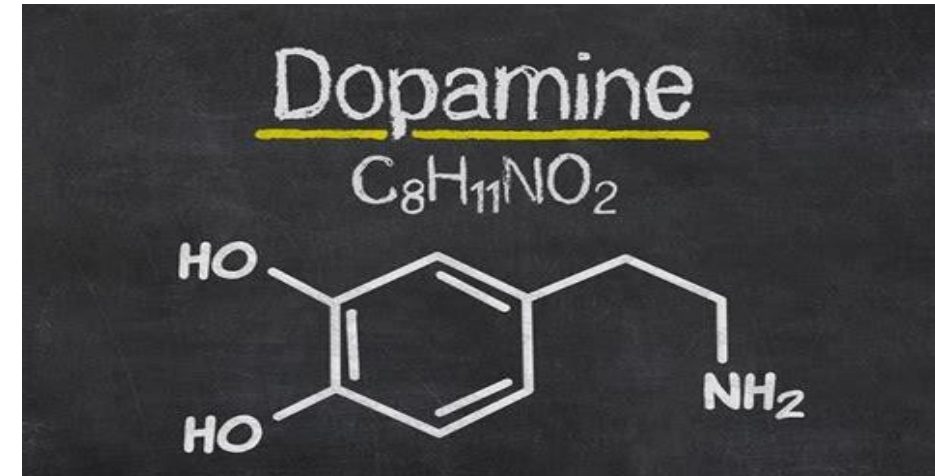
- Circadian rhythm is regulated by genes:
PER1, PER2, PER3, CRY1, CRY2, CLOCK, BMAL1, CK1e (1-3)
- Polymorphism in CLOCK gene: associated with delayed/short sleep, ADHD, Bipolar-II, depression (4, 5)
- BMAL1 and PER2 genes: less solid circadian rhythm in ADHD vs controls (6)

The circadian rhythm is controlled by:

Dark & light regulate melatonin production

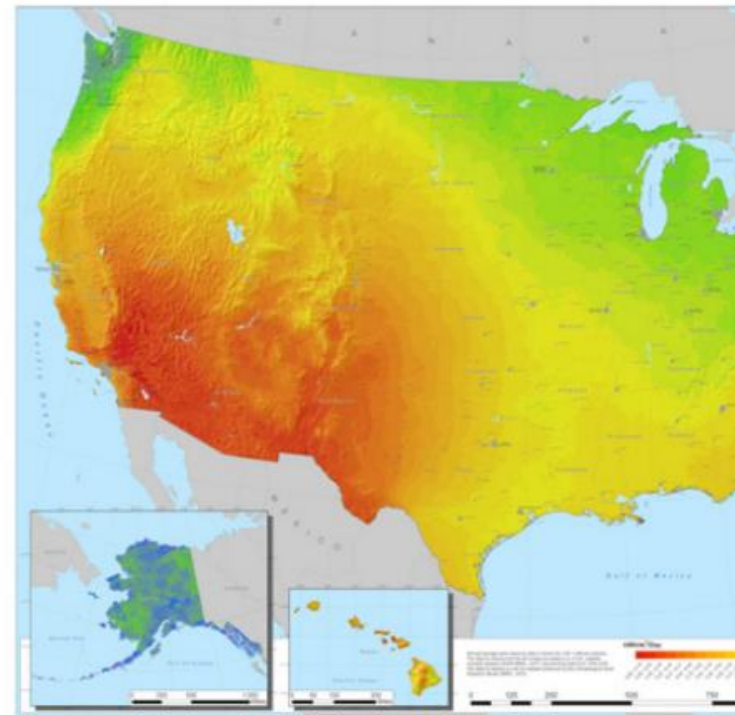
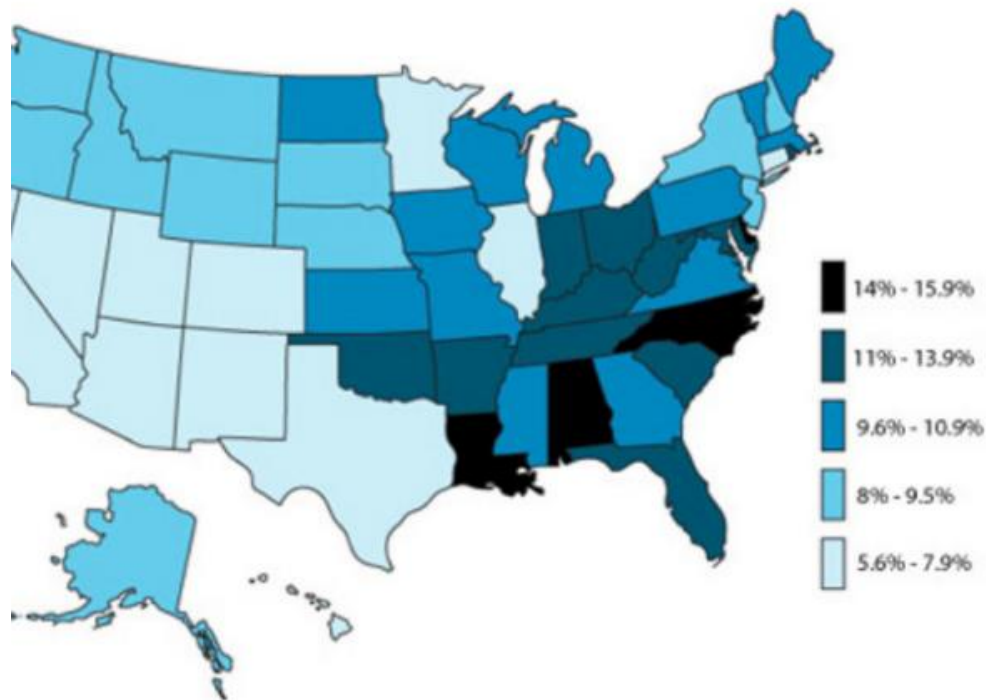


- *So in ADHD: dysregulation of both melatonin & dopamine ...*



ADHD prevalence lower in countries with intense daylight, in both US and European data, in both children and adults

Solar Intensity explained 34%–57% of the variance in ADHD prevalence



Arns et al 2013:

The preventative effect of high Solar Intensity might be related to improvement of circadian clock disturbances in ADHD

ADHD and circadian rhythm

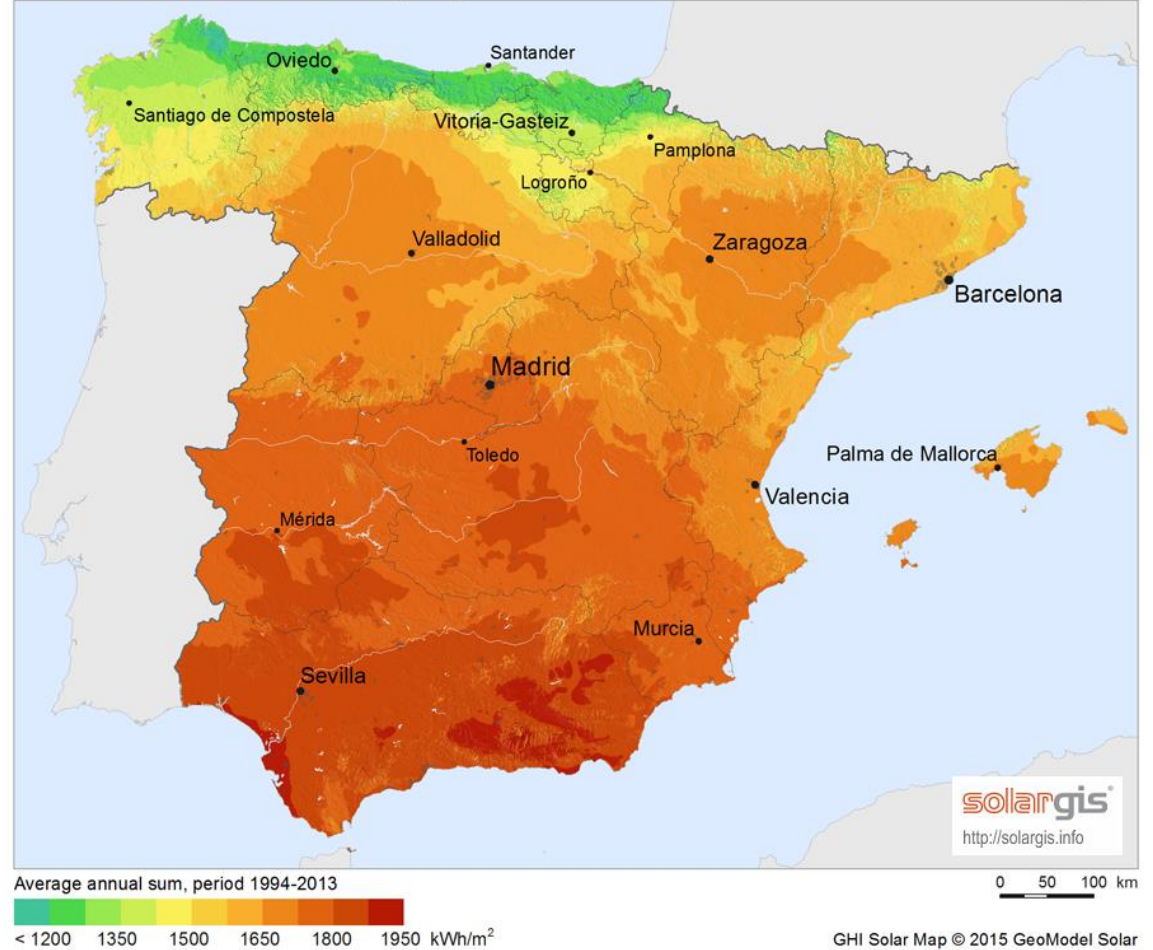
Prevalence of ADHD in adults: Netherlands: 5%; Spain: 1.2%

Fayyad ea 2017

Global Horizontal Irradiation Netherlands



Global Horizontal Irradiation (GHI) Spain

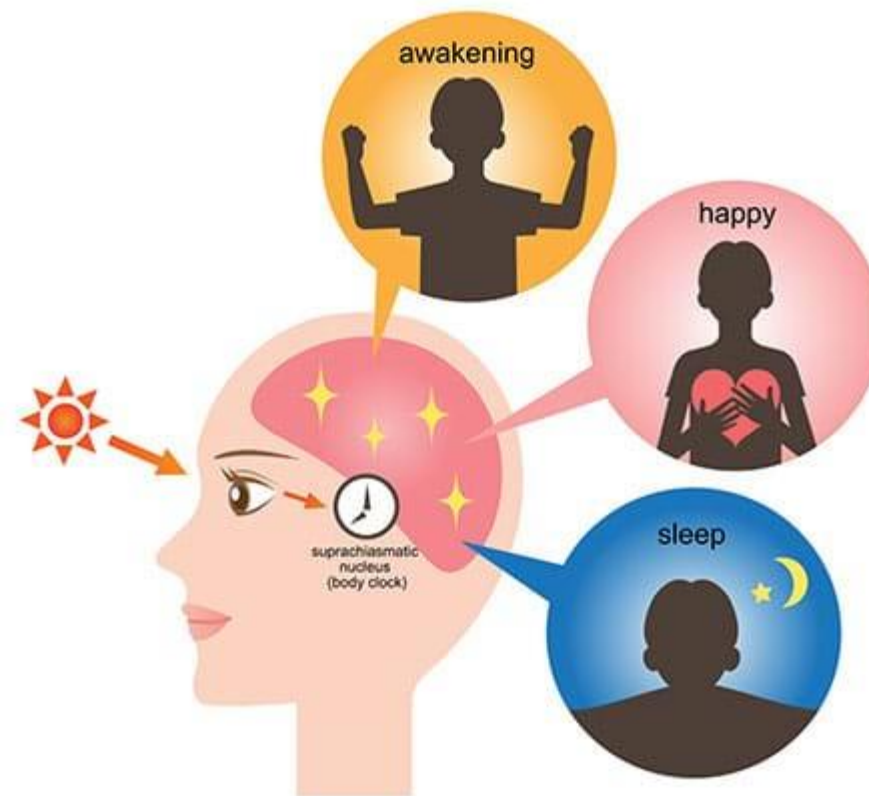


Source: www.solargis.com.

Adult ADHD often comes with **with circadian based disorders:**

75% has other disorders (mean 3 disorders):

- Depression (**60% SAD**) 25-50%
- Anxiety 25%
- Substance Use Disorders 20-45%
- Personality Disorders 6-25%
- Eating Disorders (Bulimia) 9%
- Binge eating 86%
- Obesity 30%
- Sleepproblems, DSPS pattern 78%



Kooij 2001 NTG;145(31):1498-501; Kooij 2004, Psychol Med;34(6):973-82, Kooij 2010, book Adult ADHD; van Veen 2010, Biol Psychiatry 67(11): 1091-6; Biederman 1993, AJP;150(12):1792-8; Kessler 2006, AJP;163(4) :716-23; Pagoto 2009, Obesity;17(3):539-44. Davis 2009, J Psychiatr Res;43(7):687-96.

Characteristics of 40 consecutive ADHD patients

	Sleep Onset Insomnia (SOI)	No SOI
N	31 (78%)	9 (22%)
Male	17 (55%)	4 (44%)
Age, mean (SD)	28.2 (7.6)	30 (11.9)
ADHD, combined type	29 (94%)	5 (56%)
ADHD, inattentive type	2 (6%)	4 (44%)
Alcohol (U/wk)	6.76	5.67
Nicotine (Sig/day)	8.16	1.11
Sleep diagnosis	ns	ns

C/ Late sleep separates the subtypes ...

Question: is hyperactive behaviour adaptive in order to stay awake?

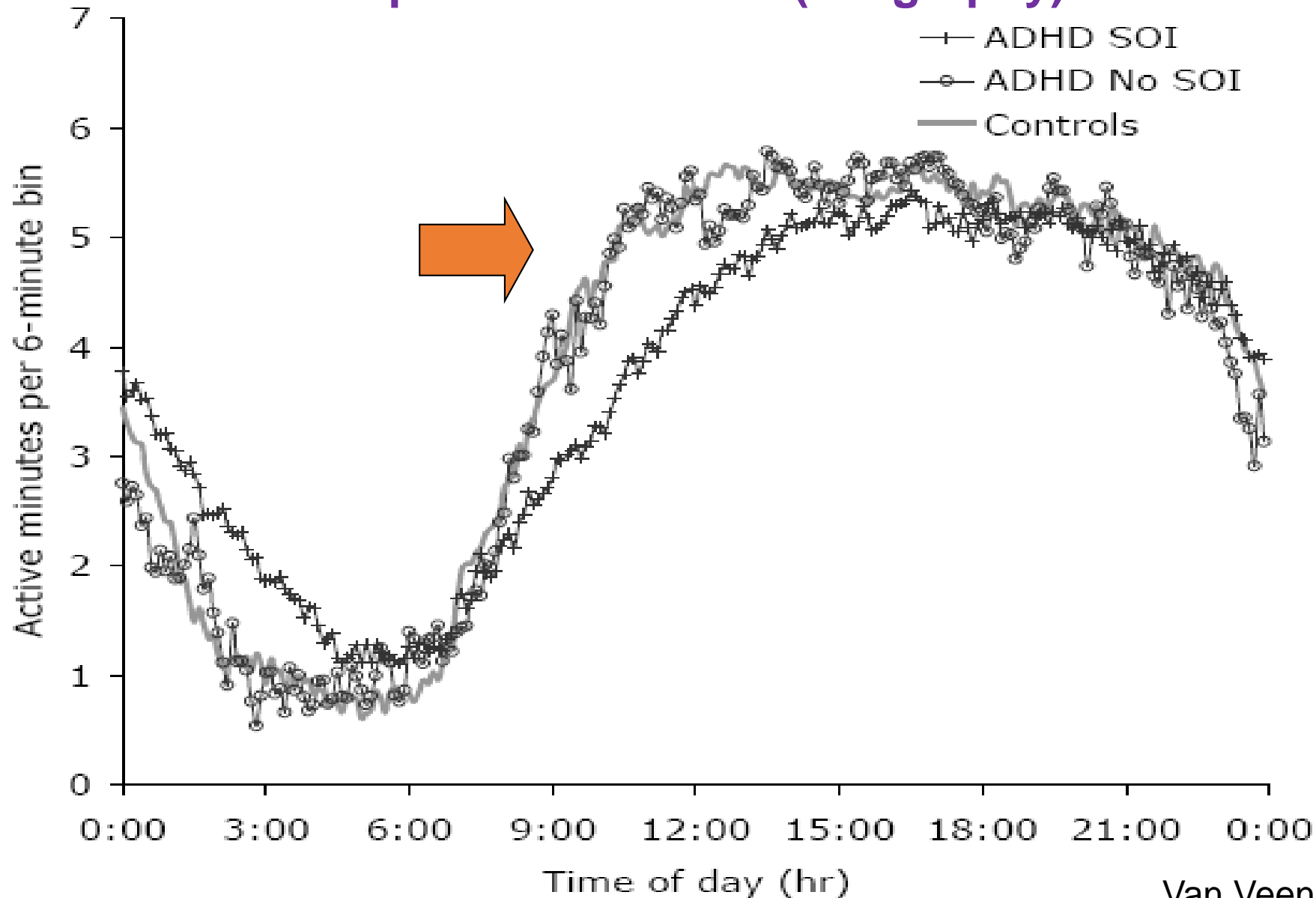
Dim Light Melatonin Onset (DLMO): delayed

N= 40 adults with ADHD w/wo Sleep Onset Insomnia versus healthy controls

	ADHD Total	ADHD + SOI	ADHD - SOI	HC	<i>p</i> : ADHD vs HC	<i>p</i> : SOI vs HC
DLMO (hr ± sd)	22:57 ± 1:20	23:15 ± 1:19	22:00 ± 0:54	21:34 ± 0:45	0.000	0.000

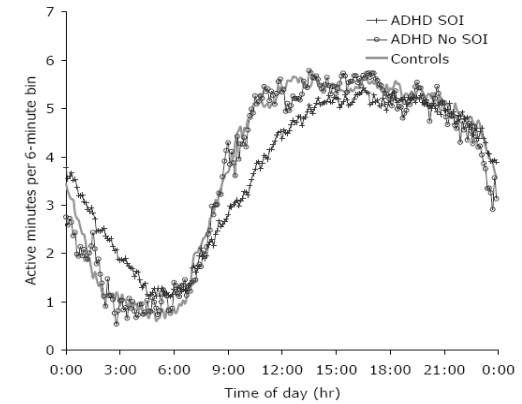
- 78% of consecutive ADHD patients had Sleep Onset Insomnia (SOI)
- DLMO: 105 min later in SOI vs controls
- After DLMO, it generally takes still 2 hours to fall asleep
- In ADHD it takes 3 hrs ...

24 hour movement patterns in ADHD + and – SOI, compared to controls (actigraphy)

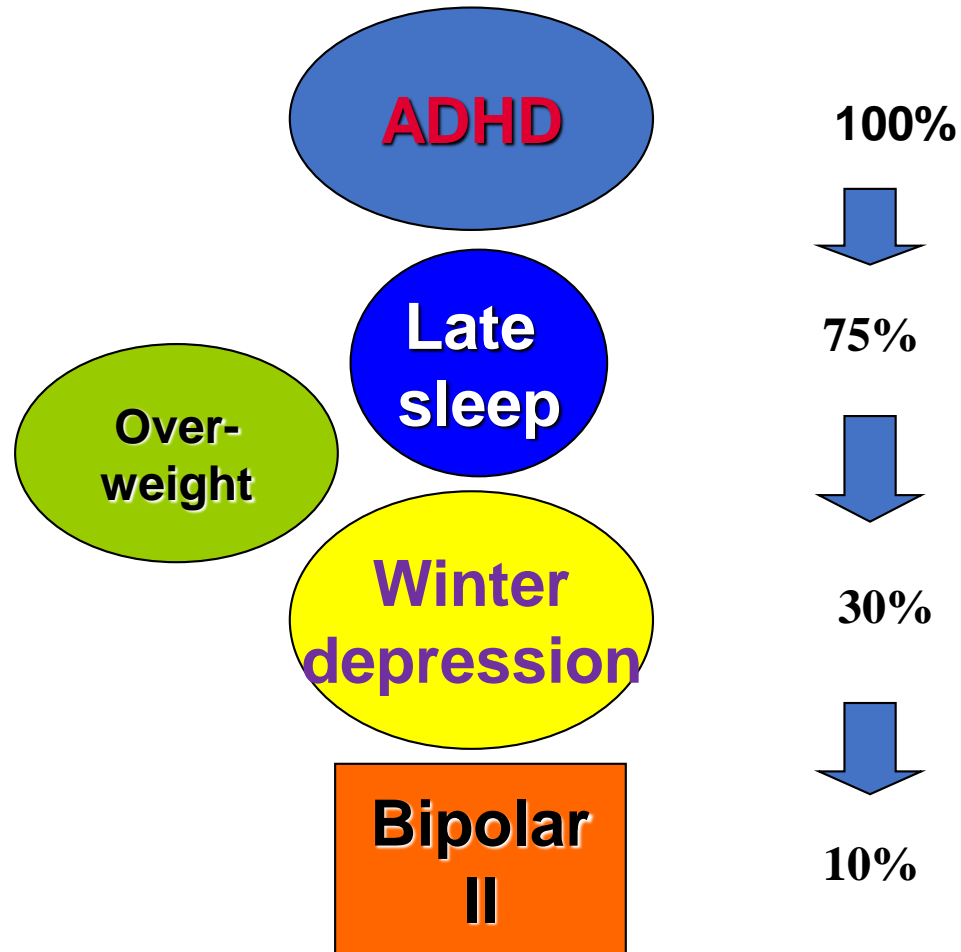


ADHD with late sleep versus controls (n=24)

- Activity, core and skin temperature, and melatonin:
all equally delayed
- Longer period between DLMO and sleep onset (3 vs 2 hrs)
- Variable bed times; mean bed time **2:52 AM**
- **Mean of 5 hrs sleep** on workdays
- Variable sleep times not caused by variability of DLMO times



ADHD, circadian rhythm, sleep, mood & season

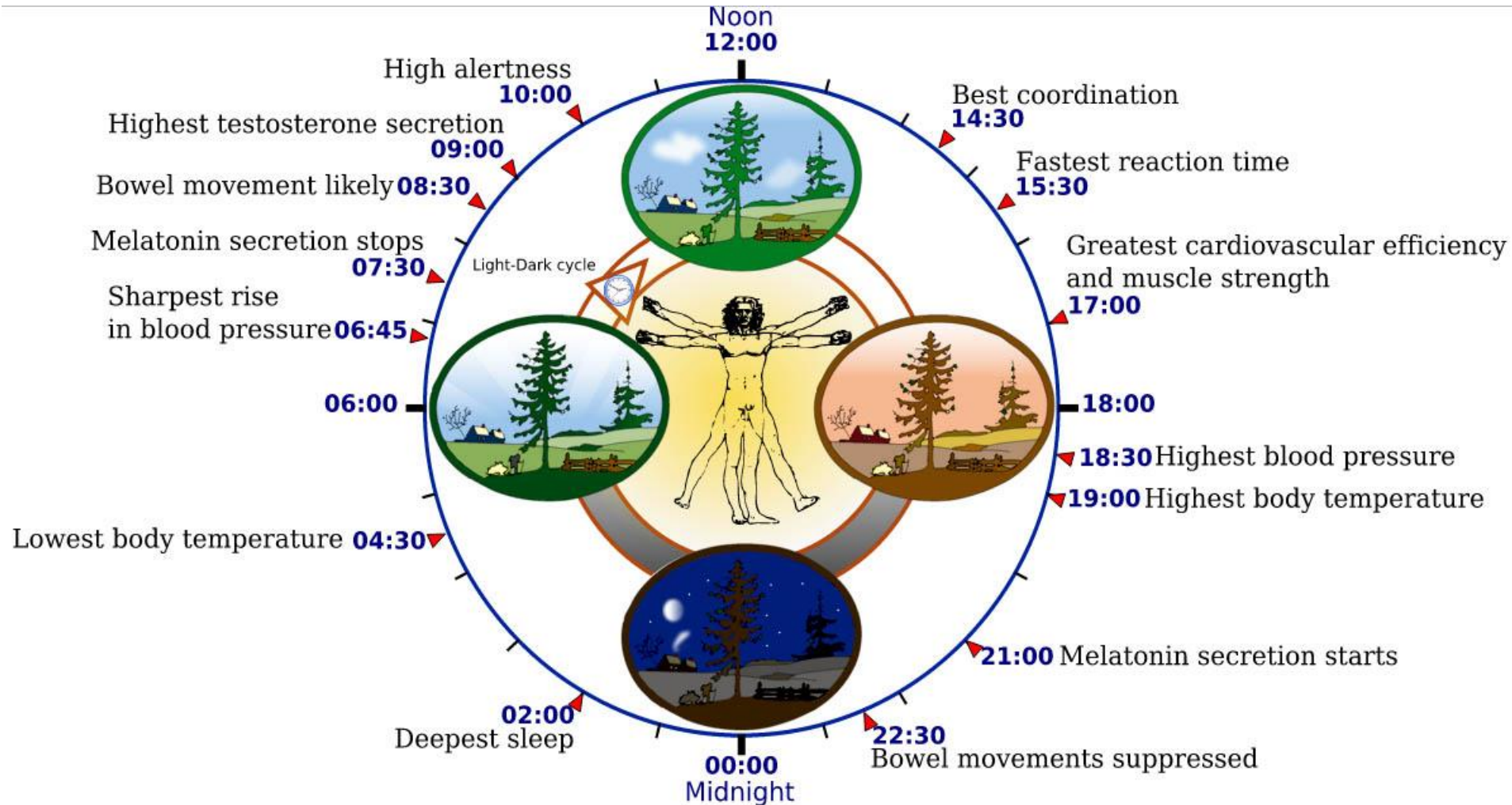


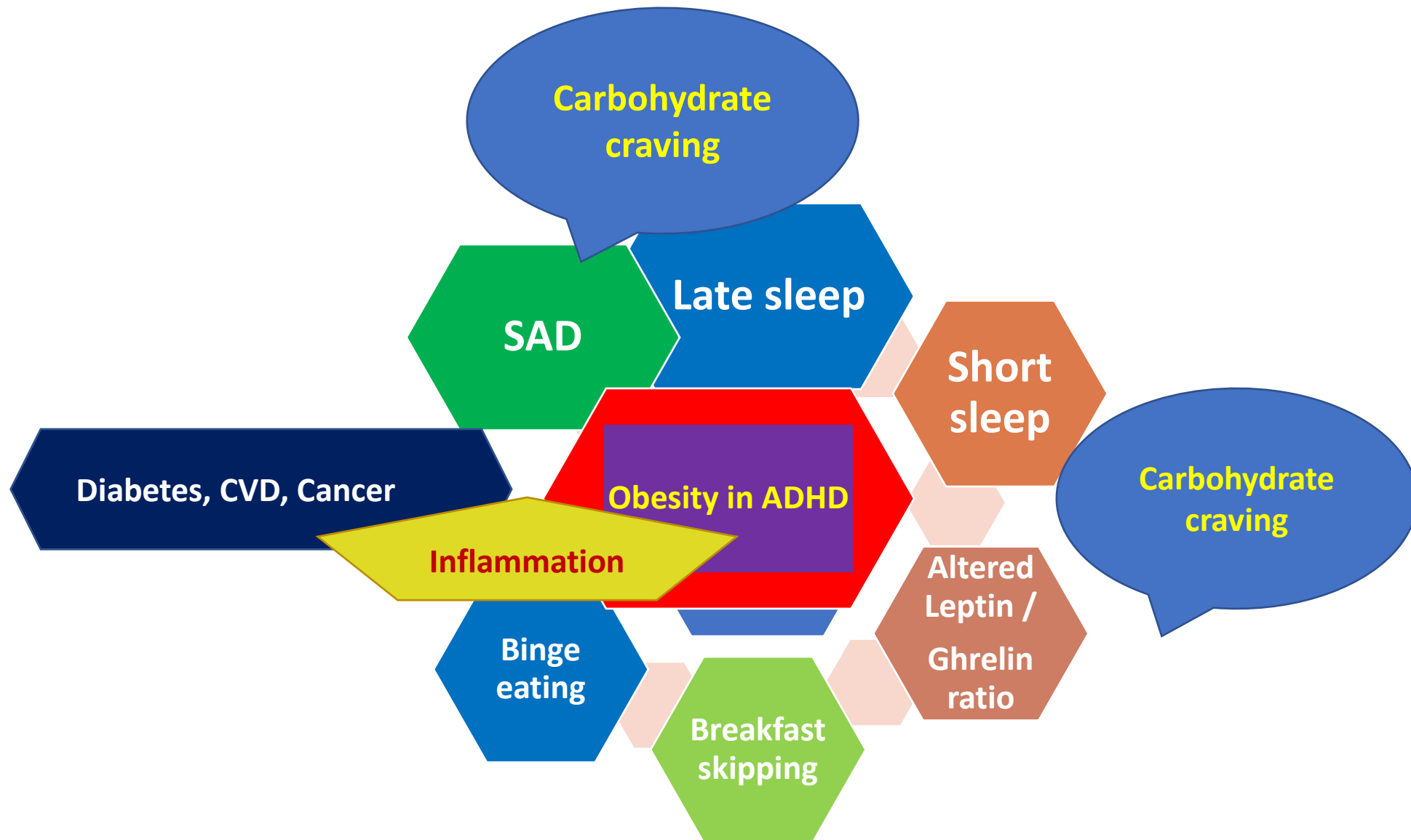
Delayed Sleep & Health in ADHD

- Late sleep: 75% of children & adults with ADHD
- **Late sleep = short sleep** due to school / work



Biological clock & organic rhythms





Hypothesised cascade of events

Kooij & Bijlenga 2013; Kooij 2012, book Adult ADHD; Dubois 2009; Boere 2008; Davis 2009; Mota 2008; Copinschi 2000; Spiegel 2005; Irwin 2017

Proposed treatment / prevention of obesity in ADHD

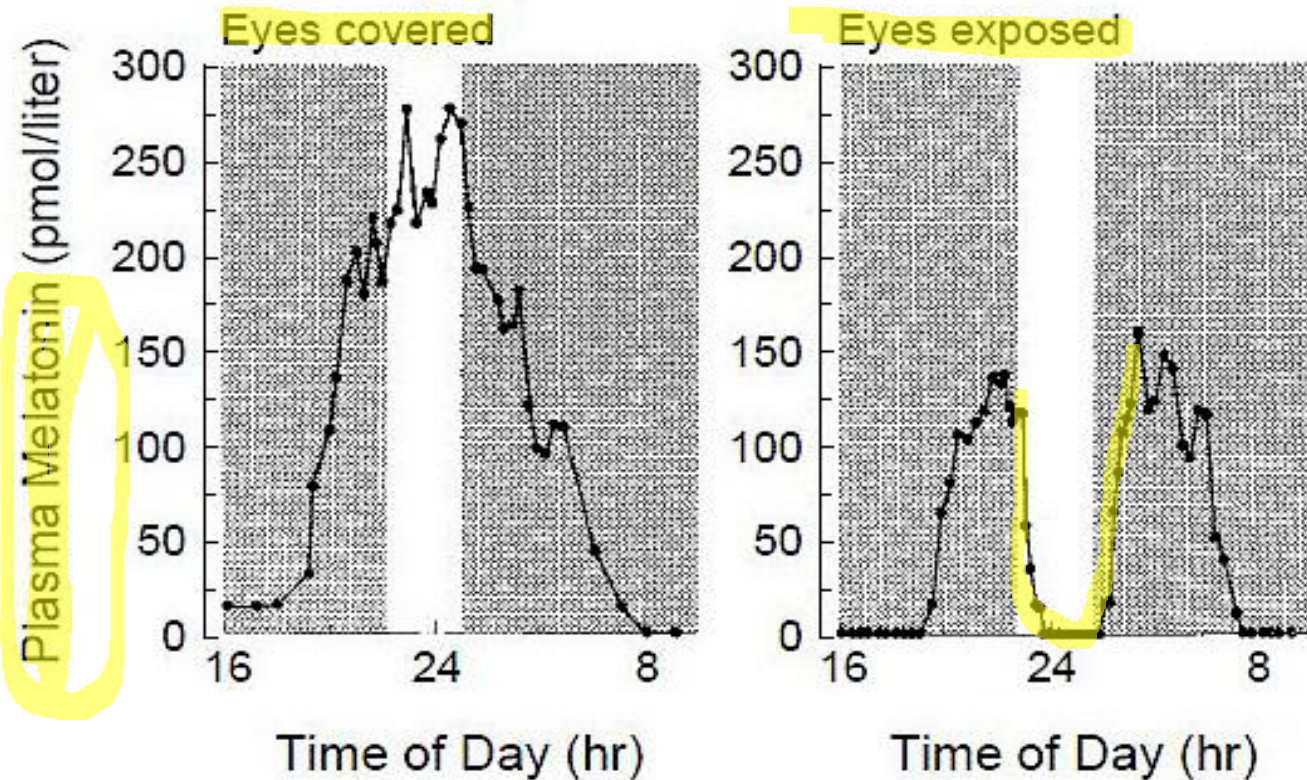
To reset the clock and increase sleep duration:

- Psycho education *on the meaning of time*, the light/dark cycle for sleep, appetite, metabolic entrainment, mood and health
- Sleep hygiene (early to bed and early to rise ...)
- No light@night, shower before going to bed, bedsocks
- Melatonin in evening
- Light in morning

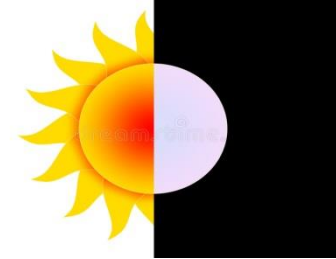
To reduce binge eating and weight gain:

- Treatment of comorbidity (depr/anx)
- Treatment of ADHD with stimulant
- Exercise, diet

Influence of light on melatonin production



Sleep hygiene: Let your day be bright, and your night as dark as possible ...



- Limit drinks after 8 pm to prevent visits to toilet @night
- Don't use light when visiting toilet
- Good ventilation, good mattress
- Prevent light waking you up: dark curtains, no light in bedroom of lamps or clocks
- No screens or dim light after 9.30 pm, or after ingestion of melatonin
- If needed, use dark or red sunglasses while watching TV
- Temperature control: hot shower before bed, bed socks
- Go to bed and get up at the same time every day, also in weekends
- Strive for 7-8 hrs of sleep between 11 pm and 7 am
- No napping > 30 min during daytime
- Use light in the morning to advance the rhythm if needed
- Limit use of sunglasses to synchronise with day light

Melatonin: an Inhibitor of Breast Cancer

Steven M. Hill^{1,3,4,5}, **Victoria P. Belancio**^{1,3,4,5}, **Robert T. Dauchy**^{1,3,4,5}, **Shulin Xiang**^{1,3,4,5},
Samantha Brimer², **Lulu Mao**^{1,3,4,5}, **Adam Hauch**², **Peter W. Lundberg**², **Whitney Summers**¹,
Lin Yuan^{1,3}, **Tripp Frasch**^{1,5}, and **David E. Blask**^{1,3,4,5}

¹Department of Structural and Cellular Biology, Tulane University School of Medicine New Orleans, LA 70112

²Department of Surgery, Tulane University School of Medicine New Orleans, LA 70112

³Tulane Cancer Center and Louisiana Cancer Research Consortium, Tulane University School of Medicine New Orleans, LA 70112

⁴Circadian Cancer Biology Group, Tulane University School of Medicine New Orleans, LA 70112

⁵Tulane Center for Circadian Biology, Tulane University School of Medicine New Orleans, LA 70112

Abstract

This review discusses recent work on melatonin-mediated circadian regulation and metabolic and molecular signaling mechanisms involved in human breast cancer growth and associated consequences of circadian disruption by exposure to light at night (LEN). The anti-cancer actions of the circadian melatonin signal in human breast cancer cell lines and xenografts heavily involve MT₁ receptor-mediated mechanisms. In estrogen receptor alpha (ER α)-positive human breast cancer, melatonin, via the MT₁ receptor, suppresses ER α mRNA expression and ER α transcriptional activity. As well, melatonin regulates the transactivation of other members of the

Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis

[Russel J. Reiter](#)^{1,*}, [Sergio A. Rosales-Corral](#)², [Dun-Xian Tan](#)¹, [Dario Acuna-Castroviejo](#)³, [Lilan Qin](#)¹, [Shun-Fa Yang](#)⁴, and [Kexin Xu](#)⁵

Andrzej Slominski, Academic Editor

[Author information](#) ▶ [Article notes](#) ▶ [Copyright and License information](#) ▶

This article has been [cited by](#) other articles in PMC.

Abstract

Go to:

There is highly credible evidence that melatonin mitigates cancer at the initiation, progression and metastasis phases. In many cases, the molecular mechanisms underpinning these inhibitory actions have been proposed. What is rather perplexing, however, is the large number of processes by which melatonin reportedly restrains cancer development and growth. These diverse actions suggest that what is being observed are merely epiphenomena of an underlying more fundamental action of melatonin that remains to be disclosed. Some of the arresting actions of melatonin on cancer are clearly membrane receptor-mediated while others are membrane receptor-independent and involve direct intracellular actions of this ubiquitously-distributed molecule. While the emphasis of melatonin/cancer research has been on the role of the indoleamine in restraining breast cancer, this is changing quickly with many cancer types having been shown to be susceptible to inhibition by melatonin. There are several facets of this research which could have immediate applications at the clinical level. Many studies have shown that melatonin's co-

Melatonin treatment

- **To fall asleep:** 1-3 mg at 22:00 in order to sleep at 23:00
- No light after intake of melatonin!
- Long acting melatonin (Circadin[®]) for those who wake up at 3 am after taking shortacting melatonin at bedtime
- No light exposure of tablets of melatonin! (tablets may be photosensitive)

Light therapy in the morning: for low mood & late sleep

- Especially in winter more sleep phase delay in ADHD
- More difficult to get up on time
- Strong early artificial morning light usually works as time cue, like sunlight in summer
- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light therapy device of 10.000 lux at 20 cm to the eyes, and timer 30 min before (fixed) wake up time
- Duration: 1-2 weeks for winterdepression, 3 weeks for DSPS. Repeat when relapse.
- Wake Up Light uses only 75 W and does not wake all patients with delayed sleep phase



Rybak ea 2006



Light therapy 2019: Smart glasses!



THE GLASSES

- ✓ Light- and chronotherapy embedded
- ✓ Patented
- ✓ High quality materials
- ✓ App and Bluetooth controlle
- ✓ Rechargeable





Indications:

Winterdepression
Jet Lag
Delayed sleep phase
& ADHD??

www.propeaq.com

Correcting Delayed Circadian Phase with Bright Light Therapy Predicts Improvement in ADHD Symptoms: A Pilot Study

Rachel E. Fargason, MD, Aaron D. Fobian, PhD, Lauren M. Hablitz, PhD, Jodi R. Paul,
PhD, Brittany A. White, MS, Karen L. Cropsey, PsyD, and Karen L. Gamble, PhD[†]

Department of Psychiatry and Behavioral Neurobiology
University of Alabama at Birmingham, Birmingham, AL, USA.

Financial/Material support: UAB Health Services Foundation General Endowment Fund
Actigraphy Program and UAB Psychiatry departmental funds (Birmingham, AL, USA)

Disclosures: All authors have no direct or indirect affiliations or financial interests in
connection with the content of this paper to disclose.

[†]Author for Correspondence: Karen L. Gamble

E-Mail: klgamble@uab.edu

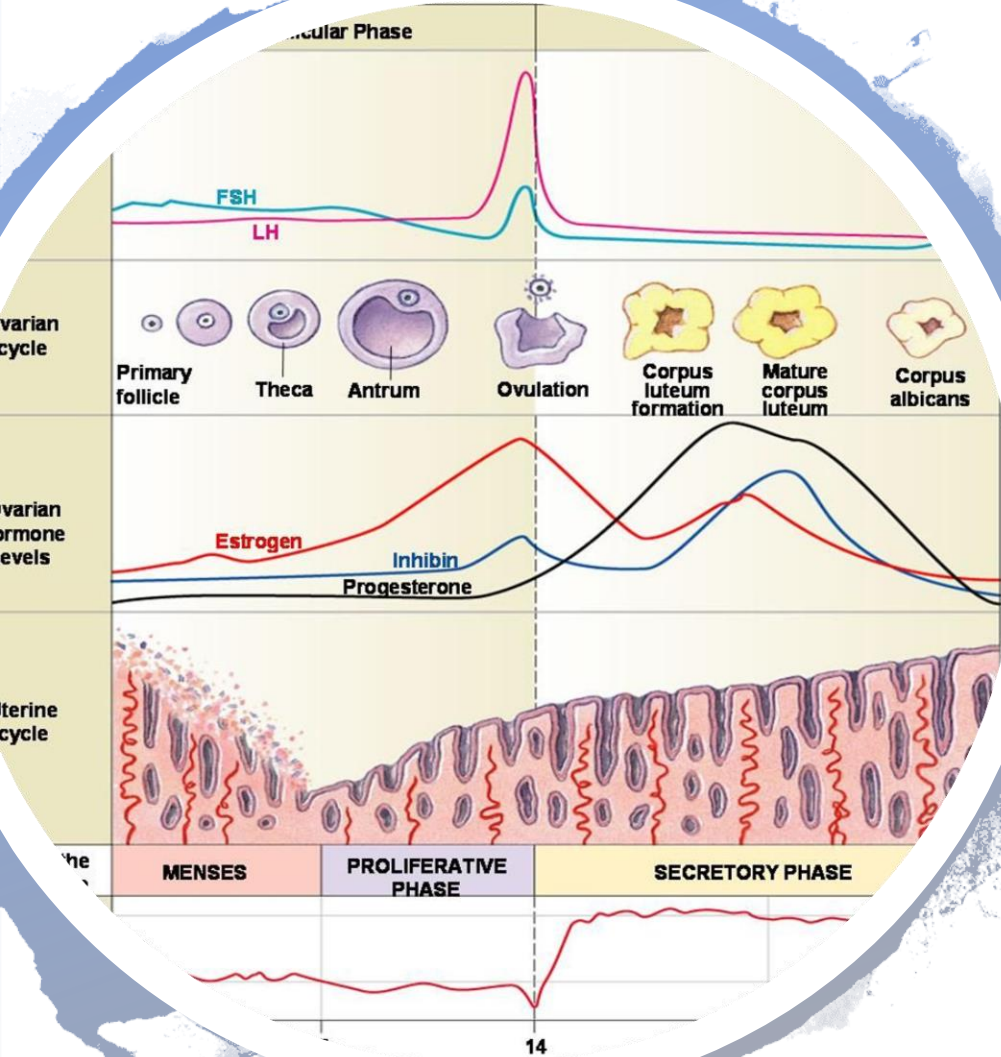
Phone: 205-934-4663

Fax: 205-975-4462

Address: Psychiatry and Behavioral Neurobiology

Discussion

Hormonal Moodchanges in women with ADHD



J J Sandra Kooij

Psychiater, PsyQ Den Haag

Associate professor psychiatrie, VUMc

50^e ADHD Netwerk Meeting

14 mrt 2019

Women & mood

- Women have twice the risk for depression compared to men
- Women have a fivefold increased risk for seasonal depression

Goldstein ea 2019; Wirtz-Justice 2018

Mood disorders in ADHD



- In 55% lifetime diagnosis of depression (n=115)
- In 27% seasonal depression: 72.9% of females and 52.2% of males

Prevalence of Adult
ADHD:

One in 5
mood disorder
patients

The prevalence of ADHD in
Mood Disorders is:

15-20% in
bipolar disorder

8% in
depression

22% in
dysthymia

Fayyad ea 2017

**ADHD
prevalence
increases with
severity and
chronicity of
Depression**

NESDA study: N=2053, 3 groups:

Healthy Controls /Depression /Depression + Anxiety:

ADHD prevalence :

- 0.4% in healthy controls
- 5.7% in remitted depression
- 22.1% in current depression

ADHD symptoms were significantly increased among:

- **Severe** depression (OR=6.8),
- **Chronic** depression (OR=3.8),
- **Earlier age of onset** of depressive symptoms (OR=1.5),
- **Comorbid anxiety** disorders (OR=3.4).

Conclusion:

ADHD symptom rates increased across clinical stages of depression, up to **22.5% in chronic depression**

Clinical
experience:

Premenstrual
mood problems
in women with
ADHD

**Women with ADHD report
severe premenstrual mood
instability &
increased severity of ADHD:**

Inattention,
inability to
focus

Impulsivity

Irritability and
anger
outbursts

Depressed
mood

Increased
sleep
disturbance

Anxiety, panic
attacks

Suicidal
thoughts

Symptoms recur
next
premenstrual
period

Efficacy of ADHD
medication
seems reduced

= DANGER WEEK !!



The causes of mood swings are generally hormonal.

Besides premenstrual, also postnatal & perimenopausal mood changes

- From clinical experience, postnatal depression and perimenopausal depression also seem more severe and more frequent than normal
- But no data so far
- Research question:

Are hormonal mood problems indeed more severe and more frequent in women with ADHD compared to women without?

- PMS in 20-30% of women in general
- PMDD in 3-8%

1st Pilot study 2016

- Dutch ADHDWoman conference 2016
- N=200 participants

Self report questionnaire on mood changes to the level of clinical depression during:

- the menstrual cycle : premenstrual dysphoric disorder (PMDD) (=more severe than PMS)
- the postnatal period : postpartum depression (PPD)
- the perimenopausal period

Questionnaire
consisted of
validated
scales,
adapted for
selfreport



Neuropsychiatric Interview Plus version 5.0 (M.I.N.I. Plus) for Premenstrual Dysphoric Disorder (PMDD)



Edinburgh Postnatal Depression Scale (EPDS) for life-time Post Partum Depression (PPD)



Greene Climacteric Scale (GCS) for Perimenopausal Mood Symptoms



Munich Chronotype Questionnaire (MCTQ) for sleep characteristics



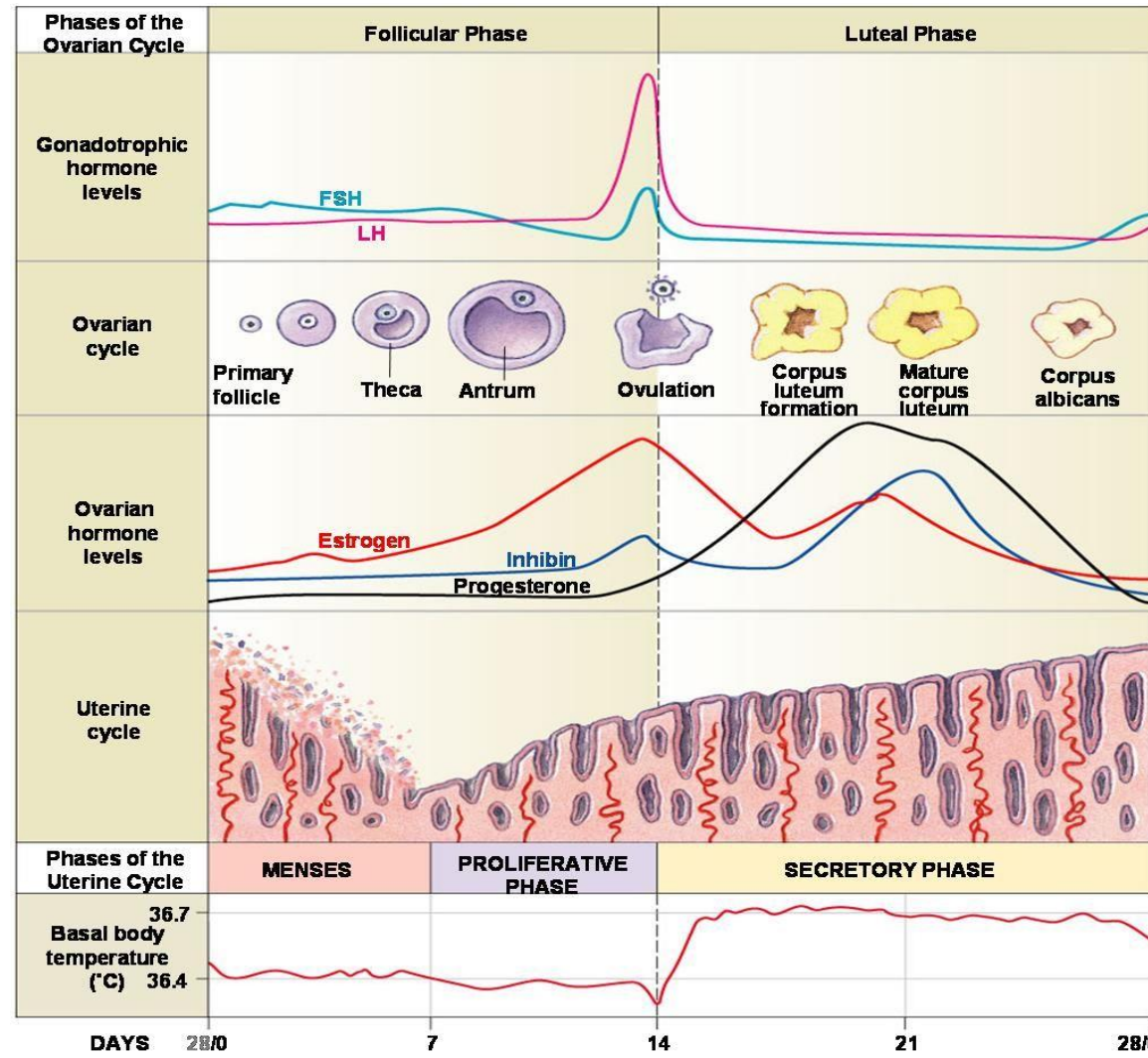
ADHDWoman 2016




Vraag	Stemmen
Wat is het verband tussen hormonen en emotionele labiliteit bij ADHD?	64
Waarom ben ik <i>of</i> hyperactief <i>of</i> compleet oververmoeid?	31
Wat veroorzaakt <i>of</i> problemen bij ADHD?	23
Wat is de rol van hormoonwisselingen van ADHD?	21
Wat is het effect van hormonen op je	14
Wat is de invloed van hormonen op je	11

Women with ADHD were asked to vote for their most urgent question to science:

Highest votes for hormonal mood changes during the lifecycle





Results Premenstrual Dysphoric Disorder

- N=200 women
- No clinical diagnoses but 'indication for PMDD'
- Comparing prevalences of possible PMDD between women with and without ADHD


Results:

- **62%** of ADHD woman had an indication for **PMDD**, versus **3-8%** in controls



Results Postpartum Depression

- **67%** of ADHD women had an indication for **PPD**, versus **13-19%** in controls



Results Perimenopausal Depression

(Peri)menopausal women with ADHD
had a **2 fold increased severity**
of mood and somatic symptoms
compared to controls

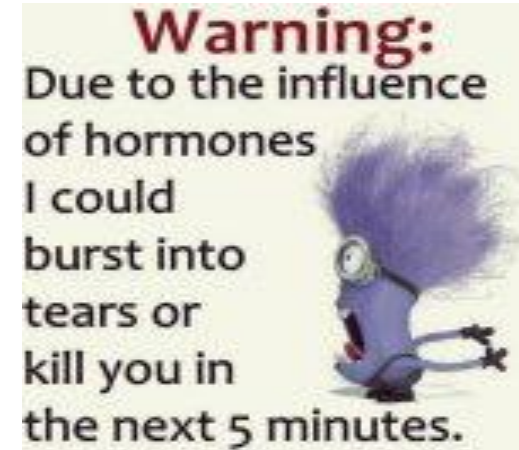
Barentsen 2001; Bromberger & Kravitz 2011

Replication study

Women
diagnosed
with ADHD at
PsyQ

- Outpatient Clinic for Adult ADHD at PsyQ, the Hague, the Netherlands
- N=209 women with diagnosed ADHD
- Age 18-71 years
- Same questionnaires
- Expectation: lower prevalences compared to 1st pilot study in participants ADHDWomen conference

Results PMDD in 2nd study



- Comparison with women from the general population
- **Indication of PMDD** in women with ADHD: **46% versus 3-8%**
- Also severity increased: in 70% ≥ 6 symptoms of PMDD (range 0-13)
- Higher use of contraceptives in PMDD group

Results PPD in 2nd study

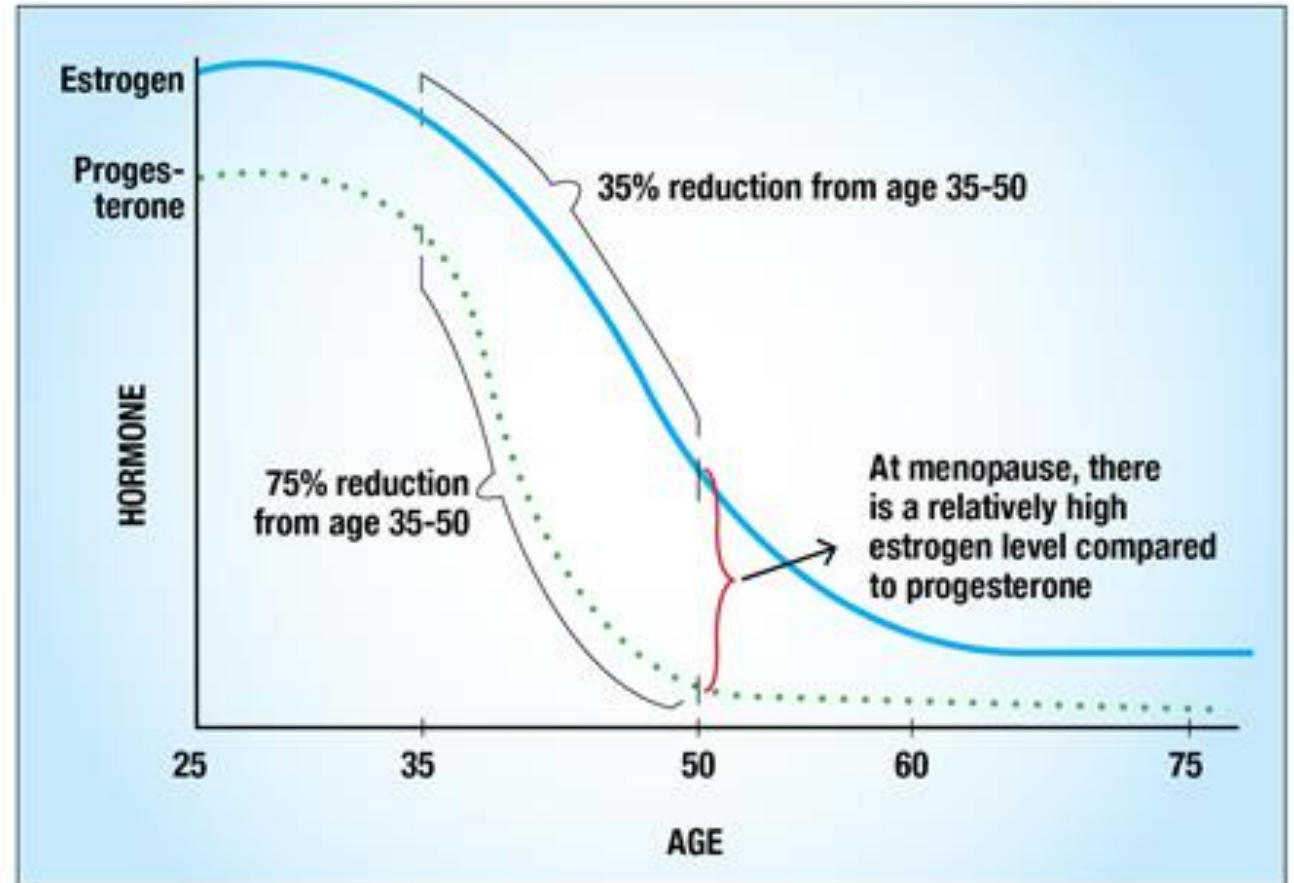
- Of 85 women with children, **58%** reported lifetime postnatal depressive symptoms, versus **13-19%** in the general population

Dorani, in preparaton; O'Hara & McCabe 2013; Gavin 2005



Results Perimenopausal Depression 2nd study

- N=37 perimenopausal women with ADHD reported a **3-fold increased** number of symptoms of anxiety, depression and somatic complaints vs women from the general population



Summary

- Confirmation of increased PMDD, PPD and perimenopausal mood symptoms in ADHD women in a clinical sample
- Three periods of hormonal changes
- Why are these episodes more severe in ADHD?
- How can we treat them better?

ADHD Women Conference		Women diagnosed with ADHD	Controls
PMDD	62%	46%	3-8%
PPD	67%	58%	13-19%
Menopausal Depressive symptoms	2x increased	3x increased	

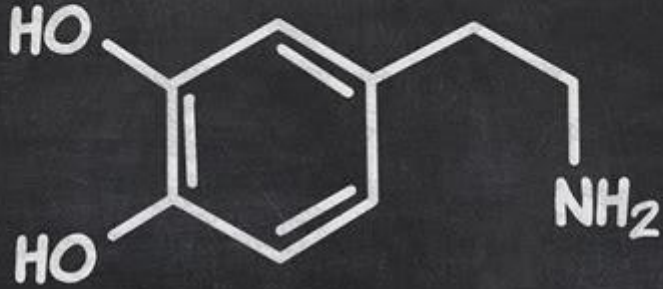
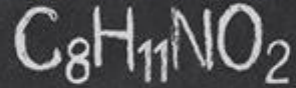
Why?

Little research on hormonal influences on the brain in women

Cycle often exclusion criterion due to changing hormonal levels, more research in males

No studies in women with ADHD

Dopamine



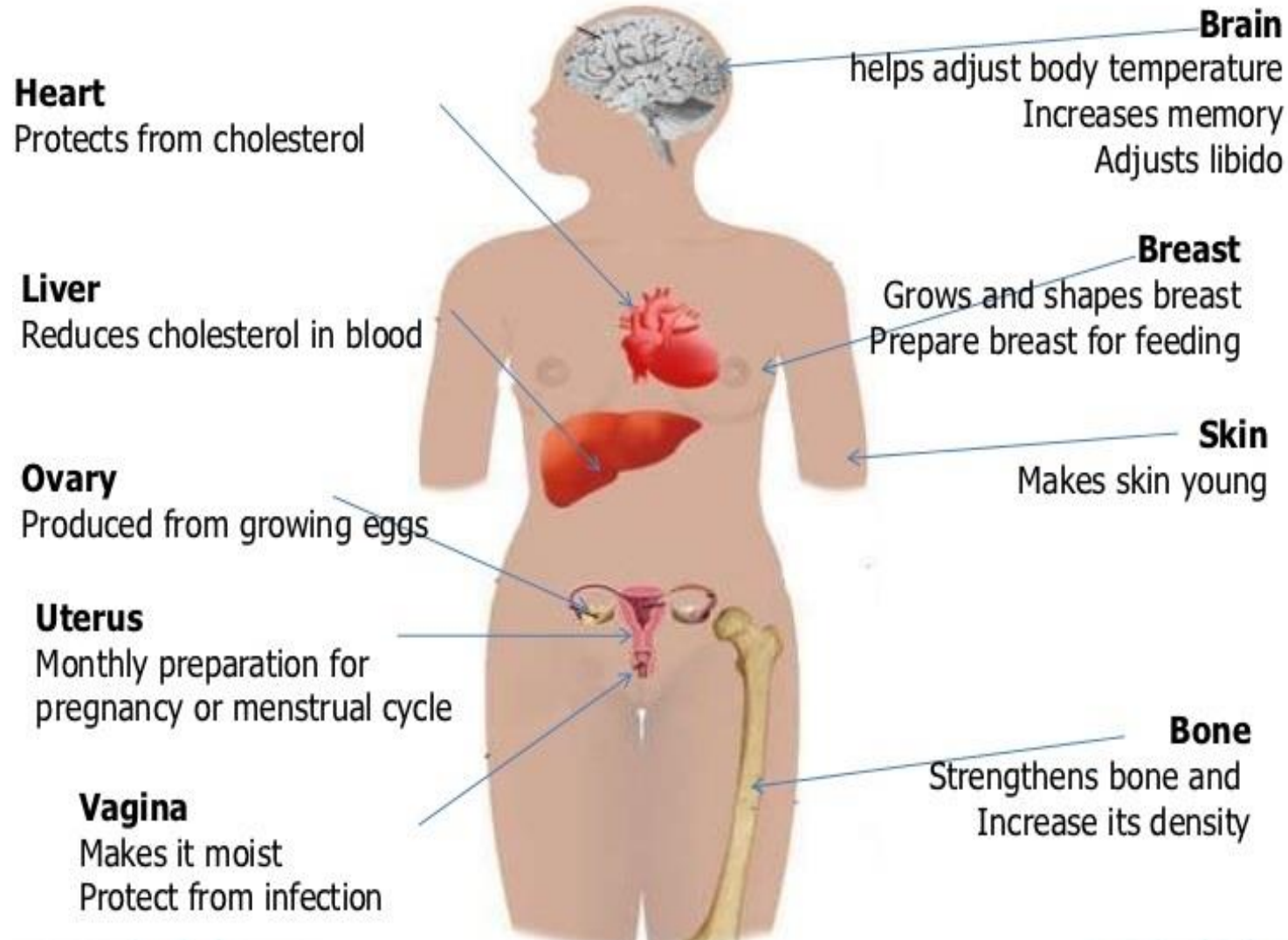
- ADHD = low dopamine levels brain
- Estrogen & progesteron influence serotonin and dopamine
- Sex hormones play a role brain cel development
- Ovarian hormones directly effect the brain regarding cognition, memory, learning and emotion
- Estrogen influences blood flow and uptake of glucose, and this changes during the cycle



Estrogen

Haimov-Kochman 2014; Volkow 2009; Barth 2015; Diekhof 2015; Soares & Zitek 2008; Fanselov & Dong 2010; Hines 2010; Reiman 1996; Sacher 2014; Frey 2014; Song 2019

Estrogen effect on a Women's Body



Estrogen & Progesteron x Dopamine

Estrogen:

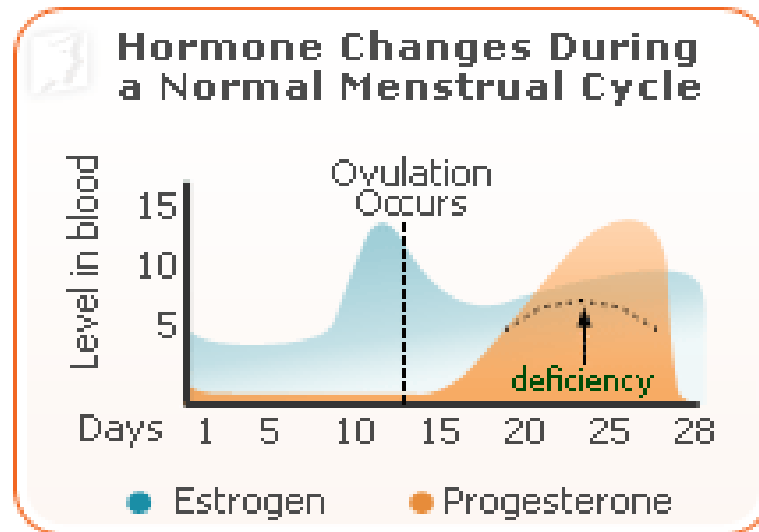
- **increases dopamine** synthesis and decreases its degradation, reuptake, and recapture
- **upregulates** dopaminergic receptors
- effect of estrogen esp. in the PFC, a region with high amounts of estrogen
- It impacts working memory function by affecting dopamine levels.
- effects on limbic regions (such as the nucleus accumbens), estrogen influences emotional and motivational behaviors

Progesteron:

- effect of progesterone on dopaminergic systems **depends primarily on the previous priming by estrogen**

Hypothesis in ADHD women

- Low prefrontal dopamine in ADHD x low estrogen in the luteal phase = 2x low levels of neurotransmitters (enhancement): you're stuck
- Explaining increased mood instability and increased ADHD severity ...



Sex hormones & ADHD Symptoms Across the Menstrual Cycle

- Study in 32 normal women, 18-22 yrs, regular cycle
- ADHD symptoms x Estrogen (E) - Progesteron (P) - Testosteron (T)
- Roberts 2018

***When estrogen is low:
higher impulsivity and inattention***

- NB Stimulant response may also differ across the cycle

Treatment options in PMDD, PPD & Climacteric depression

So far these treatments have been shown effective for hormone related mood disorders in women in general:

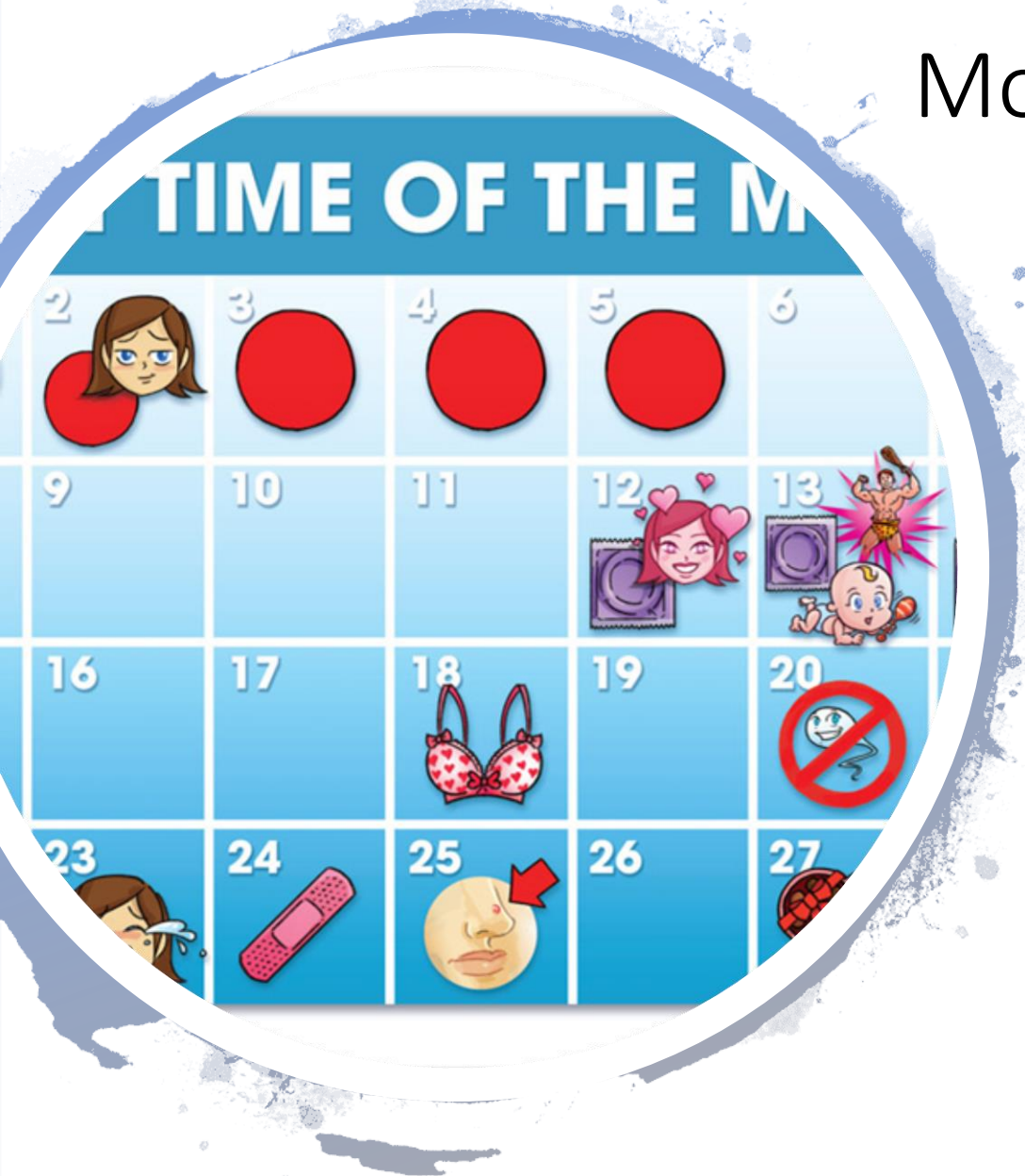
- Hormones (contraceptives, continuously without stopweek; suppletion in menopause)
- Anti-depressants (SSRIs) (for mood)

Not yet proven effective: Light therapy

Probably in ADHD women also:

- PMDD: increased dosage of ADHD meds in week before period (but no data!)

Next step: MoodCycles study in ADHD women



MoodCycles:

Measuring mood and ADHD symptoms during the cycle, cognitive performance, hormone levels, sleep, emotional lability, in ADHD women versus controls.

Twice in one cycle:

- Qb test
- Hormone levels
- Questionnaires on mood, sleep, & ADHD

MoodCycles study will start in June

Because ADHD women need it

Because we got support from PsyQ & ADHD Netwerk!

Medical Ethical approval pending

DISCUSSION