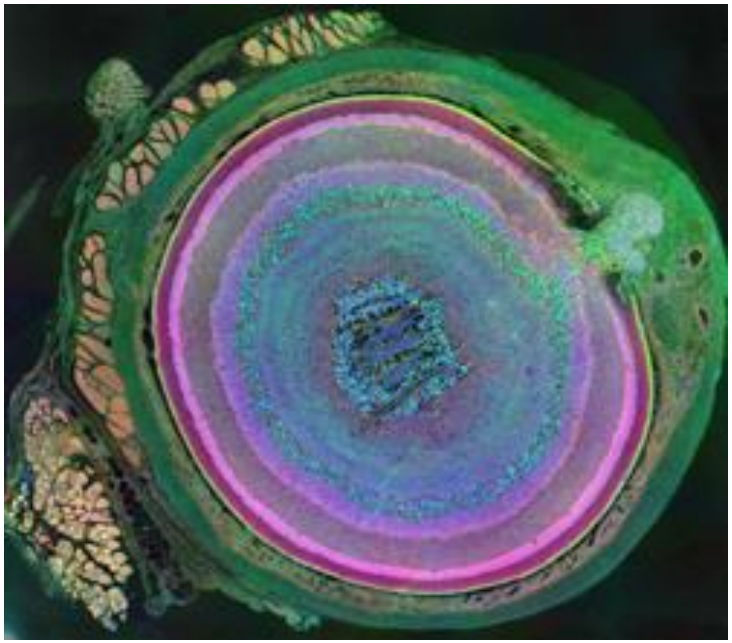
ADHD, Circadian Rhythm, Sleep & Health



ADHD Foreningen April 26th, 2018

J.J. Sandra Kooij, MD PhD

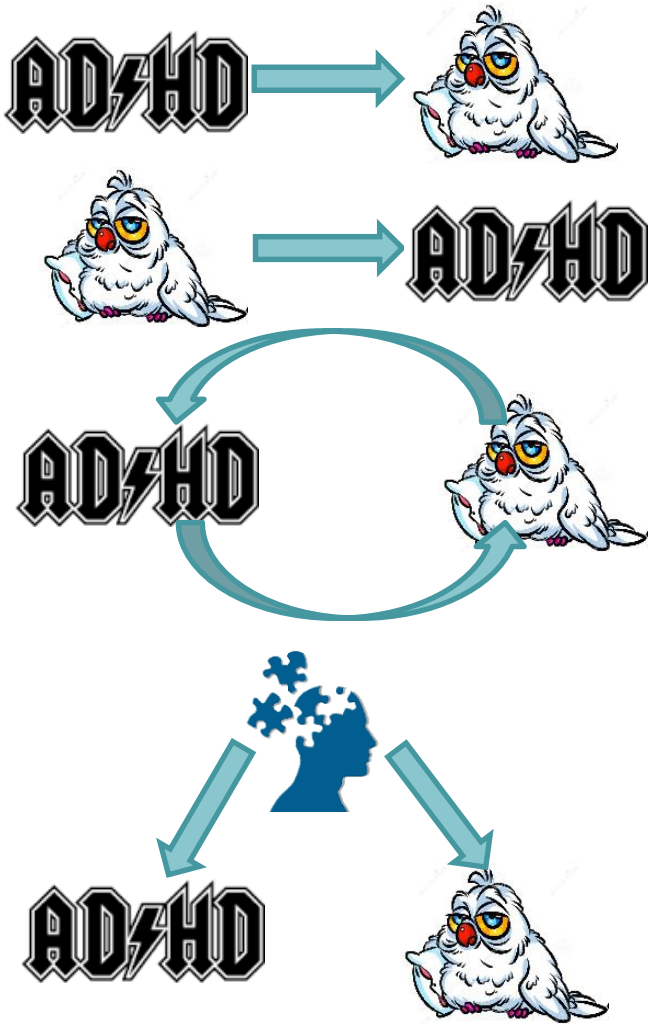
Associate Professor of Psychiatry, VUMc Amsterdam
Head Expertise Center Adult ADHD, PsyQ, the Hague, The Netherlands

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



Hvolby, Att Def Hyp Dis, 2015

ADHD and sleep in children

Increased prevalence of:

- Delayed circadian rhythm: **73%** (1)
- Parasomnias (2): Bruxism (3), Sleep anxiety (4)
- Parent-reported insomnia (5), daytime sleepiness (5), bedtime resistence (4)
- Objective Sleep-disordered breathing (2)
- Nocturnal enuresis (6)
- Variability of sleep schedule (5), sleep duration (4,7) or not (8, 9)
- Longer sleep latency (10), near-significantly (11), or not (9)

ADHD pre-scholers (1,5-5 yrs): increased nocturnal motor activity and variability of sleep duration (12)

(1) van der Heijden, Clin Pedriatics, 2005; (2) Tsai, Curr Psych Rep, 2016; (3) Mota-Veloso, Int J Paediatr Dent, 2017; (4) Vélez-Galarraga, Eur J Paediatr Neurol, 2016; (5) Craig, J Att Dis, 2017; (6) Baeyean, J Urol, 2007; (7) Melegari, J Att Dis, 2016; (8) Bergwerff, J Sleep Res, 2016; (9) De Crescenzo, Sleep Med Rev, 2016; (10) Vaidyanathan, J Can Acad Child Adol Psych, 2016; (11) Diaz-Róman, J Clin Sleep Med, 2017; (12) Melegari, J Att Dis, 2016;

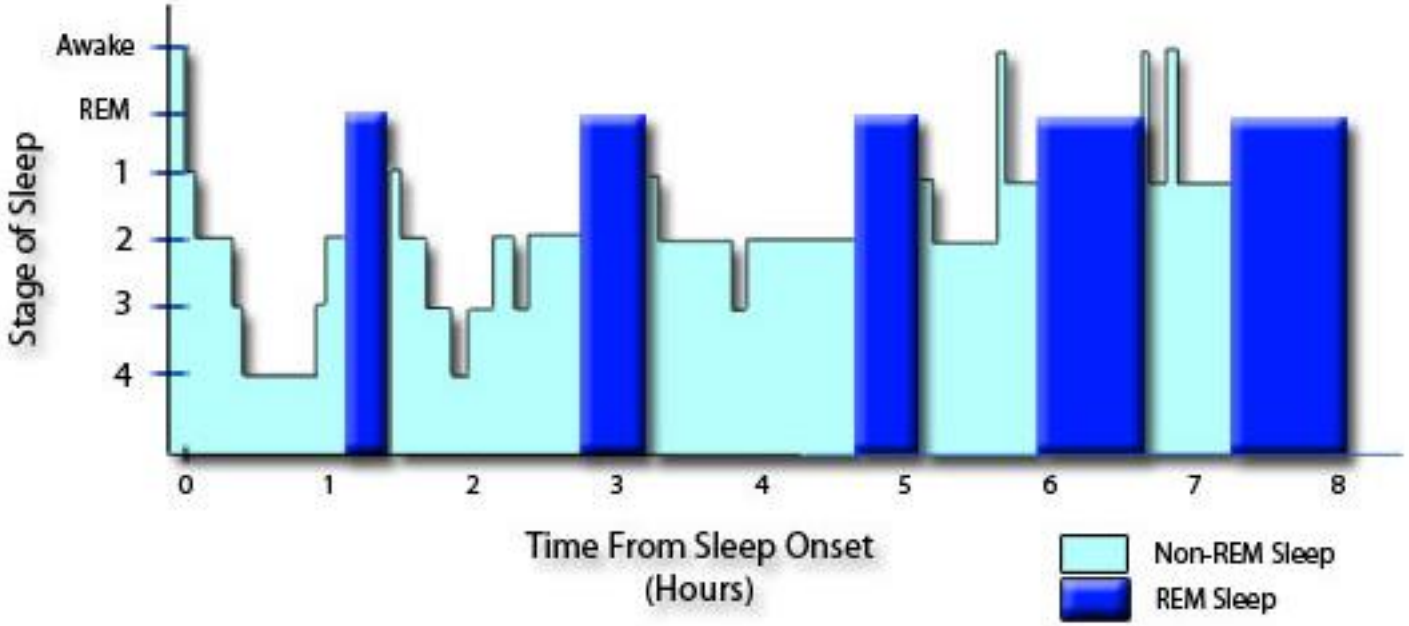
ADHD and sleep in children

- Sleep problems and ADHD independently affect QoL and social functioning (1)
- More parent-reported sleep problems in unmedicated and anxious children (2)
- More sleep problems, poorer working memory in ADHD (3)

(1) Craig, J Att Dis, 2017; (10) Bergwerff, J Sleep Res, 2016; (2) Bar, Sleep Med, 2016; (3) Scriberras, Sleep Med, 2015;

ADHD in children: sleep architecture

Sleep stages in normal sleep



ADHD in children: sleep architecture

- Higher REM proportion and shorter REM latency in ADHD (1, 3)
- REM proportion & inattention correlated in ADHD, the opposite in controls (1)
- More time in stage 1 sleep (2)
- More sleep cycles (3)

(1) Kirov, Front Psychol, 2017; (2) Diaz-Róman, J Clin Sleep Med, 2017; (3) Virring, J Sleep Res, 2016

ADHD and sleep in adolescents

- Any sleep problem: **73%** (1)
- Self-reported daytime sleepiness: 42% (1)

- Large population study: correlation between ADHD symptoms and shorter sleep, longer latency, nocturnal wake time, sleep deficiency, insomnia, DSPS (2)
    - No confounding by use of electronic devices before bed (2)
    - Small effect of depressive symptoms (2)

(1) Langberg, J Att Dis, 2017; (2) Hysing, Behav Sleep Med, 2016

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

(1)Van Veen, Biol Psych, 2010, (2) Bijlenga, J Att Dis, 2013; (3) Rogers, Br J Clin Psychol, 2016;
(2)(4) Snitselaar, Behav Sleep Med, 2016; (5) Cortese, Sleep, 2005; (6) Schredl, Eur Arch Psych Clin Neurosci, 2017;

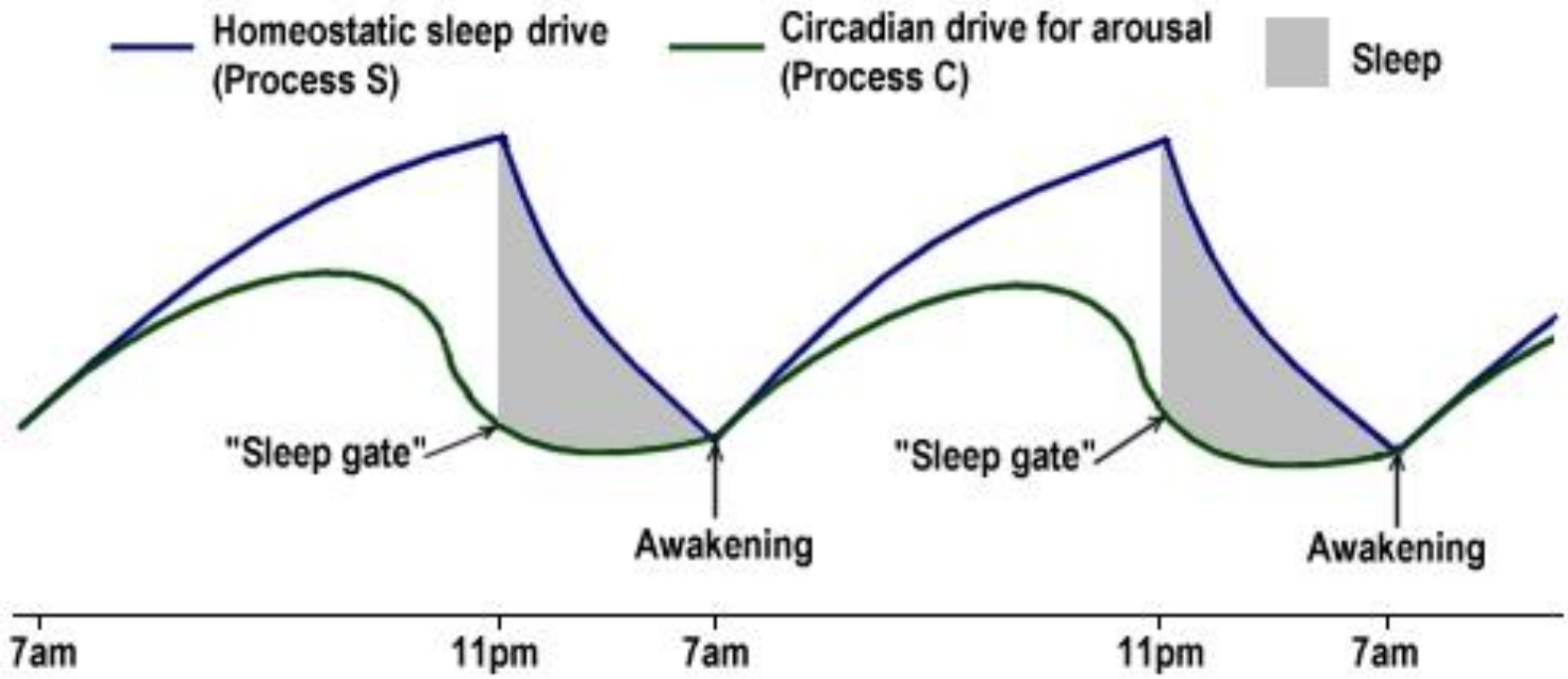
Circadian Rhythm Sleep-Wake disorders, Delayed Sleep Phase Type

DSPT is characterized by:

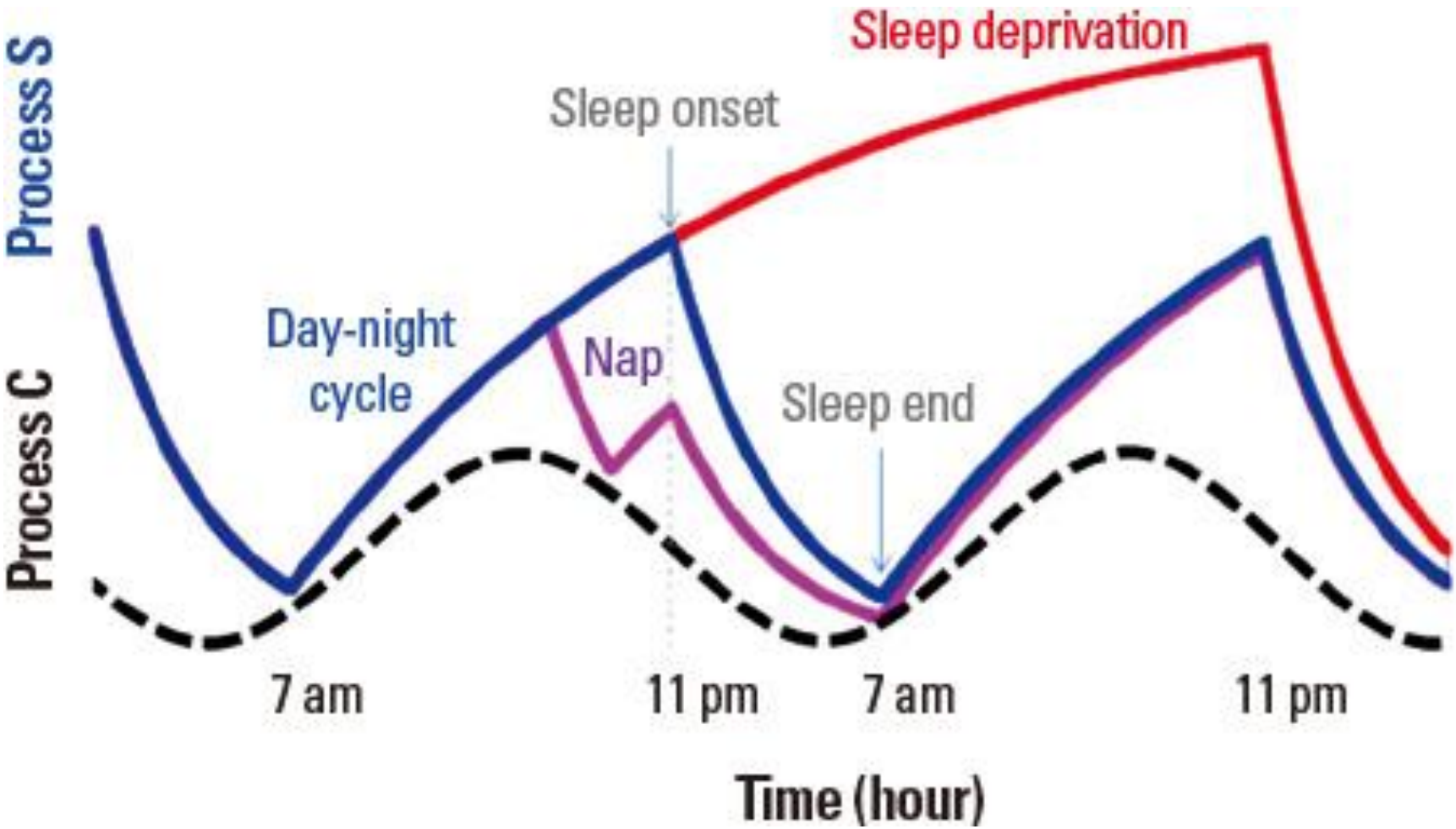
- (Very) late chronotype
- A chronic pattern of (very) late sleep and preference for late rise
- Daytime sleepiness and/or sleep onset insomnia
- Compensated for by irregular sleep pattern
- Dysfunctioning due to increased inattentiveness and/or social problems

DSM-5

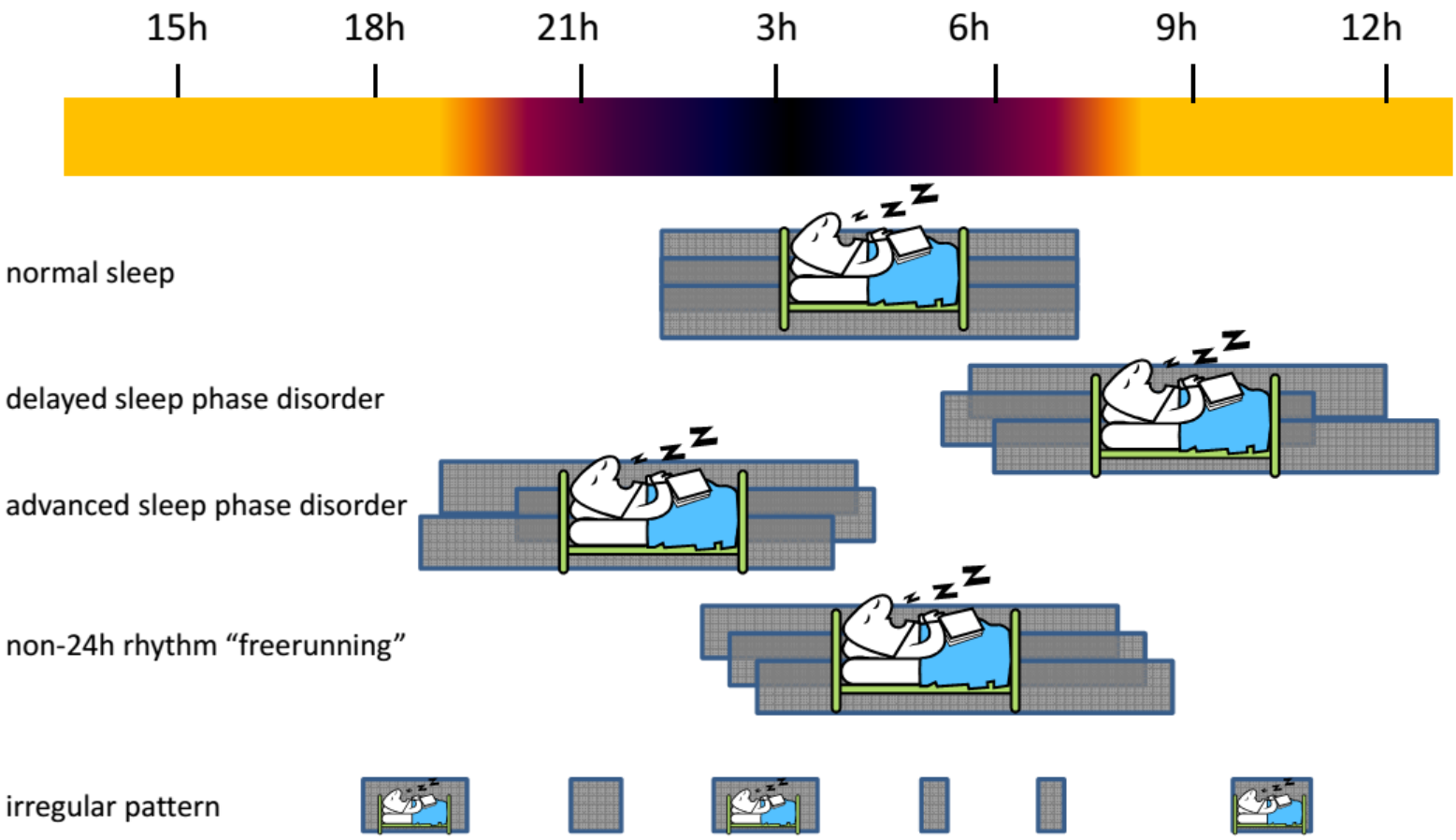
Sleep regulation



Cooperation
Process S & Process C



Circadian sleep-wake rhytm disturbances



NRC
2 okt 2017

Nobelprijs gaat naar de biologische klok

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

Trending

Hoe Oranje na he
falende voetbalp
De implosie van Sebastian V
van de spanning
CATALONIE
Honderdduizenden demons
tegen afscheiding
Mister Ikea: 'Hoezo niet echt
een massaproduct is?'
Ze vragen zich ineens af: hoo

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, BP-II, depression (4, 5)

•BMAL1 and PER2 genes: less solid circadian rhythm in ADHD vs controls (6)

(1) Chen, Carcinogenesis, 2005; (2) Savvidis & Koutsilieris, Mol Med, 2012; (3) Jones, Exp Neurol, 2012 ; (4) Xu, Behav Brain Func, 2010; (5) Benedetti, Am J Med Genet B Neuropsych, 2003; (6) Baird, Mol Psych, 2011;

The circadian rhythm is mainly controlled by

- Genes
- Time of melatonin onset at night, induced by darkness at night

And by:

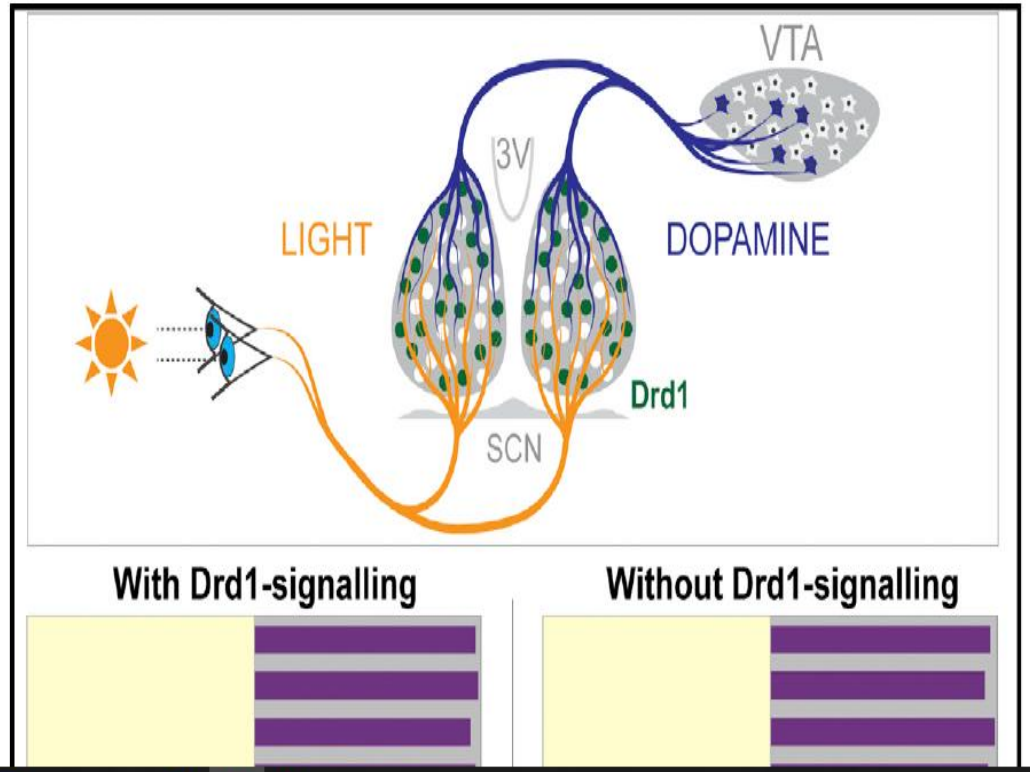
- Timing of (day)light in the morning
- That stops the melatonin production via the melanopsin system in the eyes
- Dopamine, a wake-up call for the brain!

Current Biology

Grippo ea, August 2017

Direct Midbrain Dopamine Input to the Suprachiasmatic Nucleus Accelerates Circadian Entrainment

Graphical Abstract



Authors

Ryan M. Grippo, Aarti M. Purohit, Qi Zhang, Larry S. Zweifel, Ali D. Güler

Correspondence

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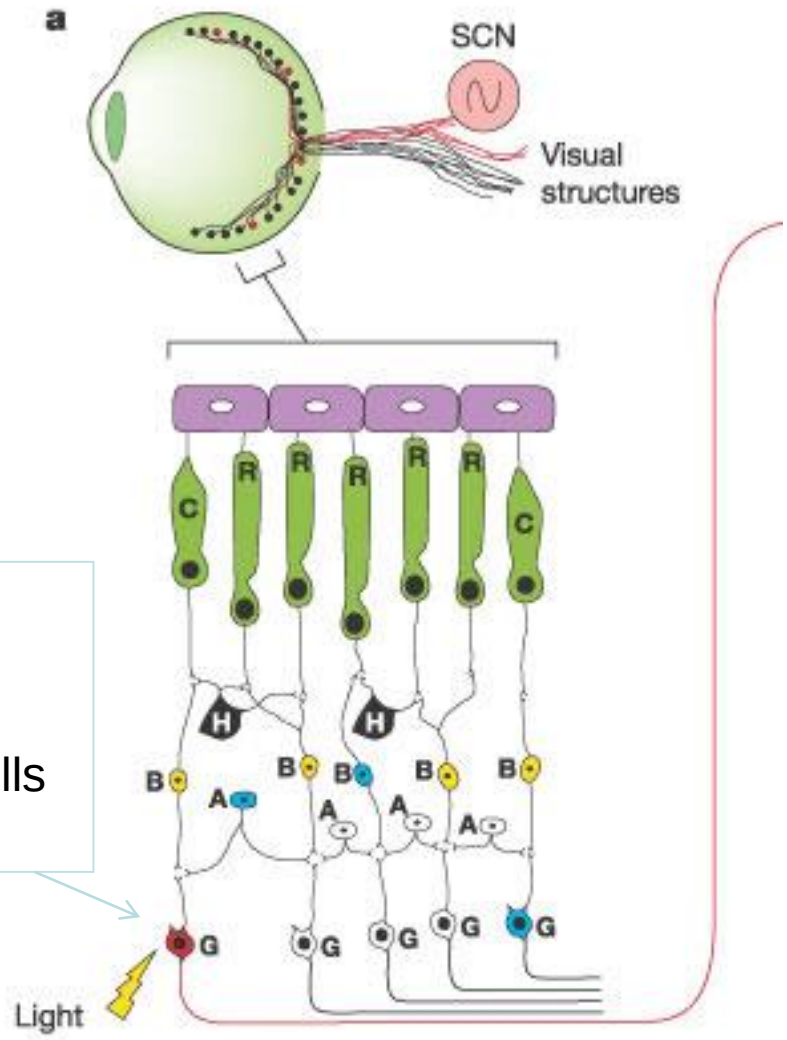
In Brief

Grippo et al. demonstrate a direct functional connection from the midbrain dopamine neurons to the central circadian clock. This D1 dopamine-

ADHD and circadian rhythm: the role of the eye



Melanopsin-containing Retinal Ganglion Cells (mRGCs)

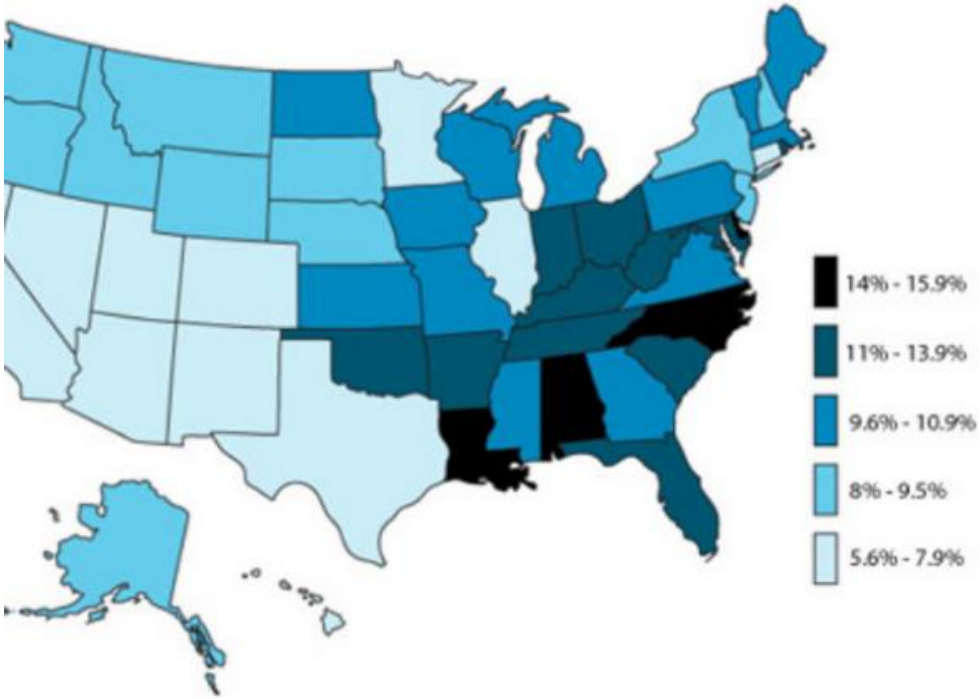
Contrast between day and night

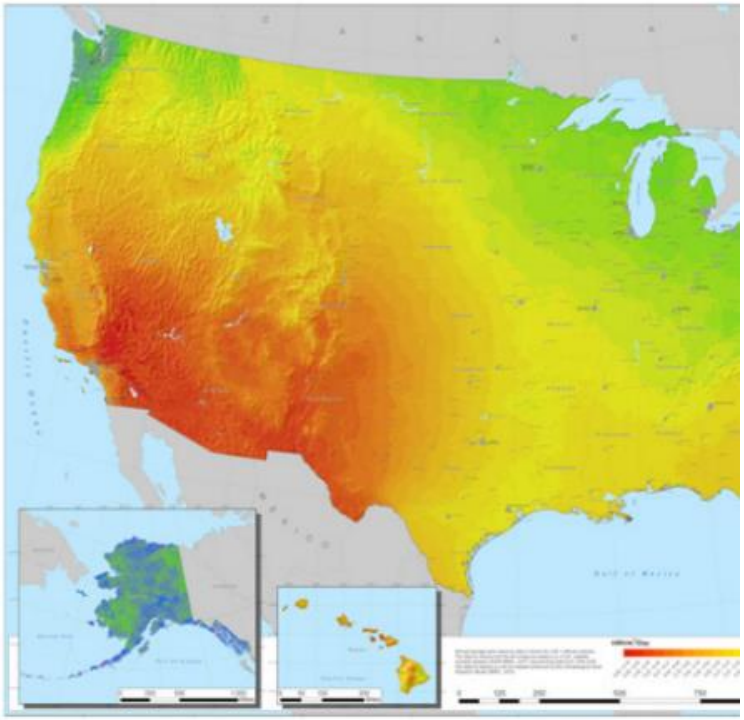
- The darker the night and the brighter the day, the more stable day and night rhythm

- So increasing the difference in light intensity between day and night will help to keep a stable sleep rhytm

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

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



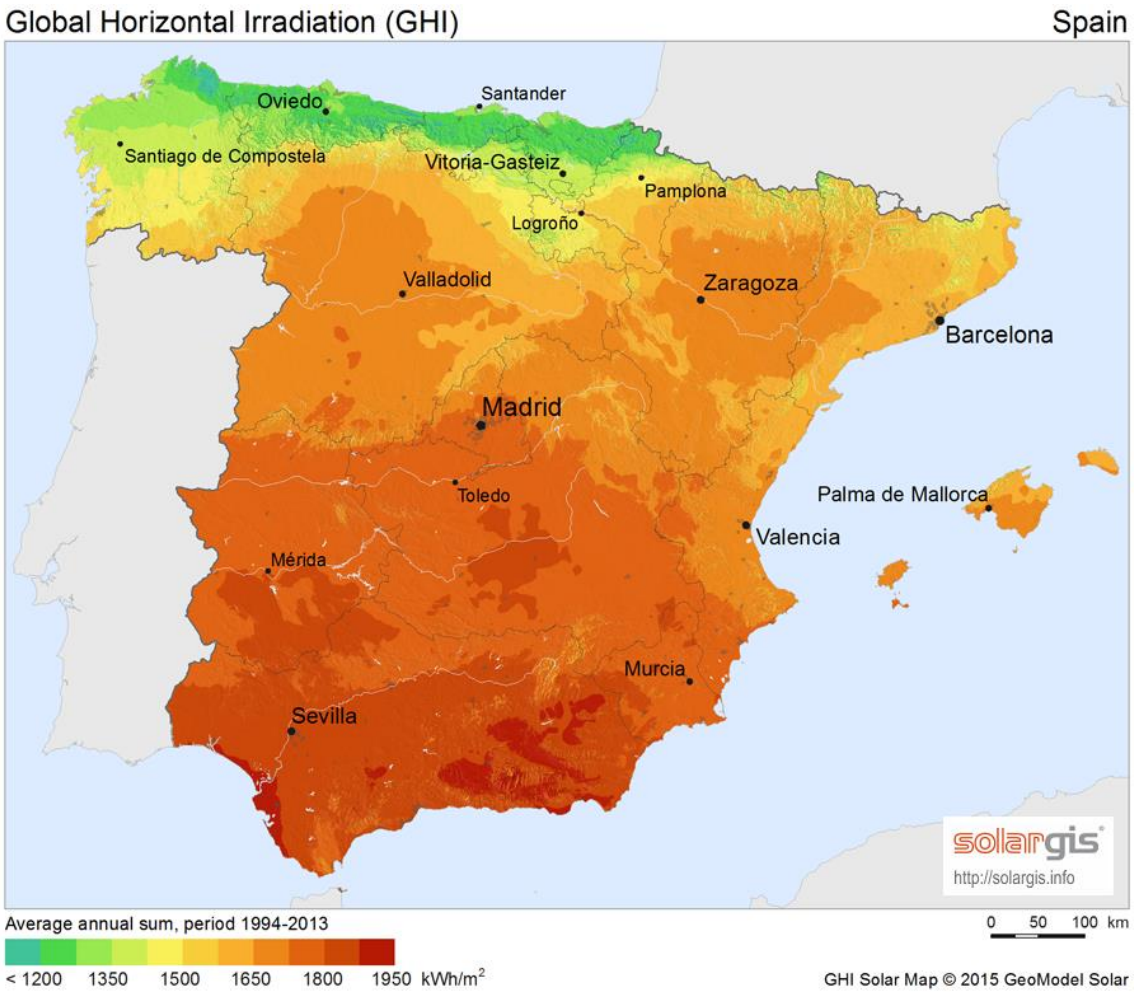


Arns ea 2013:
The preventative effect of high Solar Intensity might be related to improvement of circadian clock disturbances in ADHD

ADHD and circadian rhythm

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

Fayyad ea 2016



Source: www.solargis.com.

Are most adults with ADHD evening types?

- Evening types are more active at night, prefer to go to bed late
- They get up late as well
- Evening types may be late due to a delayed onset of melatonin
- If sleeping longer is not possible due to work or school obligations, a chronic sleep dept can result
- Working in evening- or nightshifts may be adaptive
- Question: do adults with ADHD work more often in nightshifts?
- And if so, is that a problem?
- Morningness is associated with low impulsiveness / sensation seeking, eveningness the other way round…

Barkley 1997, J Dev Behav Pediatr,18(4):271-9. Caci 2004, Eur Psychiatry.;19(2):79-84. Levitan 2004, Biol Psychiatry;56(9):665-9. Van Veen 2010, Biol Psychiatry 67(11): 1091-6; Kooij 2012, book Adult ADHD

ADHD is highly comorbid
with circadian based disorders

75% has comorbidity (mean 3 disorders):

• Depression (60% SAD)	25-50%
• Anxiety	25%
• Substance Use Disorders	20-45%
• Personality Disorders	16-40%
• Eating Disorders (BN)	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?

Van Veen 2010, Biological Psychiatry

Dim Light Melatonin Onset (DLMO): delayed

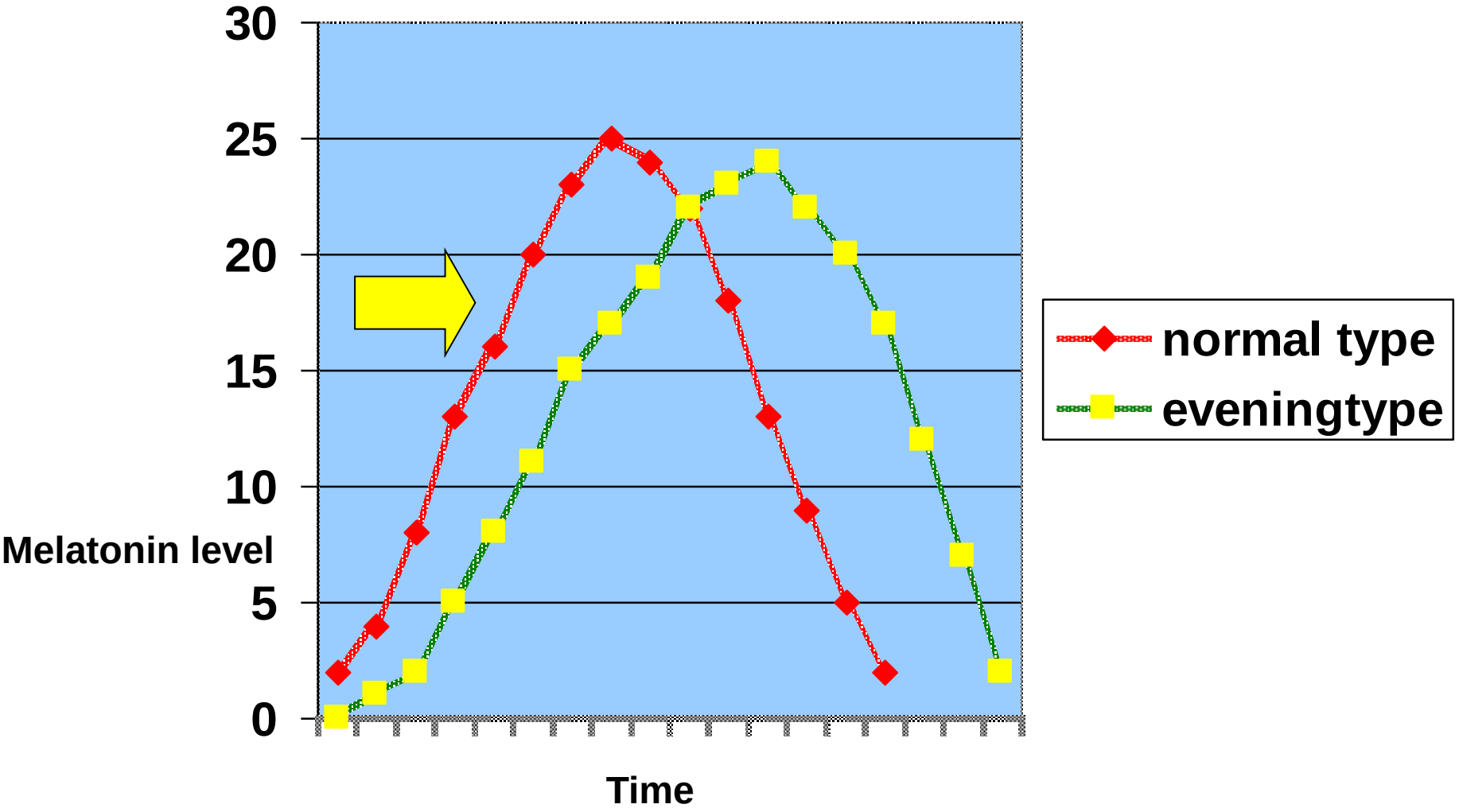
N= 40 adults with ADHD w/wo Sleep Onset Insomnia
versus healthy controls

	ADHD Total	ADHD + SOI	ADHD - SOI	HC	*p*: ADHD vs HC	*p*: 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**

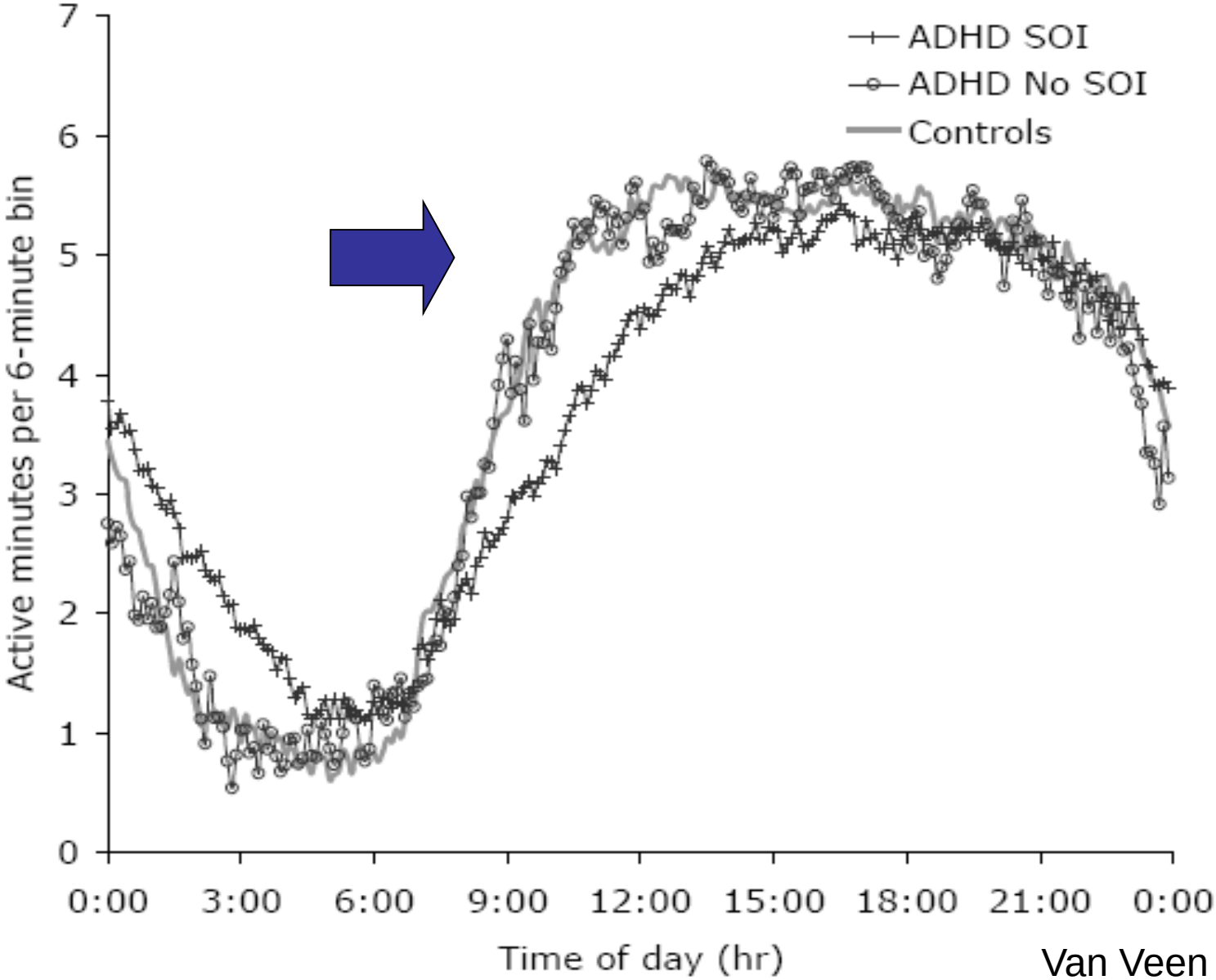
- 78% of consecutive ADHD patients had SOI
- DLMO: 105 min later in SOI vs controls
- After DLMO, it generally takes still 2 hours to fall asleep
- In ADHD it takes 3 hrs …

Van Veen ea, 2010; Bijlenga ea, 2013

Sleep phase delay in ADHD

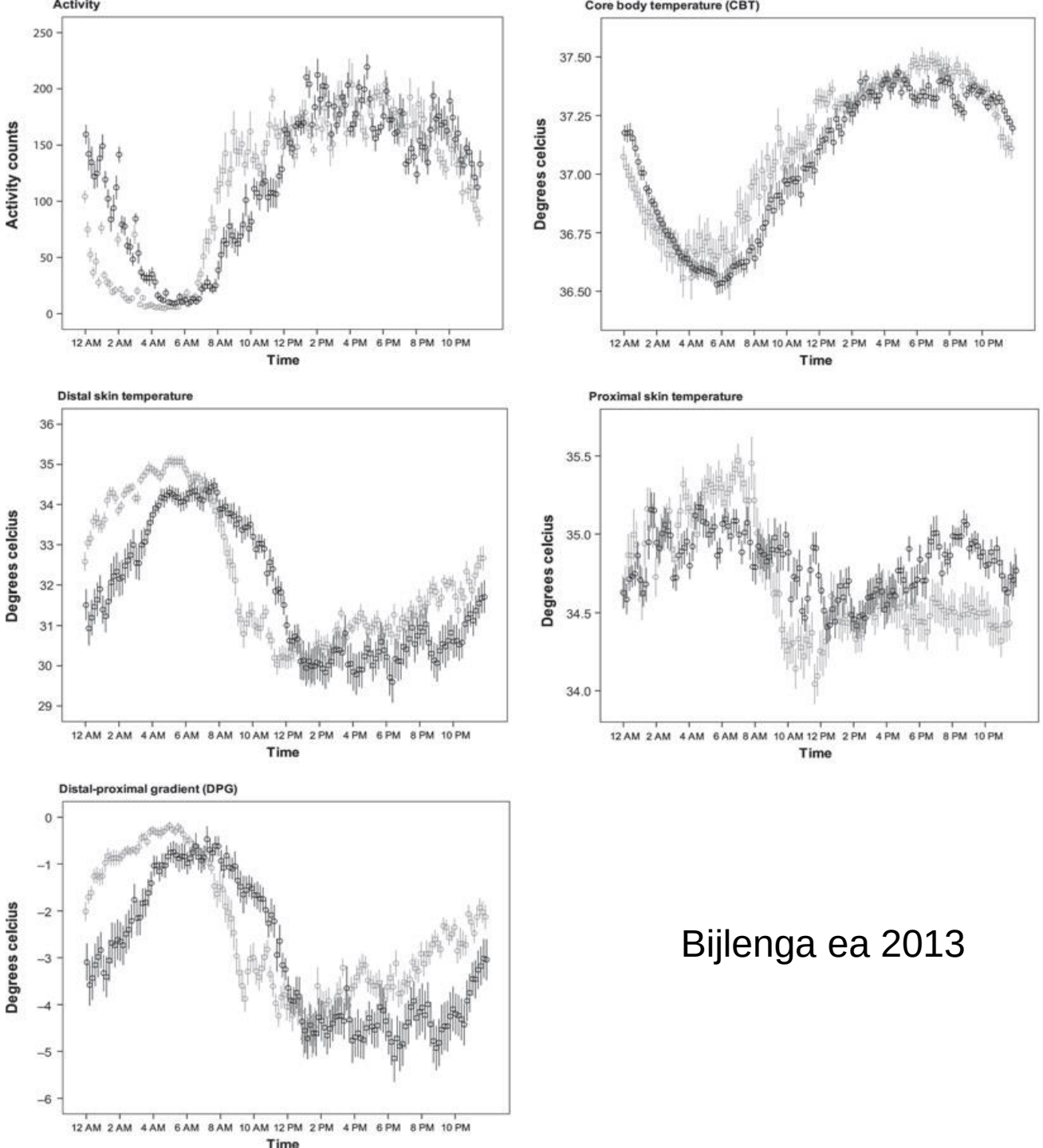


24 hour movement patterns in ADHD + and – SOI, compared to controls (actigraphy)



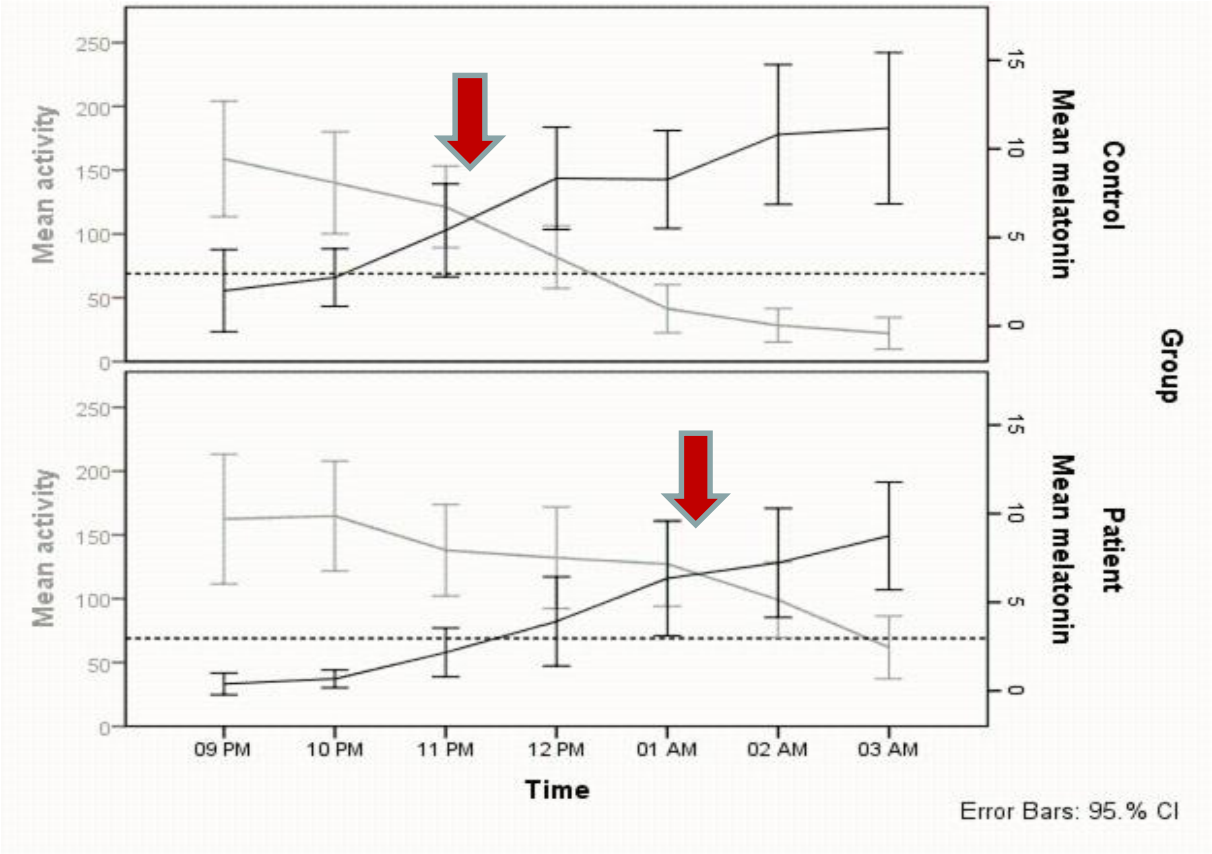
Van Veen ea 2010

24 hr Activity, Core and Skin Temperature, in ADHD versus controls



Bijlenga ea 2013

ADHD with DSPS vs. controls



Bijlenga, 2013

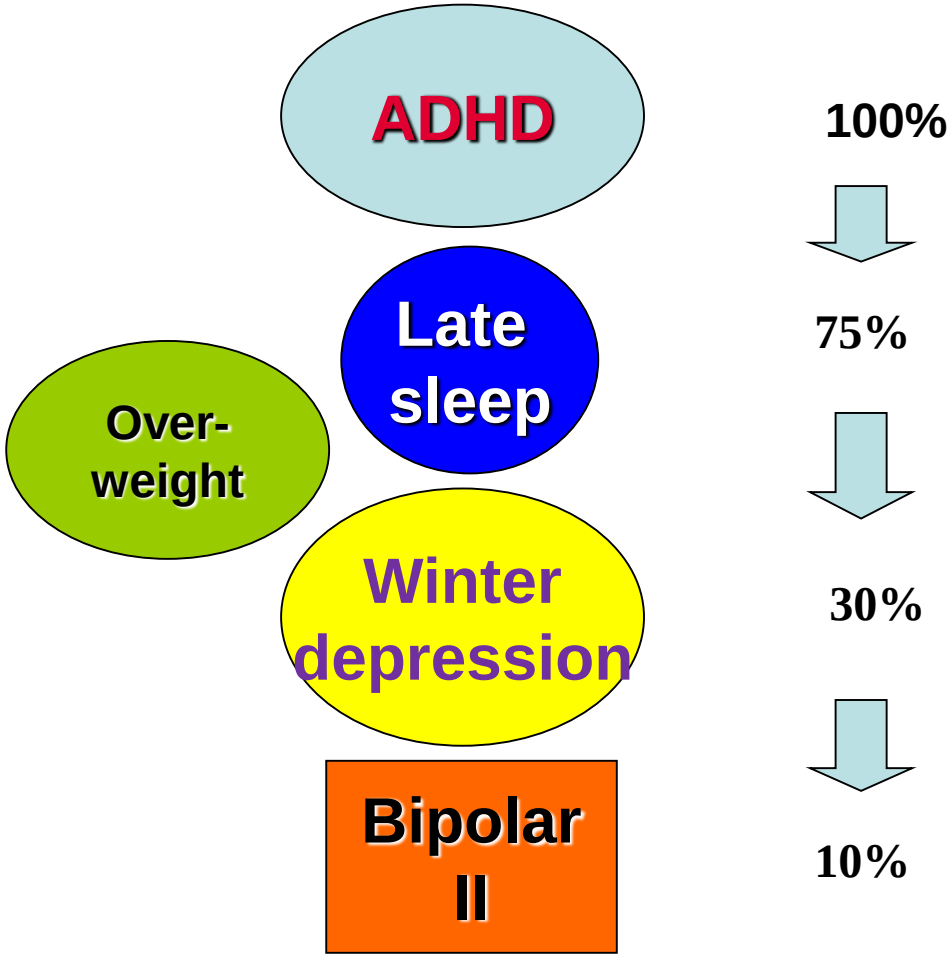
ADHD with DSPS vs controls (n=24)

- Activity, core and skin temperature, and melatonin onset equally delayed
- Longer period between DLMO and sleep onset
- 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

Bijlenga, J Sleep Res, 2013

ADHD, circadian rhythm, sleep, mood & season



Kenniscentrum
ADHD bij volwassenen

Population study

ADHD adds risk to
circadian sleep disturbance
up and above depression and anxiety

- Self-reported sleep characteristics of 2090 participants in the Netherlands Study of Depression and Anxiety (NESDA)

3 groups:

- Healthy Controls (HC), Lifetime Depression and/or Anxiety (LDA), and LDA + ADHD

ADHD increased Odds Ratio for:

- late chronotype (OR=2.6; p=.003)
- indication of DSPS (OR=2.4; p=.002)
- and short sleep duration < 6h (OR=2.7; p=.007)

Bron ea 2016

ADHD, late sleep and winterdepression

ADHD & seasonal mood changes

- Adult ADHD co-occurs with lifetime depressive disorder in 55%
- Most of them (60%) have Seasonal Affective Disorder (SAD) or winterdepression
- Open trial of Light therapy effective for SAD and ADHD, as well as for Delayed Sleep Phase
- Winterdepression has a circadian phase delay in 70%
- Are winterdepression and ADHD related via circadian disturbances?

Levitan 1999, Compr. Psychiatry, 40(4), 261-7; Johansson 2003, Neuropsychopharmacol;28(4):734-9; Amons 2006, J Affect Disord;91(2-3):251-5; Rybak 2007, Compr Psychiatry;48(6):562-71; Lewy 2006, Proc Natl Acad Sci U S A;103(19):7414-9; Kissling 2008, Am J Med Genet B, Neuropsychiatr Genet;147(3):333-8. Fargason ea 2017

DSPS & (winter)Mood (SAD)

- Both disorders of the biological rhythm
- Both increased in ADHD (1, 2)
- Difficulty synchronizing to external cues, such as light, especially when they are weak (1, 3)
- Suboptimal melanopsin system functioning in SAD (3)
- Both treated by phase resetting using light (1)
- Prevalence of SAD in ADHD: 27% (vs 3% in controls) (4)

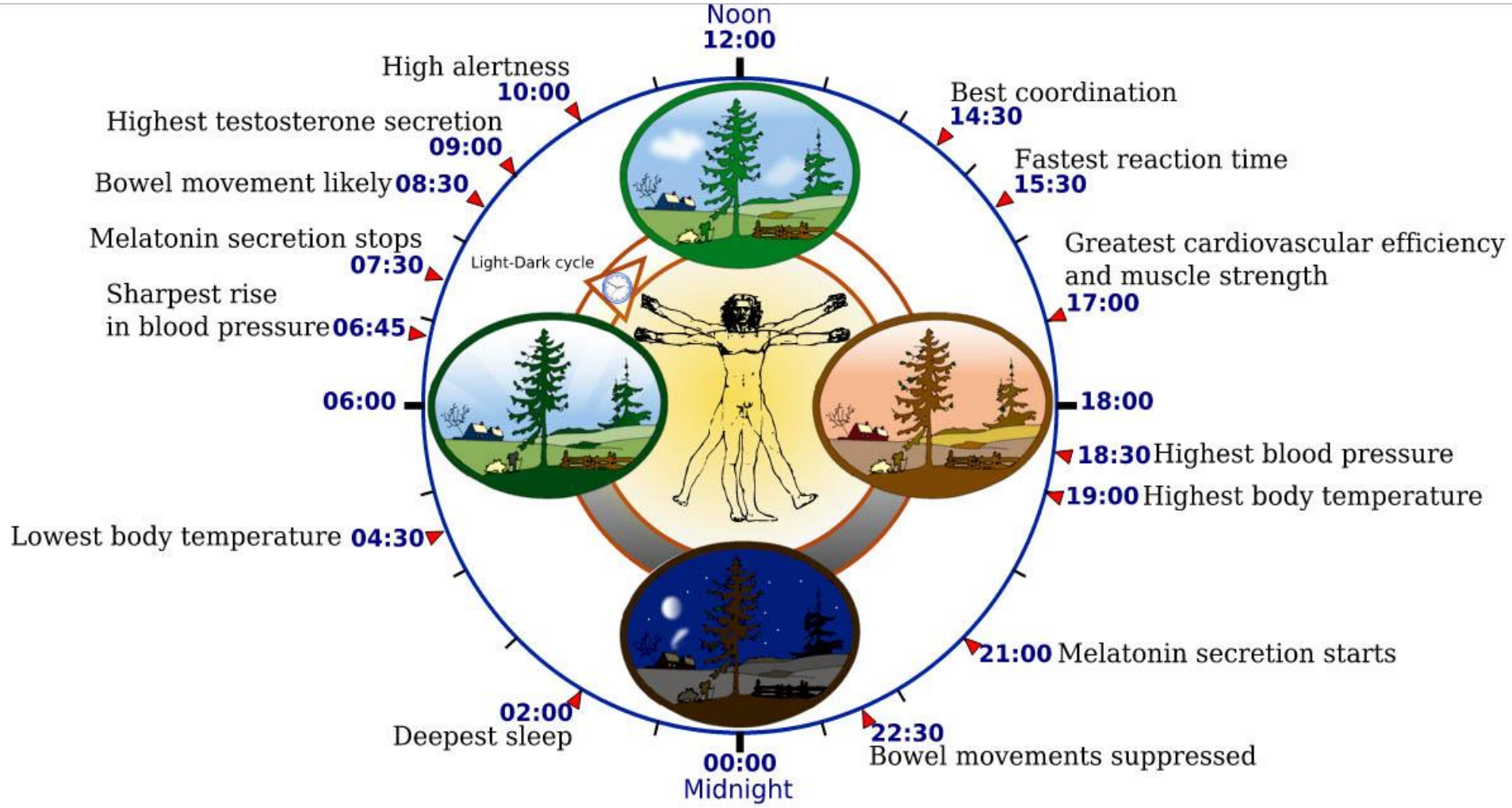
(1) Lewy, Curr Psych Rep, 2009; (2) Lee, J Aff Dis, 2011 ; (3) Shirayama, Sleep Med, 2003 ; (3) Roecklein, Psych Res, 2013; (4) Amons, J Aff Dis, 2006

Delayed Sleep & Health in ADHD

- Delayed circadian rhythm in 75% of children and adults with ADHD (DLMO measurements saliva)
- Late sleep = short sleep due to school and work obligations next morning (‘social jetlag’)
- Chronic short sleep is associated with obesity, DM-II, CVD and cancer
- Etiology: genetic, environmental, behavioral & biological: delayed onset of melatonin at night (105 min in adults, 45 min in children)

Kooij & Bijlenga 2014; van der Heijden ea 2005, 2006

Biological clock & organic rhythms



Late & short sleep and obesity

Late sleep = short sleep
➡ late meals

Possible impact of a delayed rhythm on weight and health:

- **Sleeping late** may lead to a short sleep duration
- **Short sleep** duration is associated with obesity
- Adults with ADHD tend to **skip breakfast**
- Breakfast skipping is associated with obesity
- ADHD patients suffer from eating problems in 80%, mostly **binge eating**
- Their **weight fluctuates** 10 - 20 kg's
- ADHD is sign. associated with increased BMI
- Obesity is associated with diabetes, cardiovascular disease and cancer

Kooij 2012, Dubois 2009, Boere 2008, Davis 2009, Mota 2008, Copinschi 2000, Spiegel 2005, Cortese 2016

Sleep loss causes loss of control over appetite

Leptin (satiety hormone) and ghrelin (hunger hormone):

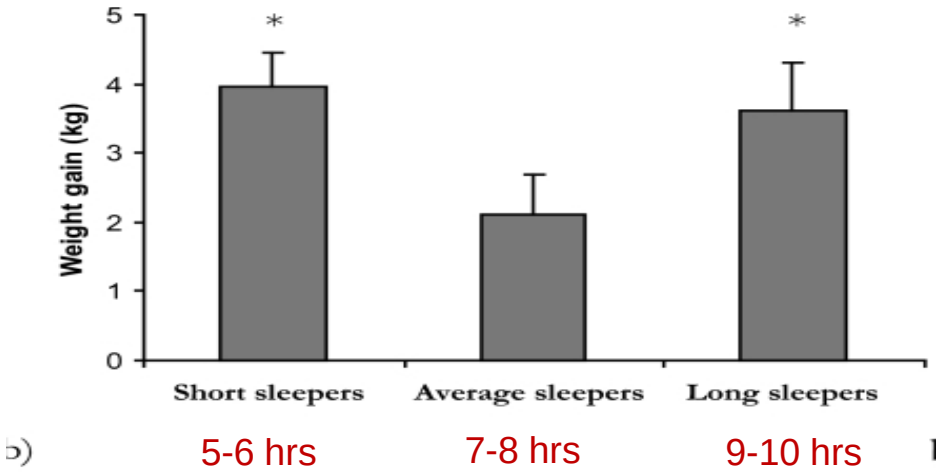
- 2 hours less sleep lowers levels of leptin, the satiety ("fullness") signal
- Sleep restriction study: leptin ↓ by 18% and ghrelin ↑ by 28%, leading to increased appetite and feelings of hunger
- 13 epidemiologic studies in adults and 8 in children: sleep loss is associated with increased BMI
- Sleep loss is a novel risk factor for insulin resistance and type 2 diabetes

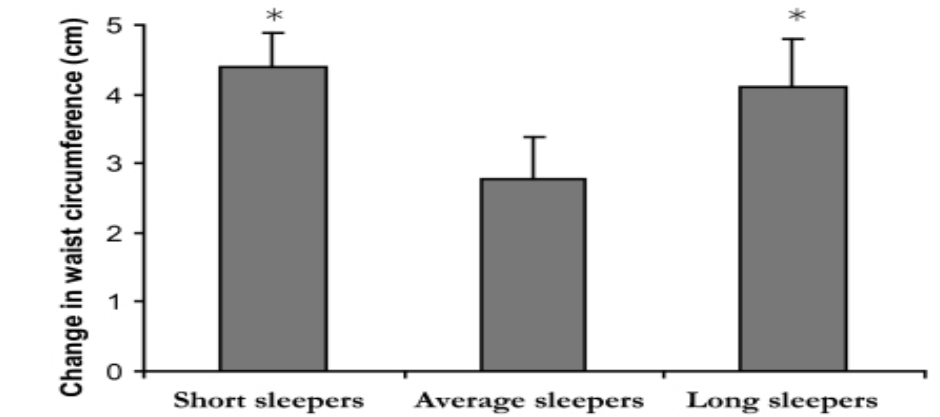
Lauderdale 2006, Am J Epidemiol;164(1):5-16; Lauderdale 2009, Am J Epidemiol;170(7):805-13. Spiegel 2005, J Appl Physiol;99(5):2008-19; Copinschi 2005, Essent Psychopharmacol;6(6):341-7; Shea 2005, J Clin Endocrinol Metab;90(5):2537-44;

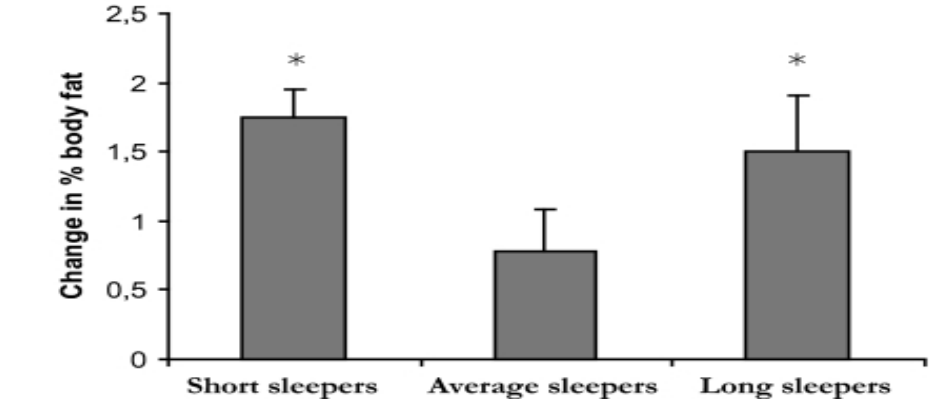
N=270 adults
6 yrs follow up

Relationship between
short & long sleep &

- **Weight**
- **Waist circumference**
- **% Body fat**

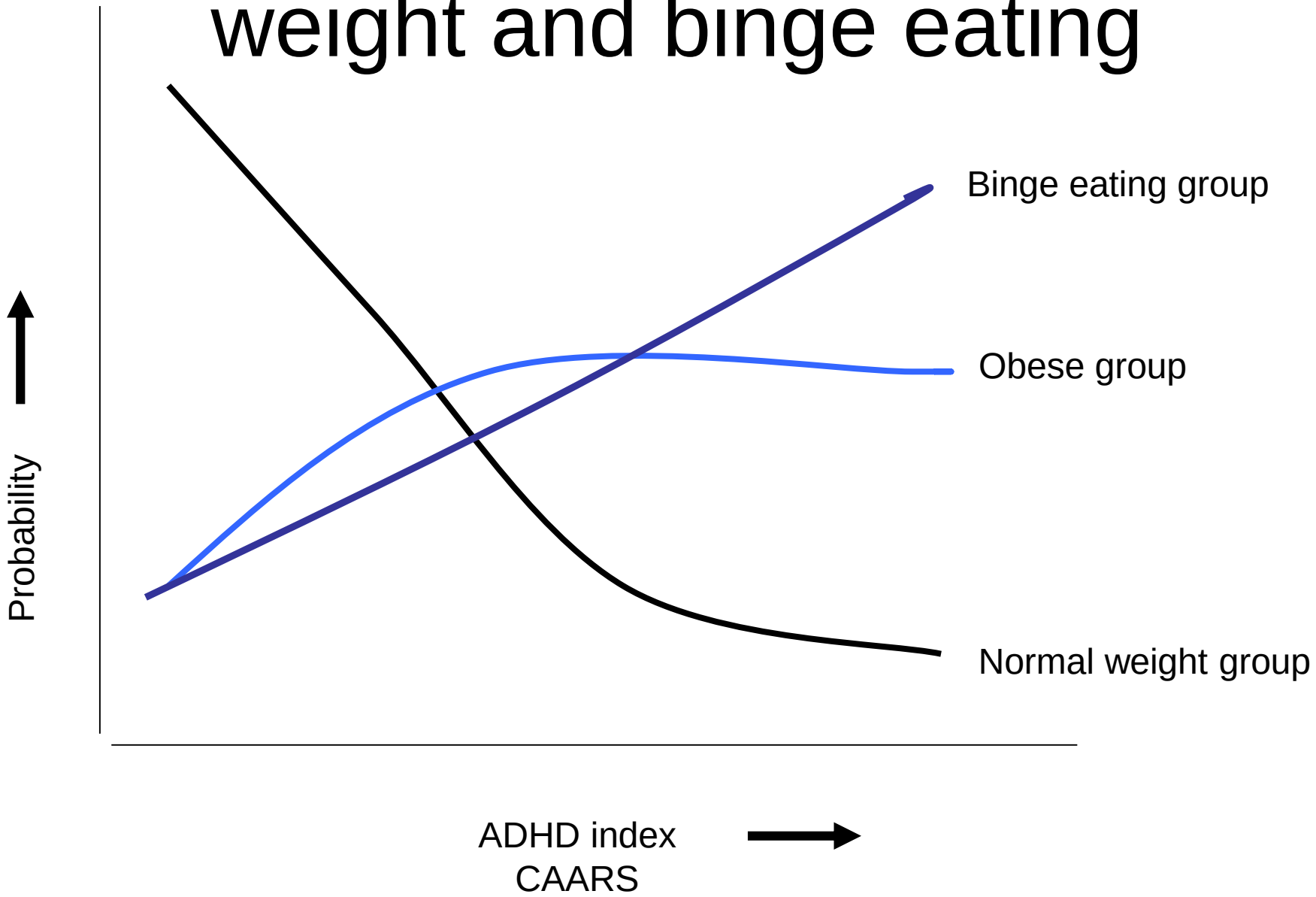






Chaput ea 2008

ADHD severity predicts weight and binge eating



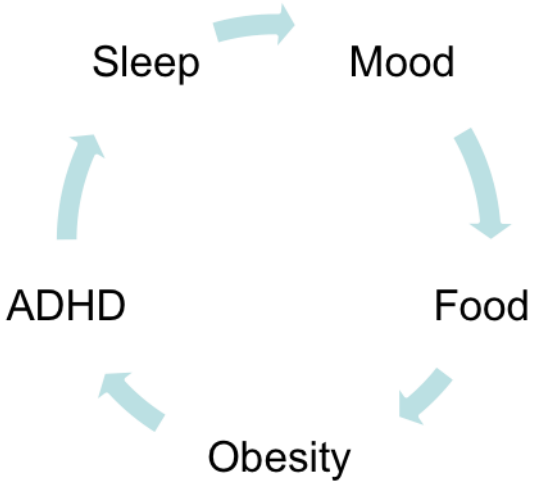
Davis 2009, J Psychiatr Res;43(7):687-96

Meta-analysis n=700.000: overweight & obesity increased in child & adult ADHD

- BMI 70% increased in adults with ADHD (28.2% vs 16.4%)
- BMI 40% increased in children with ADHD (10.3% vs 7.4%)
- After controlling for depression, age, gender etc

Cortese ea 2016

Pathways to obesity in ADHD



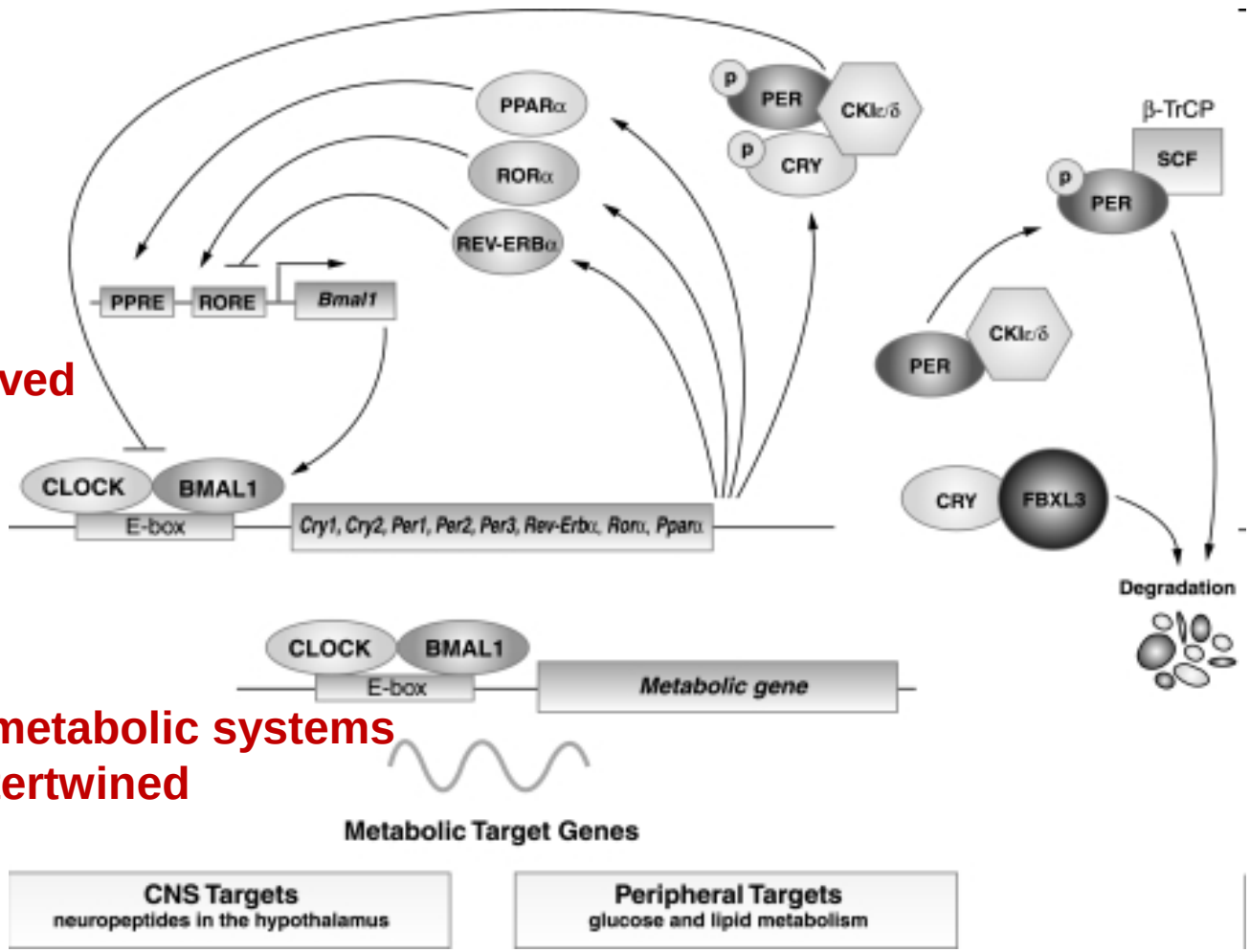
1. ADHD symptoms: impulsivity – bad planning of meals - abnormal eating patterns - sedentary lifestyle – food addiction via impaired reward system?
2. Familial genetic pathways link ADHD and obesity
3. ADHD is also increased in obesity patients
4. Chronic Short sleep due to DSPS - metabolic alterations in appetite
5. Seasonal affective disorder increased in ADHD: carbohydrate craving in winter
6. ADHD- iron deficiency - chronic inflammation – obesity?

Cortese 2014, 2017; Chen 2017; Altfas 2002; Kooij & Bijlenga 2013; Wynchank 2016; Levitan 2004; Bijlenga 2013

Sleep yourself slim!
Questions?

Genes involved in sleep & metabolism

Circadian & metabolic systems intimately intertwined



Marcheva ea 2009

ASESA: case-control study

Is ADHD less healthy?

Sleep/wake patterns,

psychiatric symptoms,

physical health,

BMI and eating patterns,

in adults with ADHD (n=202) compared to the general population (n=189)

Bijlenga ea, 2013

General characteristics

	ADHD, n=202	Controls, n=198	*p*
Women	47 %	65 %	**<.001**
Age: mean	34.9	33.0	**.121**
BMI: mean	24.8	23.2	**<.001**
BMI ≥ 30 (obese)	17 %	4 %	**<.001**
Unemployed	27 %	6 %	**<.001**
Smokes	52 %	18 %	**<.001**
>14 U alcohol p/wk	17 %	7 %	**.016**

Self-reported Morbidities

(showing only significant differences)

	% ADHD, n=202	% Controls, n=198	*p*
Depressed mood	18	6	**<.001**
Stress/ burnout/ fatigue	5	1	**<.001**
Pulmonary problems	31	16	**<.001**
Cardiovascular problems	43	18	**<.001**
Gastro-intestinal problems	33	19	**.001**
Metabolic problems	12	6	**.042**
Immune system problems	7	3	**.049**
Skeletal problems	50	36	**.005**

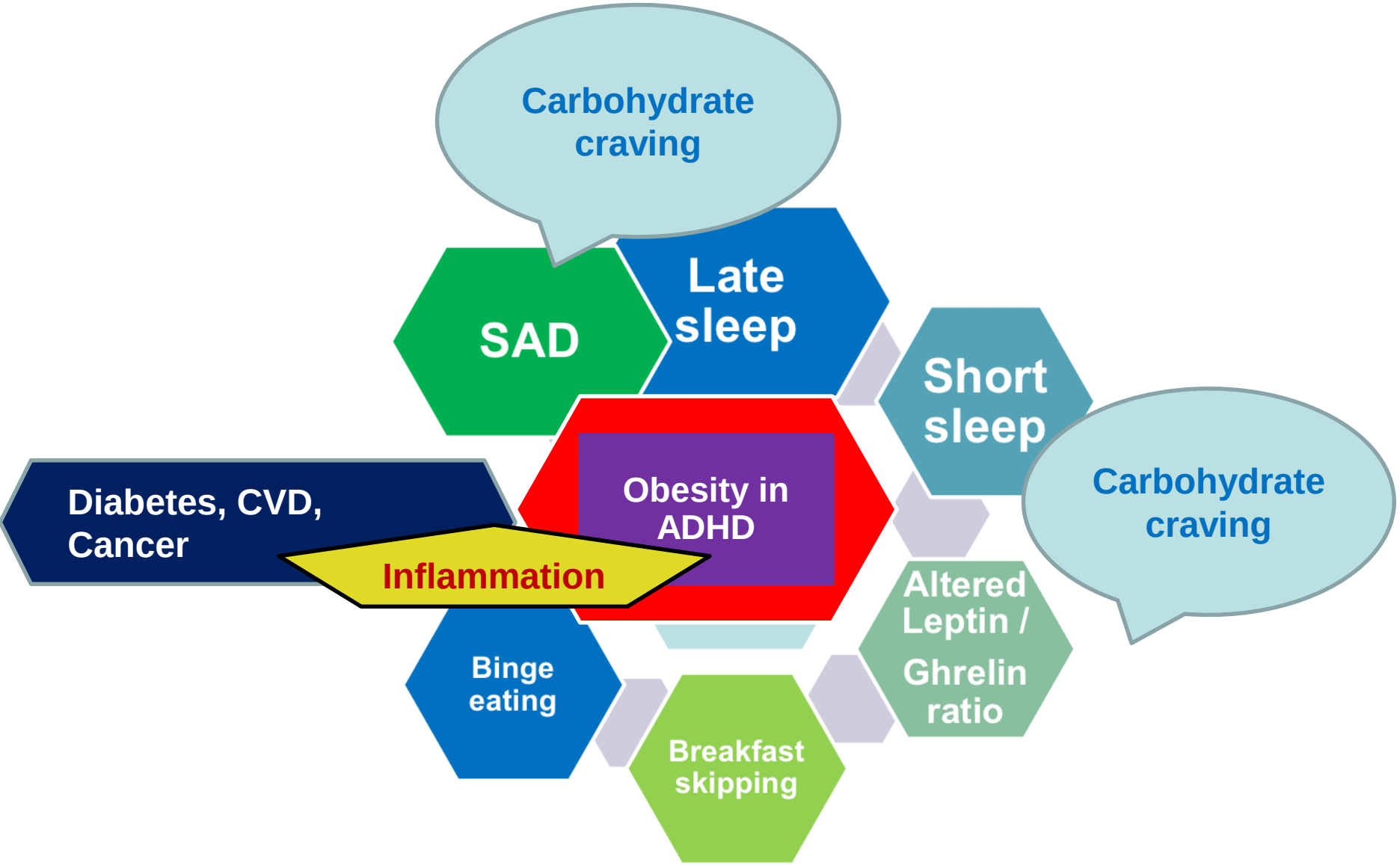
Sleep characteristics

	Age ≤ 30 yrs			*Age > 30 yrs*		
	ADHD n=83	**Controls n=106**	***P***	**ADHD n=119**	**Controls n=83**	***p***
Bed time work days: mean	23:45	23:10	.002	23:33	23:00	.001
Bed time free days: mean	01:02	0:13	<.001	0:20	23:41	.002
Sleep length work days: mean	7:25	7:55	.029	7:01	7:42	<.001
Sleep-onset latency work days: mean	0:39	0:22	.002	0:34	0:12	<.001

Indication of DSPS: 26% in ADHD vs. 2% in controls (p<.001)

Summary

- More morbidities, complaints, and unhealthy lifestyle in ADHD
- More (extreme) evening chronotype in ADHD
- More sleep problems in ADHD: shorter sleep, longer sleep-onset latency, later mid-sleep, more variable bed times
- *DSPS relates to SAD and to health problems*
- This is also apparent within the control group
- *Shorter sleep is related to a higher BMI*



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

Short sleep and cancer risk

Short sleep and cancer risk

- Shift work may be carcinogenic in the long term (IARC 2007)
- Sleep loss by shiftwork has been associated with higher incidence of breast- and prostate cancer
- Though recent meta-analysis could not confirm relationship with breast cancer

How to explain?

- Short sleep ➡ short exposure to and/or low levels of melatonin
- Melatonin has anti-oxidative properties and protects against cancer growth
- Animal and in vitro research show inhibiting effects of melatonin on cancer growth and increased survival
- In humans, first studies with melatonin in cancer patients ongoing

Schernhammer 2004, 2006, 2017; Parent ea 2012; Sigurdardottir ea 2012; Anisimov ea 2012; Travis ea 2016

HHS Public Access

Author manuscript

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Melatonin: an Inhibitor of Breast Cancer

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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 MT_1 receptor-mediated mechanisms. In estrogen receptor alpha (ERα)-positive human breast

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

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Andrzej Slominski, Academic Editor

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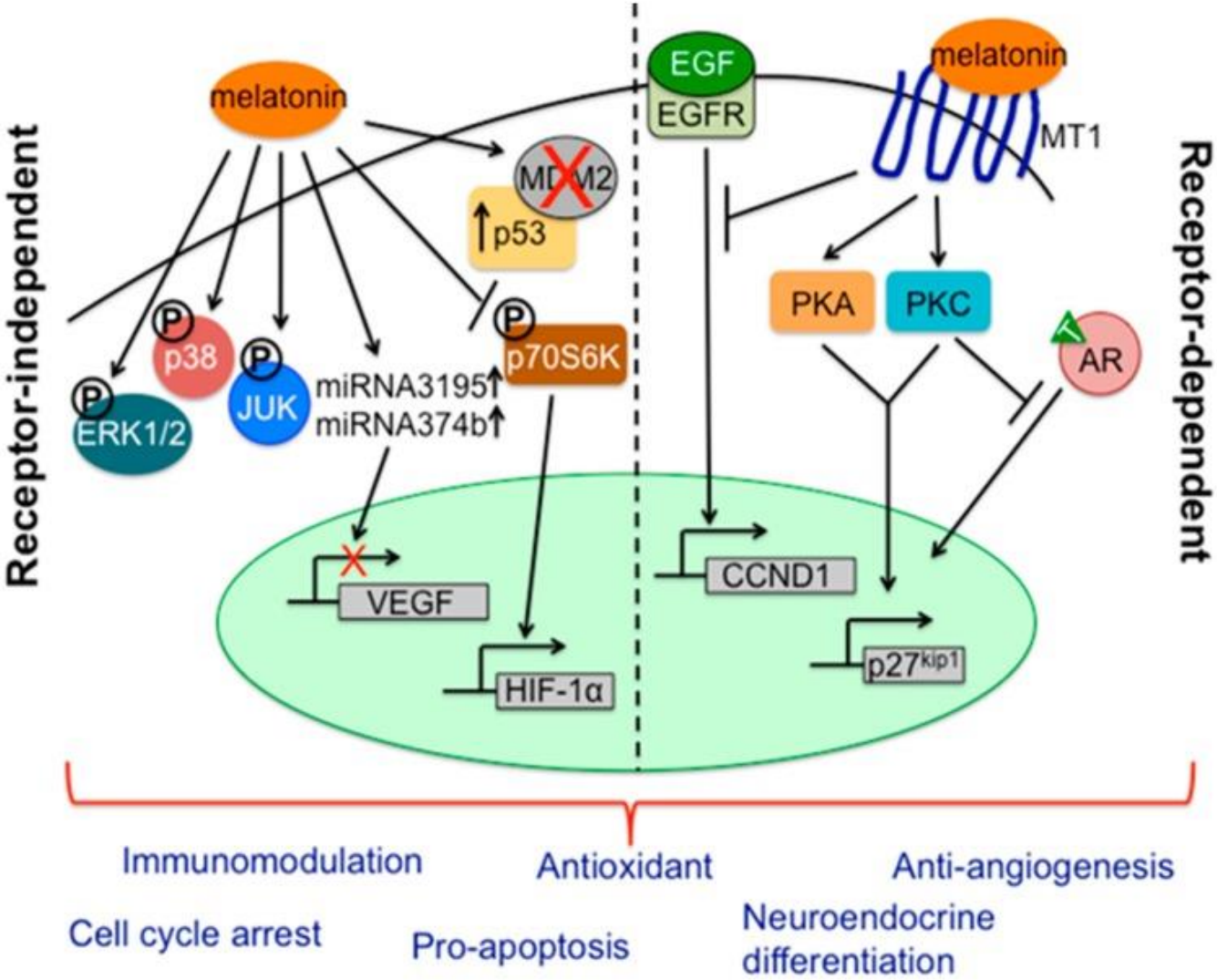
Abstract

Go to:

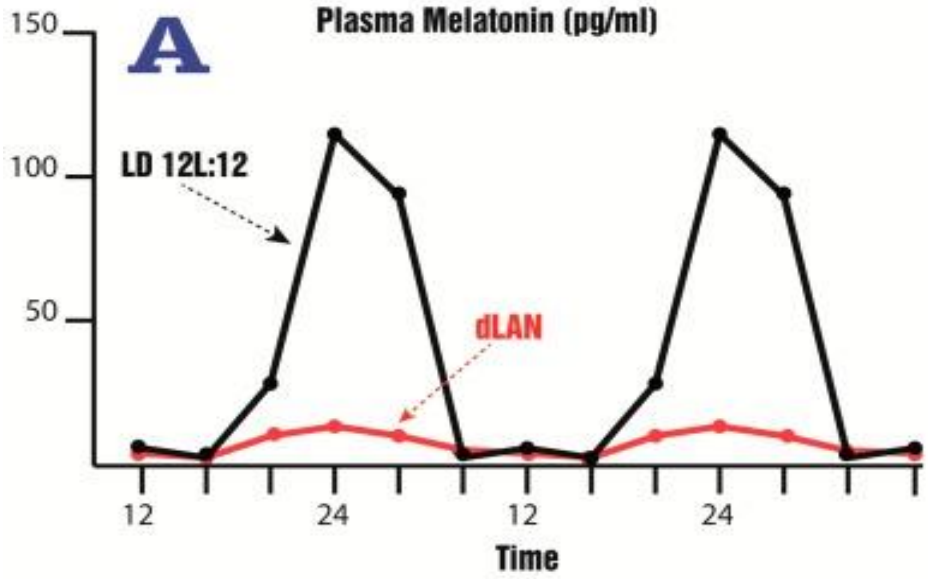
There is highly credible evidence that melatonin mitigates cancer at the initiation, progression and metastasis phases. In many cases, the molecular mechanisms underpinning these inhibitory actions have been proposed. What is rather perplexing, however, is the large number of processes by which melatonin 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-administration improves the sensitivity of cancers to inhibition by conventional drugs. Even more important are the findings that melatonin renders cancers previously totally resistant to treatment sensitive to these same therapies. Melatonin also inhibits molecular processes associated with metastasis by limiting the entrance of cancer cells into the vascular system and preventing them from establishing secondary growths at distant sites. This is of particular importance since cancer metastasis often significantly contributes to death of the patient. Another area that deserves additional consideration is related to the

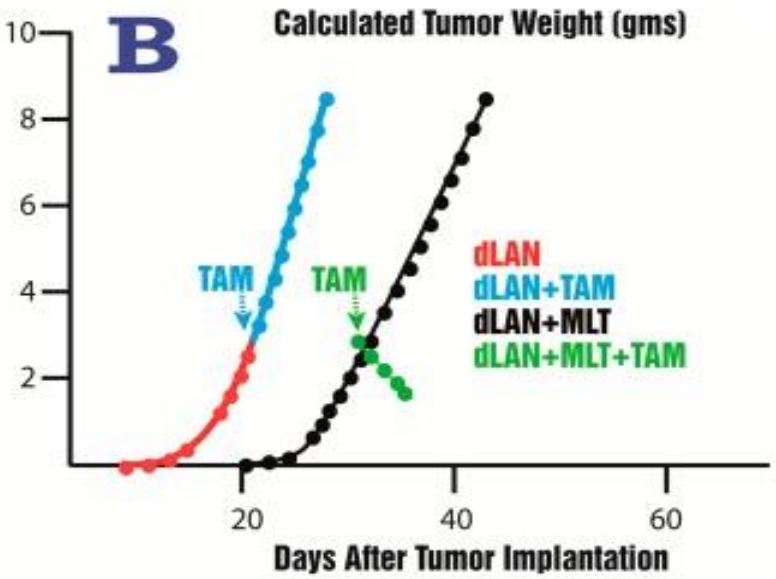
Anti-carcinogenic activity of melatonin



Reiter ea 2017

Melatonin addition to breast cancer treatment (TAM) in rats increases effectiveness





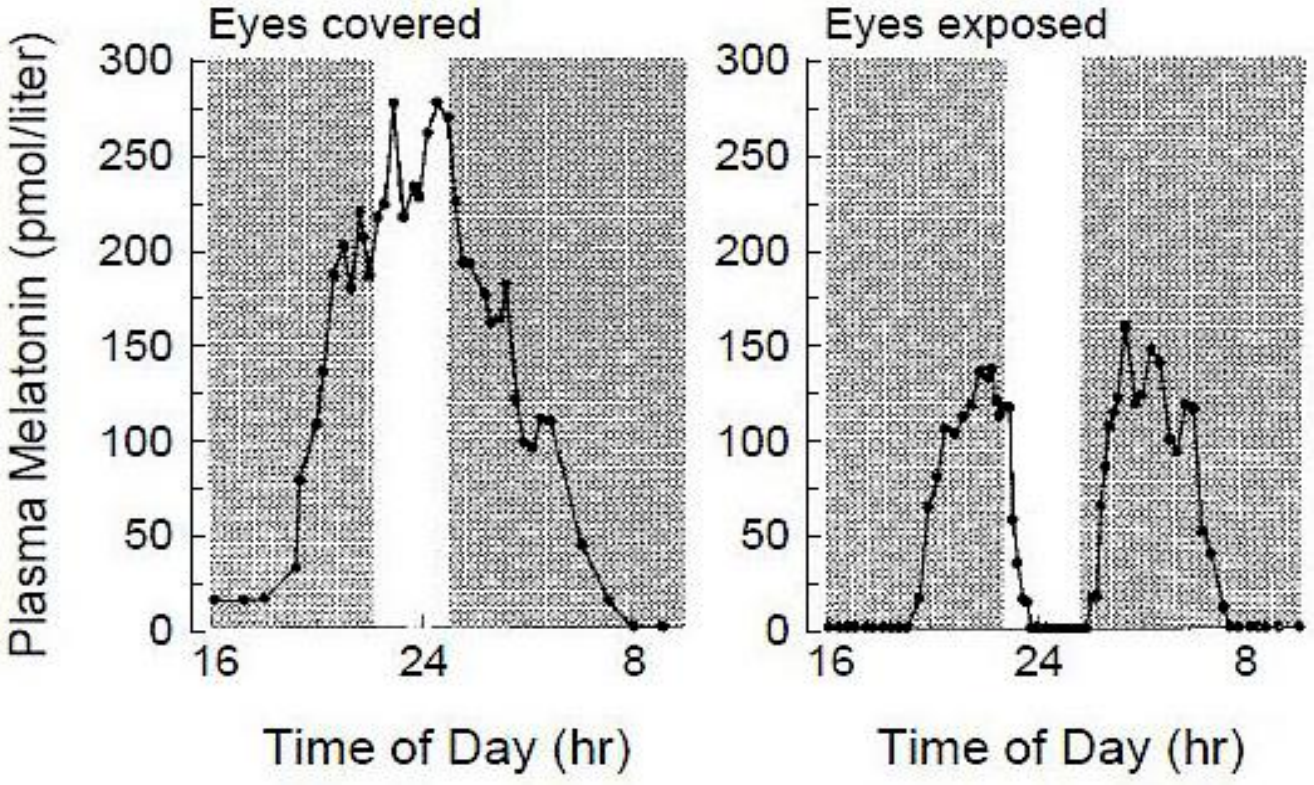
Reiter ea 2017

Cancer risk and exposure to light@night

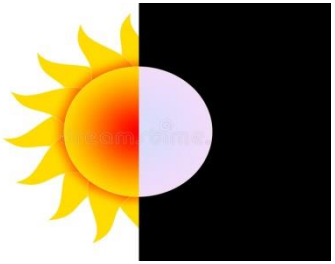
- Use of artificial light at night stops melatonin production via the melanopsin system in the eyes, direct feedback to pineal gland
- The light coming from TV, PC or Ipad also suppresses melatonin production and delays natural sleep onset easily by hours
- Light is the natural antidote to melatonin and wakes us up every day …
- Timing of light may be crucial for health in general
- So the timing of light and darkness is crucial for health!
- Incidence of breast cancer is increased in areas with higher *outdoor* light at night…

Schernhammer ea, 2006-2017; James ea 2017; Bhatti ea 2016; Flynn-Evans ea, 2009

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 matrass
- 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 treatment

- **To fall asleep**: 3 mg at 22:00 in order to sleep at 23:00
- No light after intake of melatonin!

- **To reset the clock**: 0.1 mg - 0.5 mg between 16:00 and 19:00, *advance in steps of 1.5 hour/wk, starting from the habitual sleep onset time to the desired bedtime. For instance: from bedtime at 3 am start – 3hrs= midnight, then advance dosing 1.5 hrs per week, until sleep onset is around 11 pm. Do not dose before 4 pm or after midnight.*

- 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)

Lewy 2005, 2006, continued; Kooij 2012 Book Adult ADHD; Kooij & Bijlenga 2014

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; duration: 2-3 weeks. Repeat when relapse
- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light box of 500 W directed to ceiling, or light therapy device of 10.000 lux at 20 cm to the eyes, and timer 30 min before wake up time
- Wake Up Light uses only 75 W and does not wake all patients with delayed sleep phase
- Warning: 500 W light becomes hot and contains UVA+B

Rybak ea 2006

Light therapy 2018: Light 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

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
- Temperature control: shower before going to bed, bedsocks
- Melatonin in evening
- Light in morning
- Limited use of sunglasses during daytime

To reduce binge eating and weight gain:

- Treatment of comorbidity (depr/anx)
- Treatment of ADHD with stimulant and CBT/coaching
- Timing of meals, have breakfast
- Exercise, diet

Cortese 2016; Kooij 2016

PHASE study in ADHD: can advancing the sleep phase improve health?

- Does advancing the late sleep phase improve sleep, ADHD, and biomarkers? Tx: 3 wks melatonin/placebo @night and/or light in the morning

Preliminary baseline data (n=34):

- Delayed melatonin onset (11 pm)
- Fragmented sleep: 104 min awake during night (actigraphy)
- Delayed cortisol morning
- BMI> 25 in 65%
- Dysfunctional Leptin/ghrelin ratio's or vitamine D / B12 levels: 47%
- Increased inflammation markers: 36%
- Increased fasting glucose level or after OGTT: 21%
- Increased mean 24 hr bloodpressure (>140/90): 29%
- Suboptimal heart rate intervals: 15% (pNN50)

Kooij, Vogel & Bijlenga, ongoing

frontiers in NEUROLOGY

PERSPECTIVE ARTICLE
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High prevalence of self-reported photophobia in adult ADHD

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Many adult outpatients with attention-deficit/hyperactivity disorder (ADHD) report an oversensitivity to light. We explored the link between ADHD and photophobia in an online survey ($N = 494$). Self-reported photophobia was prevalent in 69% of respondents with, and in 28% of respondents without, ADHD (symptoms). The ADHD (symptoms) group wore sunglasses longer during daytime in all seasons. Photophobia may be related to the functioning of the eyes, which mediate dopamine and melatonin production systems in the eye. In the brain, dopamine and melatonin are involved in both ADHD and circadian rhythm disturbances. Possibly, the regulation of the dopamine and melatonin systems in the eyes and in the brain are related. Despite the study's limitations, the results are encouraging for further study on the pathophysiology of ADHD, eye functioning, and circadian rhythm disturbances.

Keywords: adult ADHD, photophobia, photosensitivity, chronotype, sleep, circadian rhythm

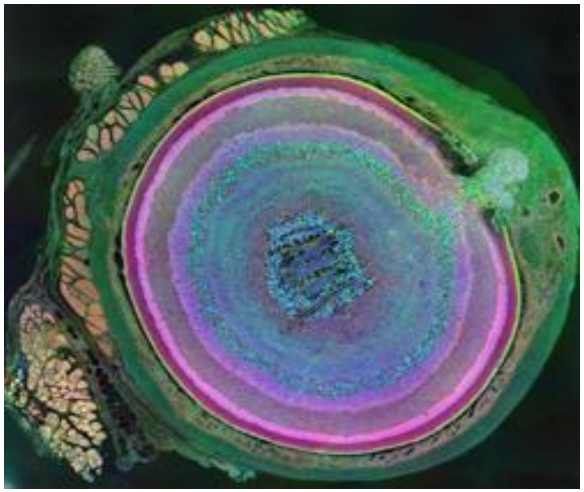
INTRODUCTION

From clinical experience, we learned that a substantial number of adult patients with attention-deficit/hyperactivity disorder (ADHD) wear sunglasses throughout the year, even on overcast days. Many of these patients report a sensitivity or even oversensitivity of their eyes to bright light. Besides this clinical observation of photophobia, there are a number of studies indicating a link between ADHD and other optical dysfunctions. In children with ADHD, 76% have reduced visual acuity, caused by more strabismus (cross-eyedness), subnormal stereoacuity (depth detection), convergence insufficiency, and smaller optic disks (1). Another study found a prevalence of 63% myopia or hyperopia, and in total 83% refractive errors in children with ADHD (2). In comparison, in a study among Dutch schoolchildren, the prevalence of myopia and hyperopia was 36% (3). Moreover, young adults with ADHD more often have problems with depth perception, periph-

suppression of melatonin in the morning is initiated by light reaching the retina of the eye (10). Melatonin may be suppressed later or less by the use of sunglasses during the day (11). This may cause the production of melatonin in the evening to be delayed, which in turn further delays the sleep/wake cycle. This is important because late sleep is associated with a short-sleep duration that on a chronic basis has a negative impact on health, with short sleep being associated with increased risks of chronic diseases such as obesity, diabetes, cardiovascular diseases, and cancer (12, 13). It is therefore important to study the potential role of the retinal functioning and its effect on chronotype, sleep, and ADHD symptoms.

The combination of our clinical experience and the findings in the available literature suggest that there may be an increased prevalence of visual problems and photophobia in adults with ADHD. In order to study a possible link between photophobia

Ongoing: the EYE-ADHD study



- ADHD in 70% oversensitive to light
- Suboptimal functioning melanopsin system in the eye in SAD (Roecklein 2013), also in ADHD?
- Many wear sunglasses during the day, preventing synchronisation with daylight
- And use light@night from screens that reduces melatonin levels and postpones sleep
- All lead to increased shift of sleep phase
- Retina contains both melatonin and dopamine receptors that project to the biological clock
- Measuring the PIPR: pupillary response to light in ADHD vs controls

Kooij & Bijlenga 2014

New research: Is light effective for ADHD?

- Comparing 2 wks of lightbox vs lightglasses
- In ADHD plus late sleep
- Effect of advancing the circadian rhythm on ADHD severity, late sleep and mood
  - Using questionnaires and objective Qb test for ADHD symptoms
- Previous pilot studies were positive

Rybak 2006; Fargason 2017

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

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Discussion