ADHD bij vrouwen

humeuren & hormonen

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TOPGGZ ERKEND

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Kenniscentrum
ADHD bij volwassenen

ADHDFUND
online crowdfunding

Subjects

- ADHD: a neurobiological disorder
- Prevalence of ADHD through the lifespan
- Underdiagnosis of girls and women
- Chronic fatigue, moodswings and mooddisorders
- Clinical picture, comorbidity, diagnostic assessment & treatment

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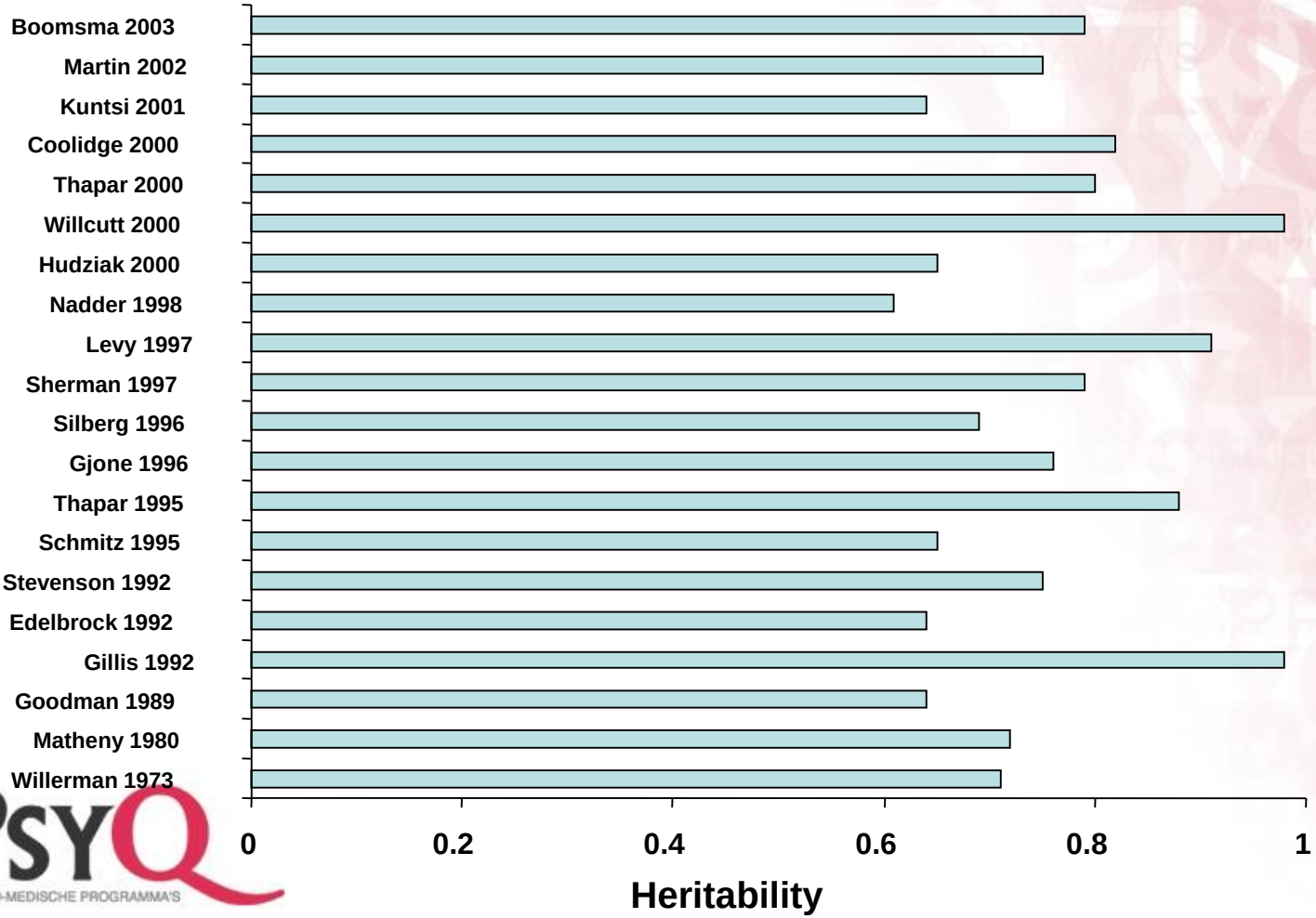
Neurobiology of ADHD

- Highly heritable (80% of variance explained by genetic factors)
- Neurobiological disorder:
  - brain 5% smaller and less active
  - 8 kandidate genes, esp. dopaminergic (DRD2,4,5, DAT1)
  - ADHD as an inhibition deficit (no brakes) based on dopamine deficiency
  - Methylphenidate: dopamine agonist; acts as inhibitor of associations, moodswings, restlessness and impulsivity

Thapar 1999; Faraone 2005; Castellanos 2002; Bush 2006
Kessler 2006; Kooij 2005

ADHD symptom scores in twin studies: highly heritable



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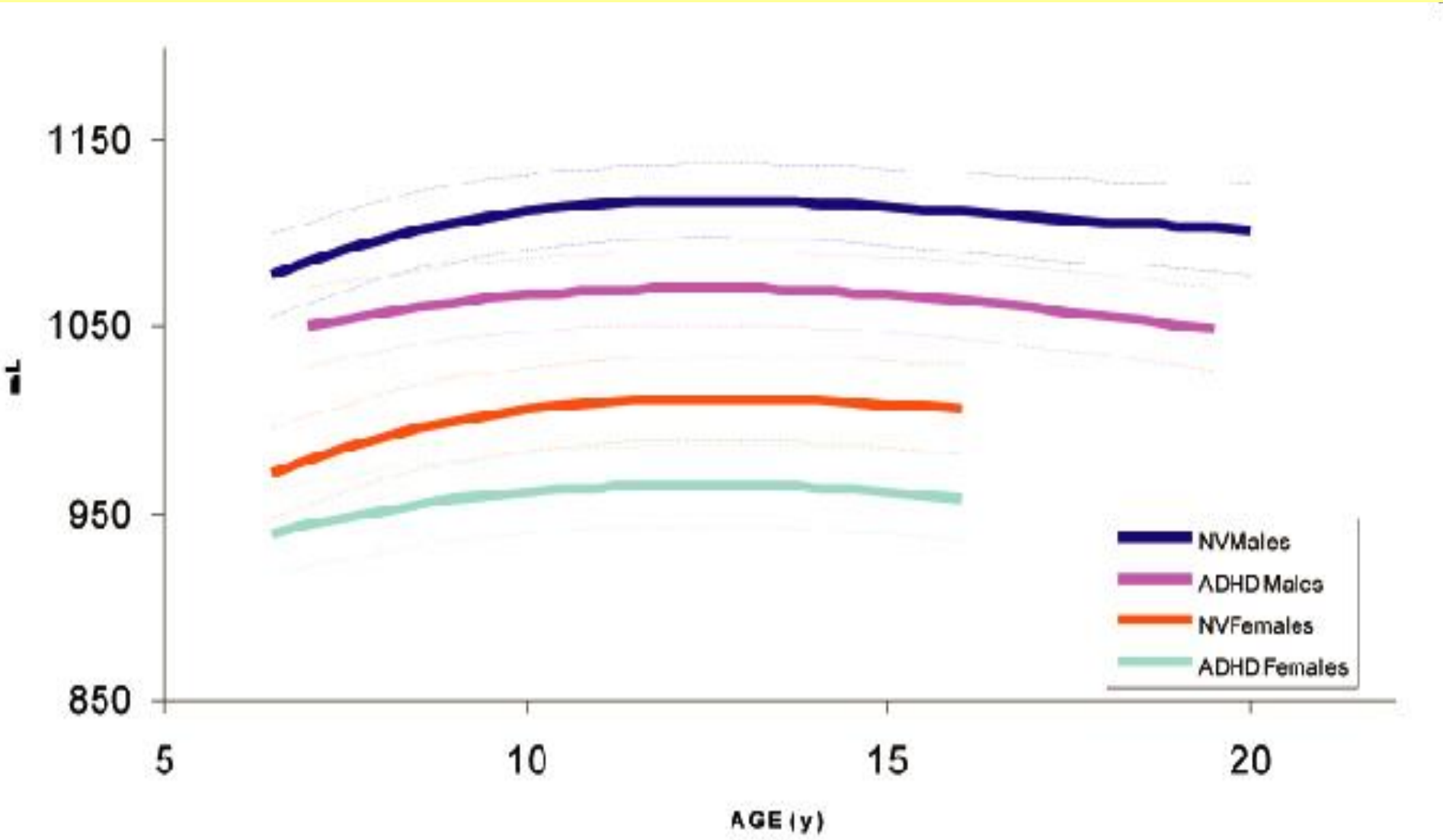
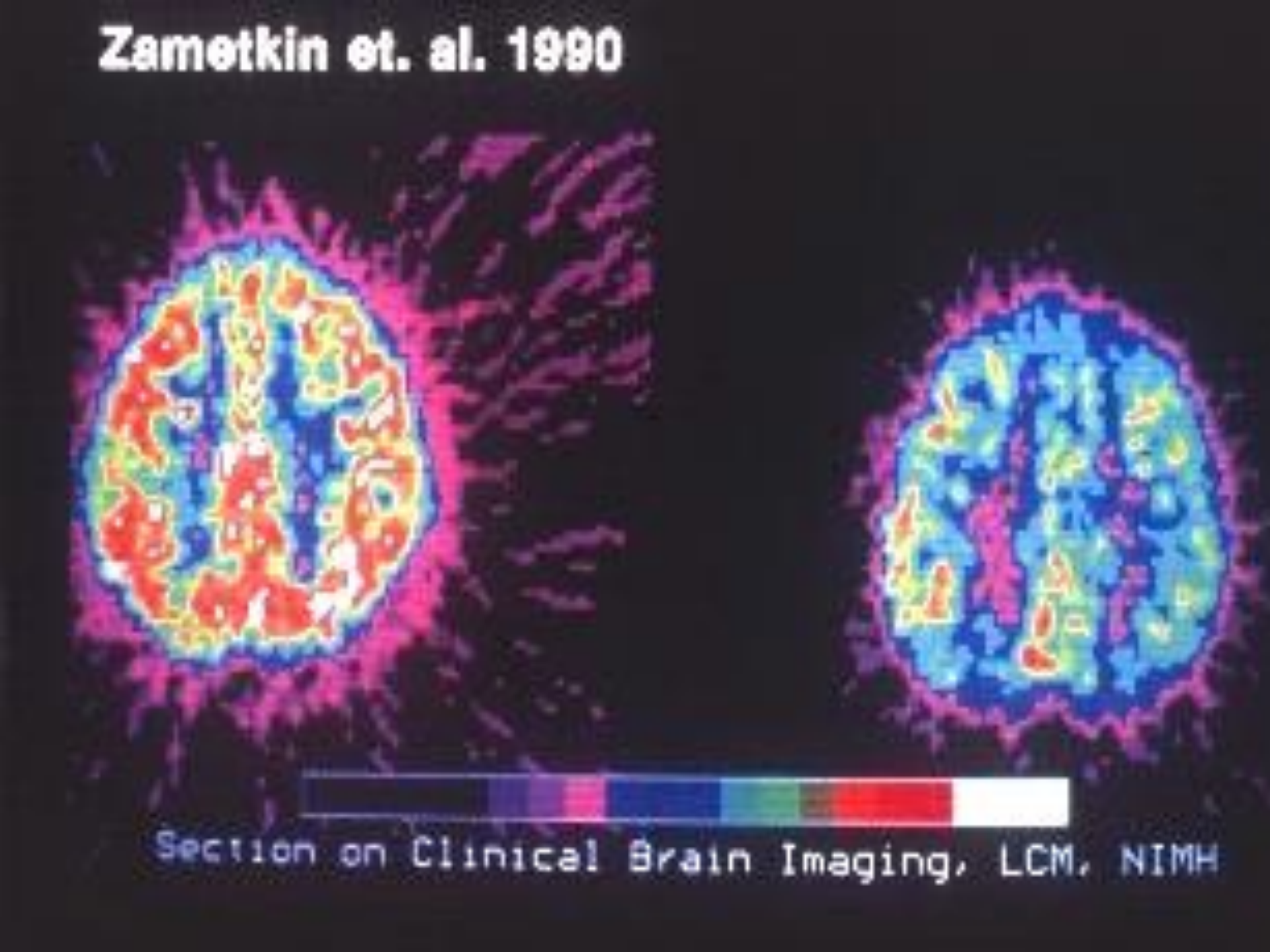
Developmental trajectories of brainvolumes

(Castellanos et al., JAMA,2002)




Zametkin et. al. 1990
Section on Clinical Brain Imaging, LCM, NIMH

The brain in ADHD compared to NCs:

Smaller,

Hypoactive

&

Impaired

functioning

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Prevalence of ADHD through the lifespan

Children

USA	4 - 8%
% persisting ADHD	50 - 60%

Adults

USA	4 - 5%
10 countries (mean)	3.4%

Older people (>65)

Sweden	3.3%
Netherlands	2.8 - 4.2%

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Faraone 2003; Kessler 2006; Murphy & Barkley, 1996; Kooij 2005; Fayyad 2007; Guldberg 2013; Michielsen 2012

ADHD and gender: Men more often ADHD?

	Children M : F	Adults M : F
Clinical studies	2 - 9 x	1 - 2 x
General population studies	2 - 3 x	1 - 1.5x

Taylor 2004; Nice guidelines 2008; Kessler 2006; Fayyad 2007; Kooij 2005

Gender differences children and adults

Childhood — M>>F

Adulthood — M=F

Underdiagnosis in girls

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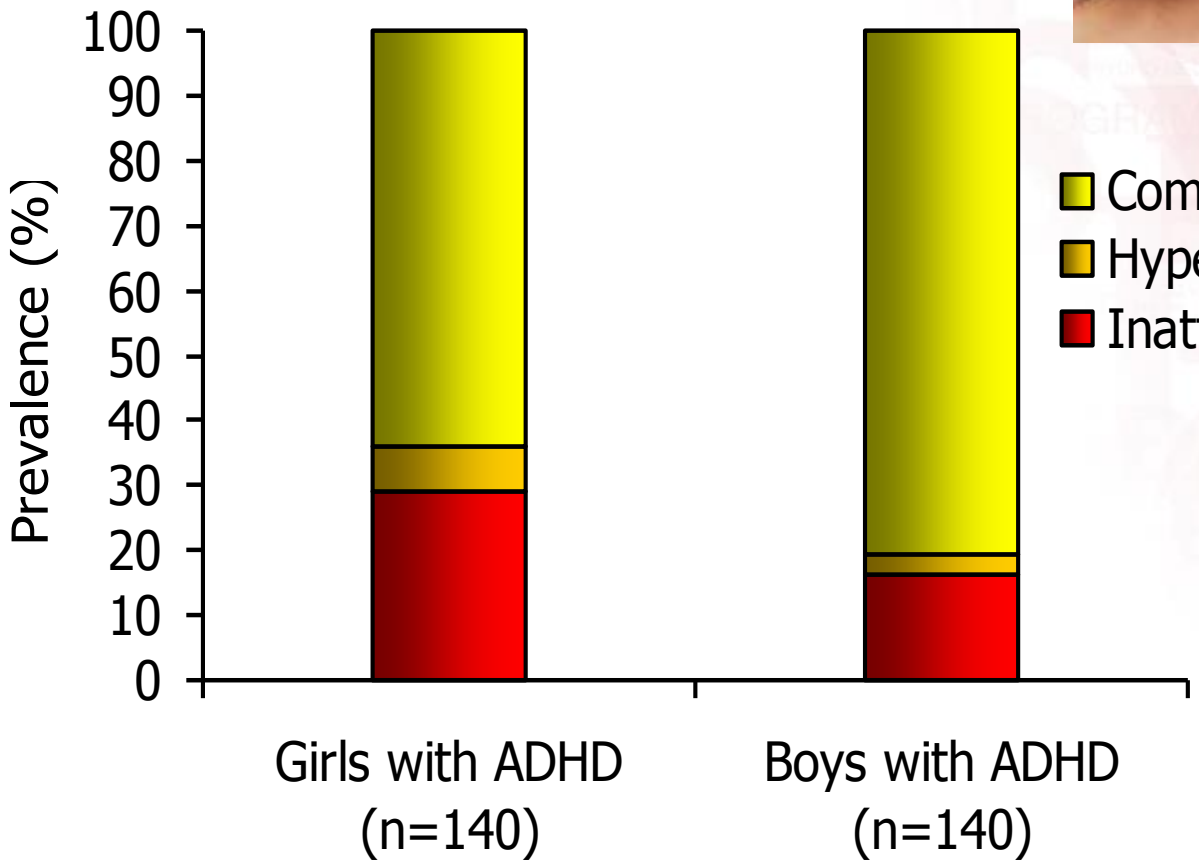
Girls have more ADD



Biederman 1994, 2004

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Girls and women 2x more often ADHD inattentive type

- But majority has still ADHD combined type
- Women have to organise themselves, family, household, childrens' agenda's and their job
- Being a women with ADHD is 'a job from hell', always late, forgetting things …
- Chaos and tiredness their daily bread
- Low selfesteem and uncertainty about capabilities the result

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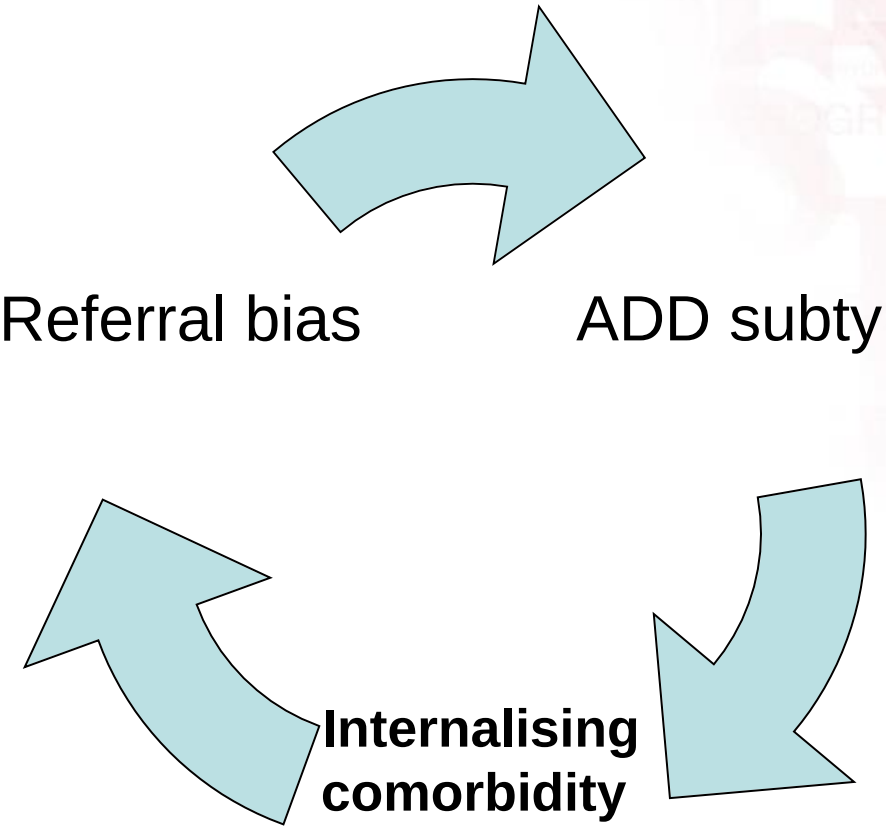
Causes of underdiagnosis of ADHD in girls



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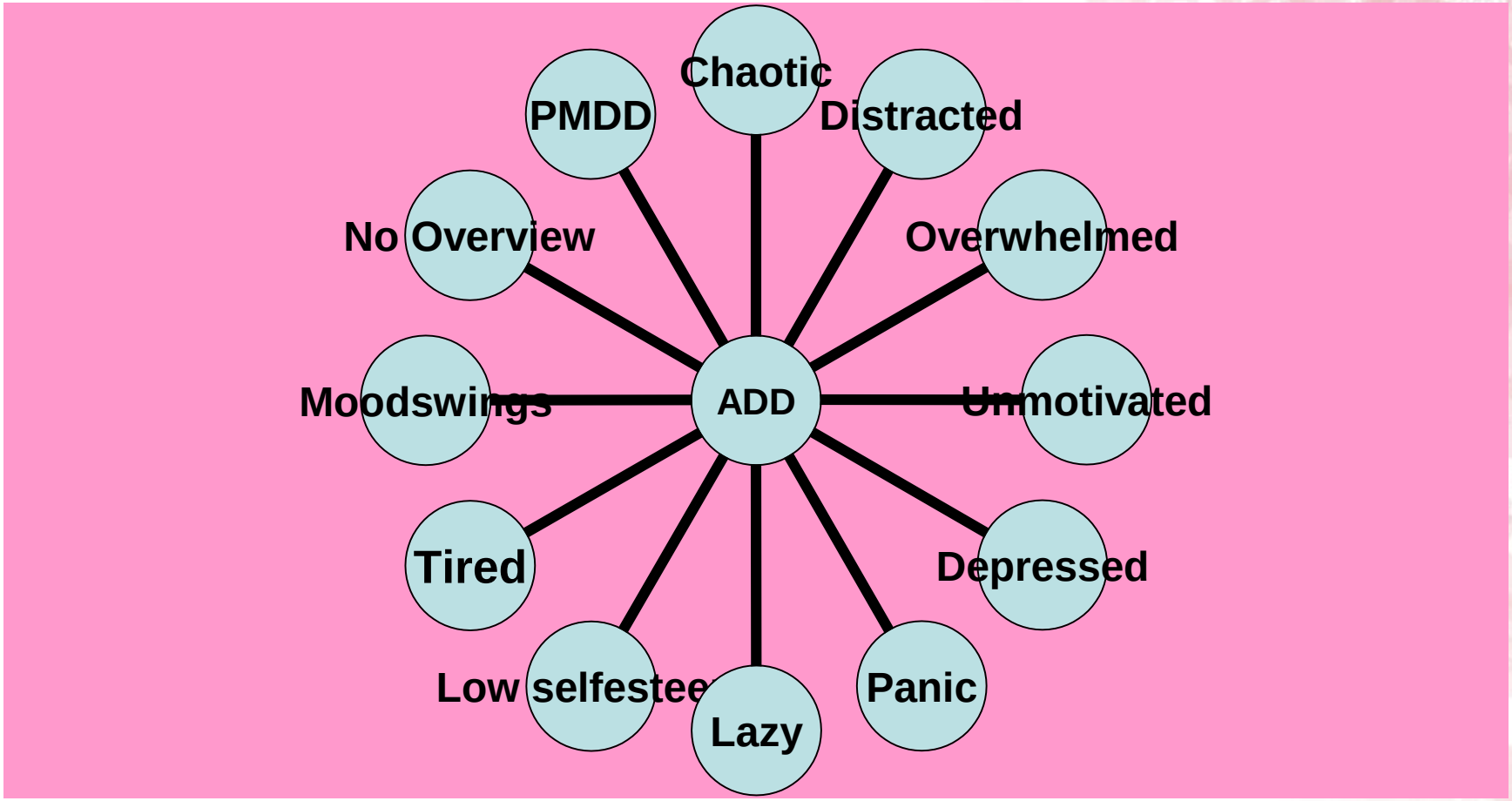
Complaints girls and women with AD(H)D



Room with a view?

Is ADHD like Chronic Fatigue Syndrome (CFS)?
Inattentive girls referred for being´tired´?

- Clinical studies: boys more often ADHD
- Epidemiological research: girls similar percentage ADHD as boys

ADHD in girls is less well known, and their behaviour less disruptive than in boys …

Boys have more often:
- ADHD, combined type
- More severe hyperactivity
- Externalising comorbidity (oppositional defiant or aggressive behaviour)

Being disruptive helps to get help….

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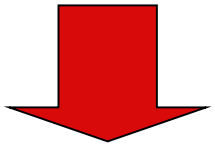
Biederman ea, 1994; 2002, 2004; 2005

Girls are not disruptive …

Inattention takes continuous mental effort,

leading to exhaustion …



… but may be chronically tired!

Proefschrift van Putten 2006

Clinical picture of ADHD

Lifetime symptoms of Attention-Deficit/Hyperactivity Disorder:

- **Inattention:** distracted, chaotic, forgetful, late, difficulty making decisions, organising and planning, no sense of time, procrastination
- **Hyperactive:** (inner) restlessness, tense, talkative, busy; coping by: excessive sporting/alcohol abuse/avoiding meetings
- **Impulsive:** acting before thinking, impatient, difficulty awaiting turn, jobhopping, binge eating, sensation seeking

In addition in 90% of adults, lifetime:

- **Moodswings** (5x/day) and **Anger outbursts**

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APA 1994; Kooij 2001, 2010; Conners 1996

Impairment in adult ADHD

In clinical as well as epidemiological samples compared to controls:

- Learning problems (60%)
- Less graduated
- Lower education
- Lower income
- Less employed, more sickness leave
- More job changes (longest job 5 yrs)
- More often arrested, divorced and more social problems
- More driving accidents, early death, teenage pregnancies, suicide attempts
- Higher (mental) health care costs

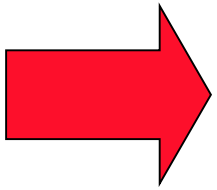
Biederman 2006; Kooij 2001, 2005, 2010; Barkley 2002; Manor, 2010; Dalsgaard 2015, 2016

Ultrakorte screener voor ADHD bij volwassenen

1. Ben je doorgaans rusteloos?
2. Ben je doorgaans snel afgeleid of chaotisch?
3. Doe je doorgaans dingen zonder eerst na te denken?

Als 1 vd 3 antwoorden = ja:

4. Heb je dit al je hele leven/ben je altijd zo geweest?



Zo ja, verdere diagnostiek van ADHD

DIVA 2.0

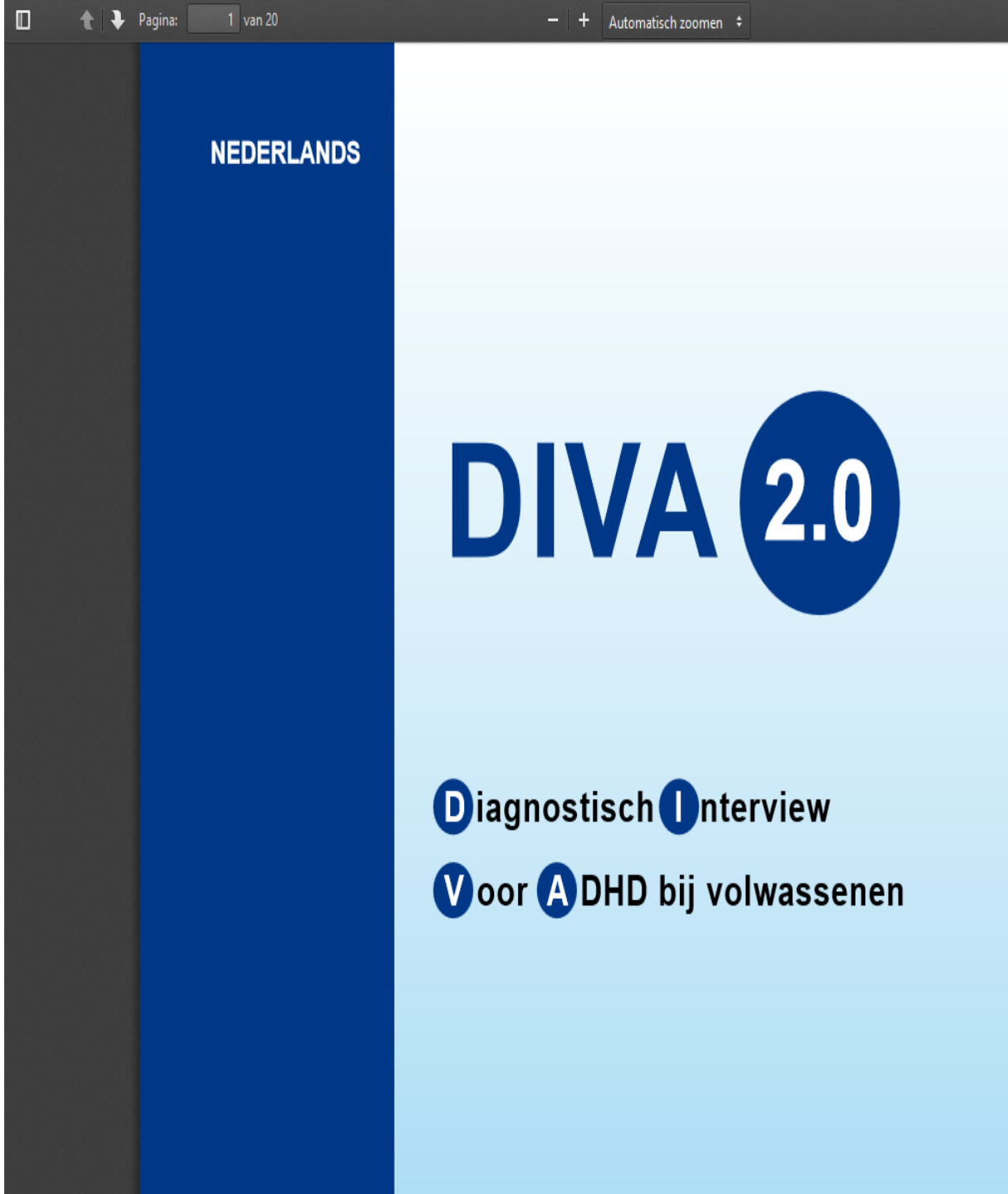
Diagnostisch Interview voor ADHD bij volwassenen

In 18 talen

All DIVAs are online free of charge at: www.divacenter.eu

DIVA 2.0 App:

DIVA 2.0



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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	6-25%
• Eating Disorders (BN)	9%
• Binge eating	86%
• Obesity	30%
• Sleepproblems, DSPS pattern	80%

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.

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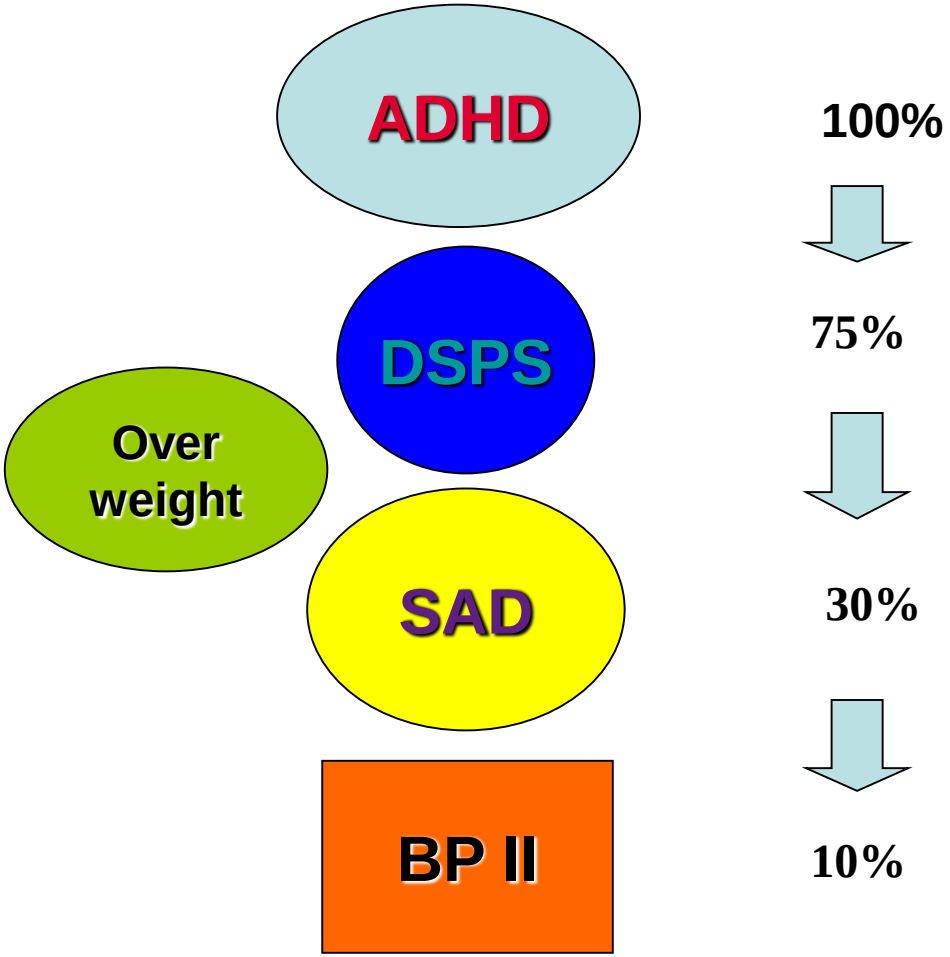
ADHD, circadian rhytm, sleep, mood and season



Goikolea 2007, Amons 2006, Lewy 2006, van Veen 2010, Bijlenga 2013

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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

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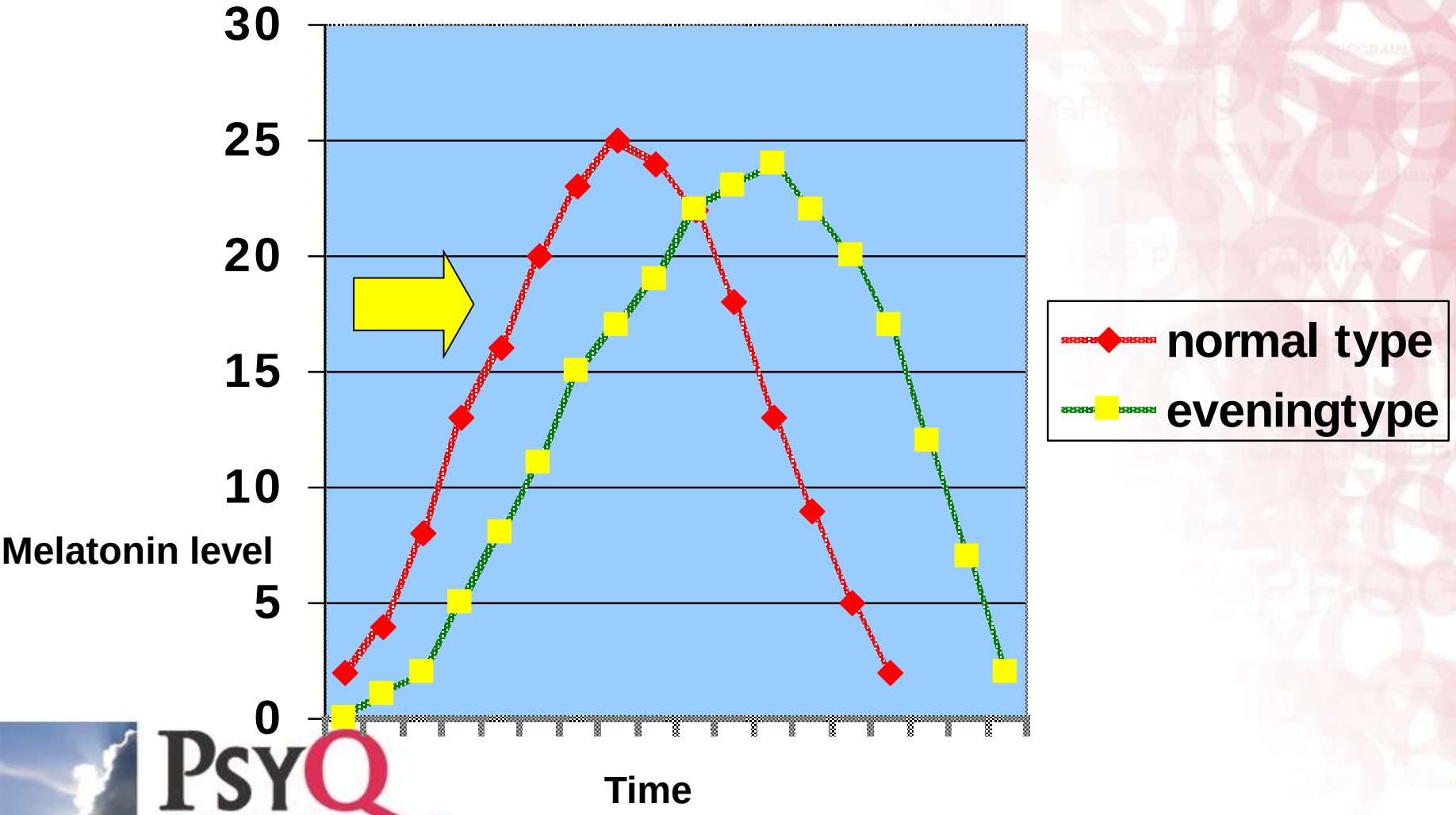
Sleep phase delay in ADHD



Dim Light Melatonin Onset (DLMO): delayed

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

versus healthy controls

	ADHD Total	SOI	no-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

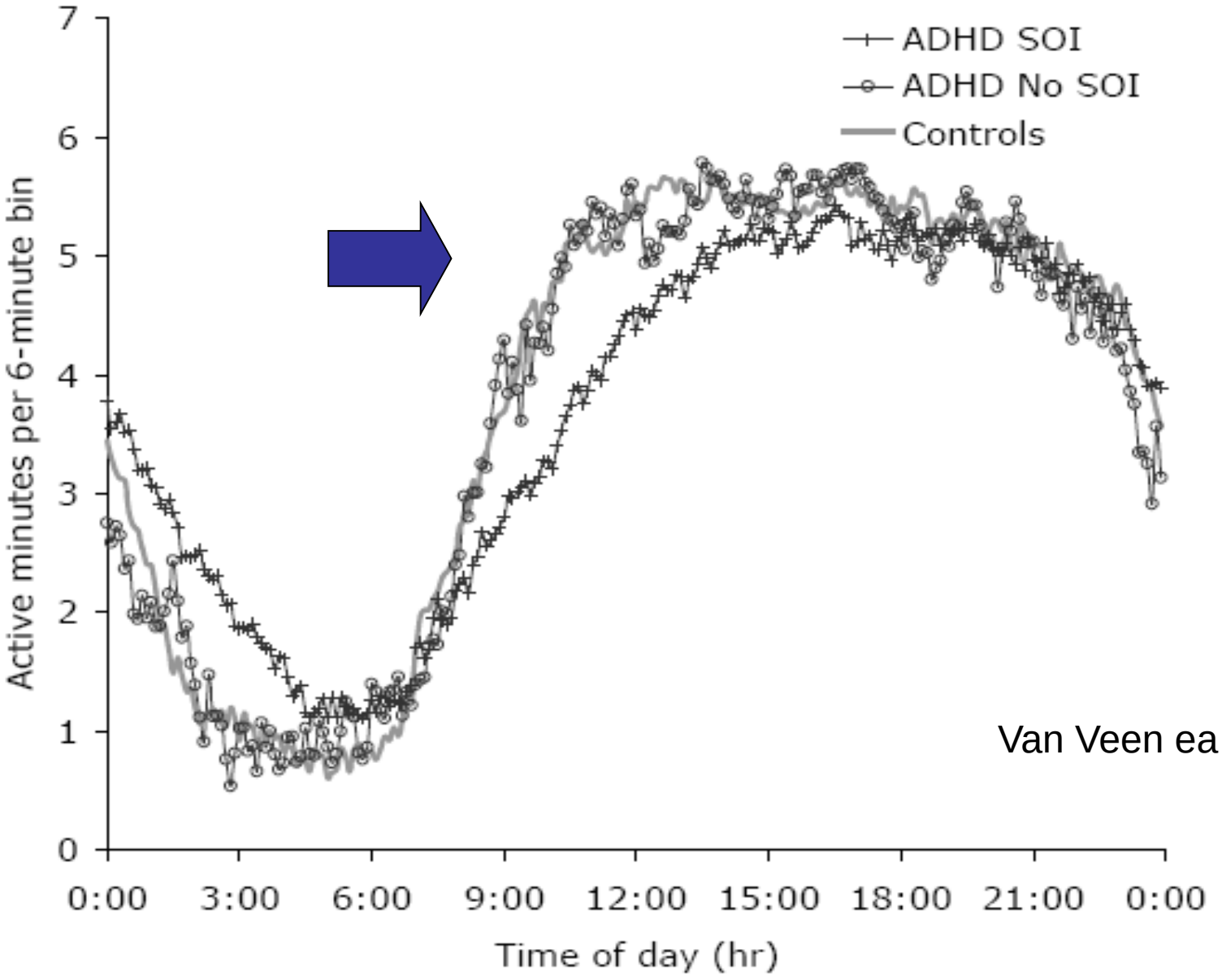
- 78% of consecutive ADHD patients had SOI

- DLMO: 105 min later in SOI vs HC

- After DLMO, it generally takes another 2 hours to fall asleep

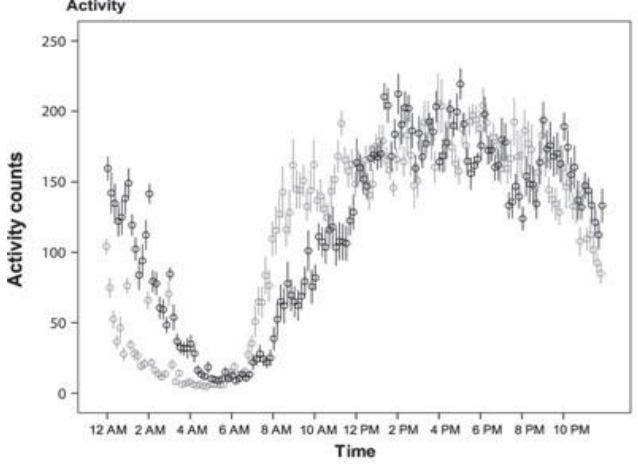
Van Veen ea, 2010

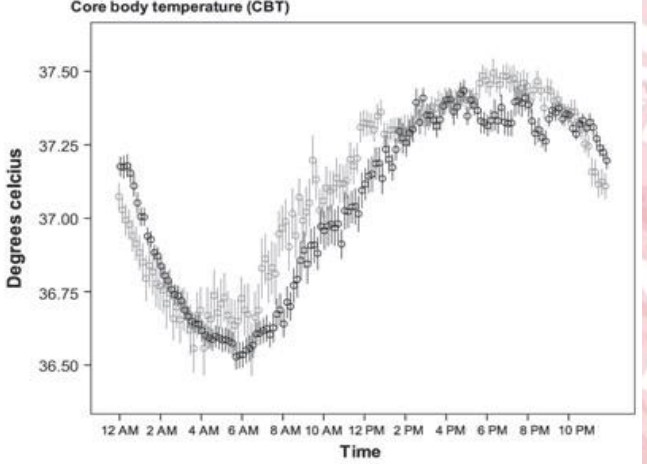
24 hour movement patterns ADHD + SOI compared to controls (actigraphy)

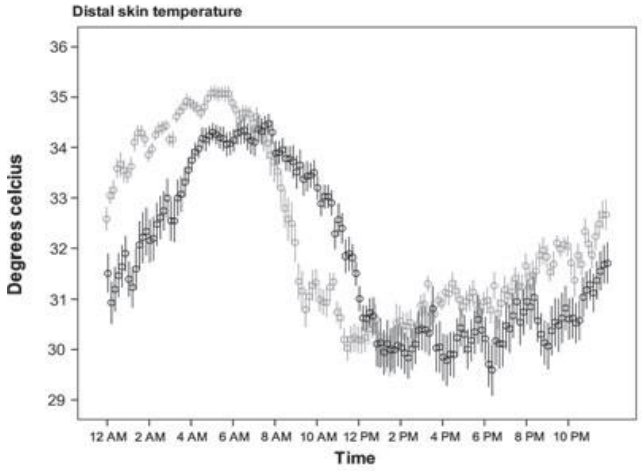


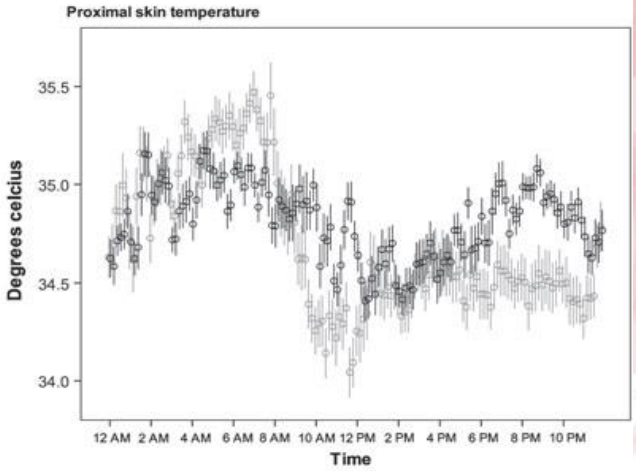
Van Veen ea 2010

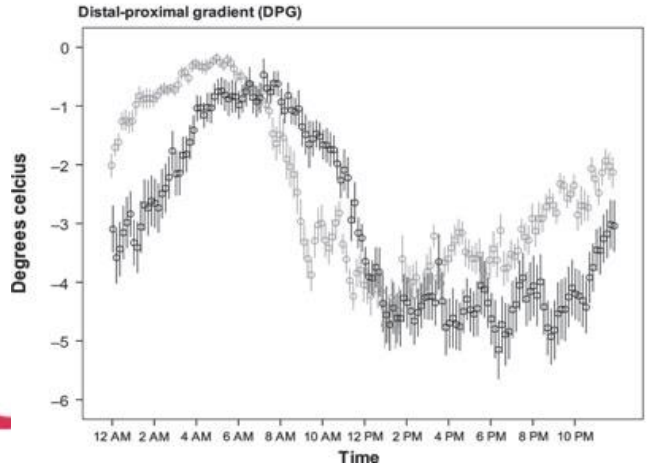
24 hr Activity, Core and Skin Temperature, in ADHD versus controls











Bijlenga, J Sleep Res 2013, Aug 16

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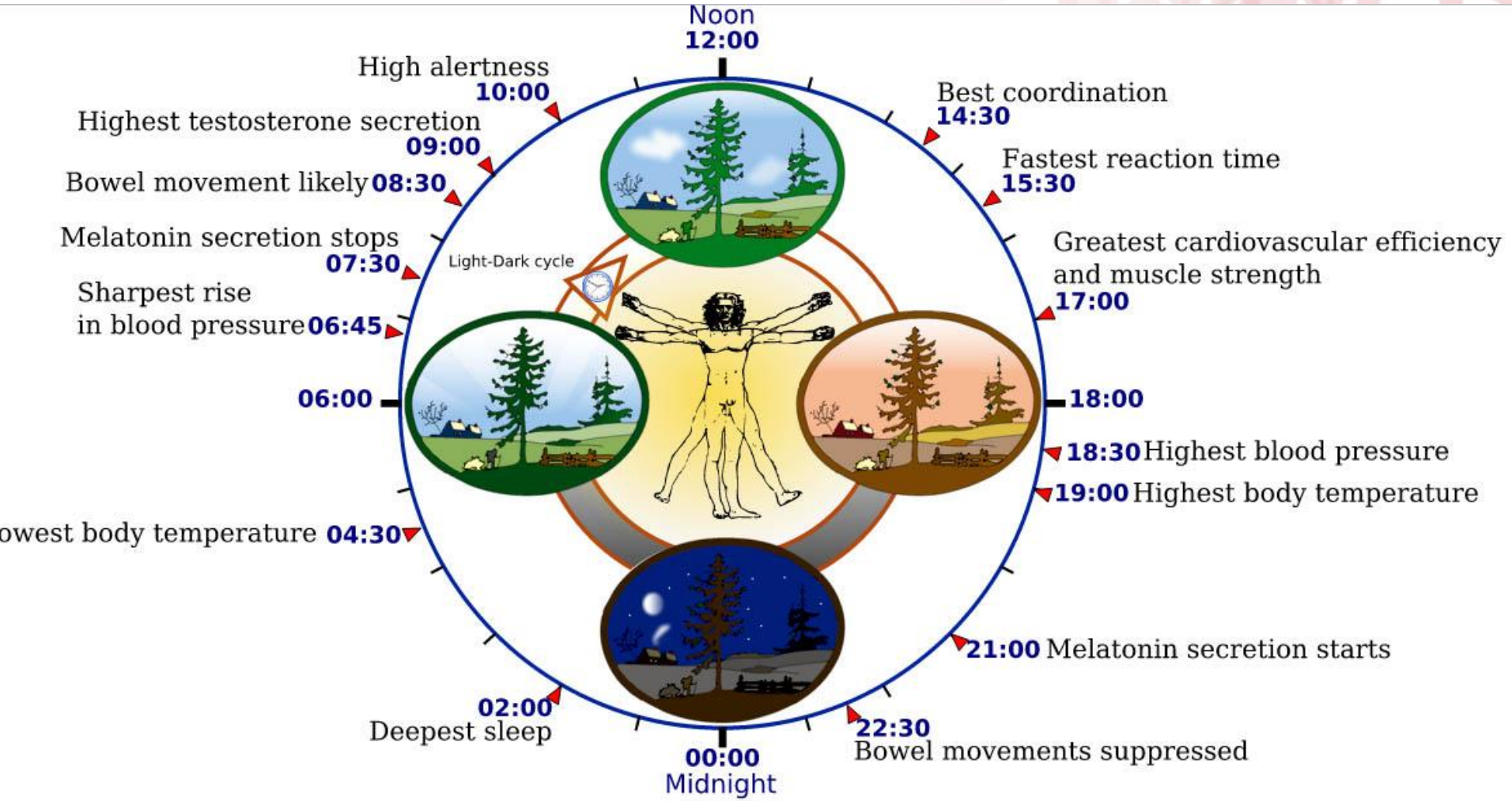
Biological clock and body rhythms



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
- SAD has a circadian phase delay in 70%
- Are SAD and ADHD related via circadian disturbances?
- Clockgenes associated with ADHD

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.

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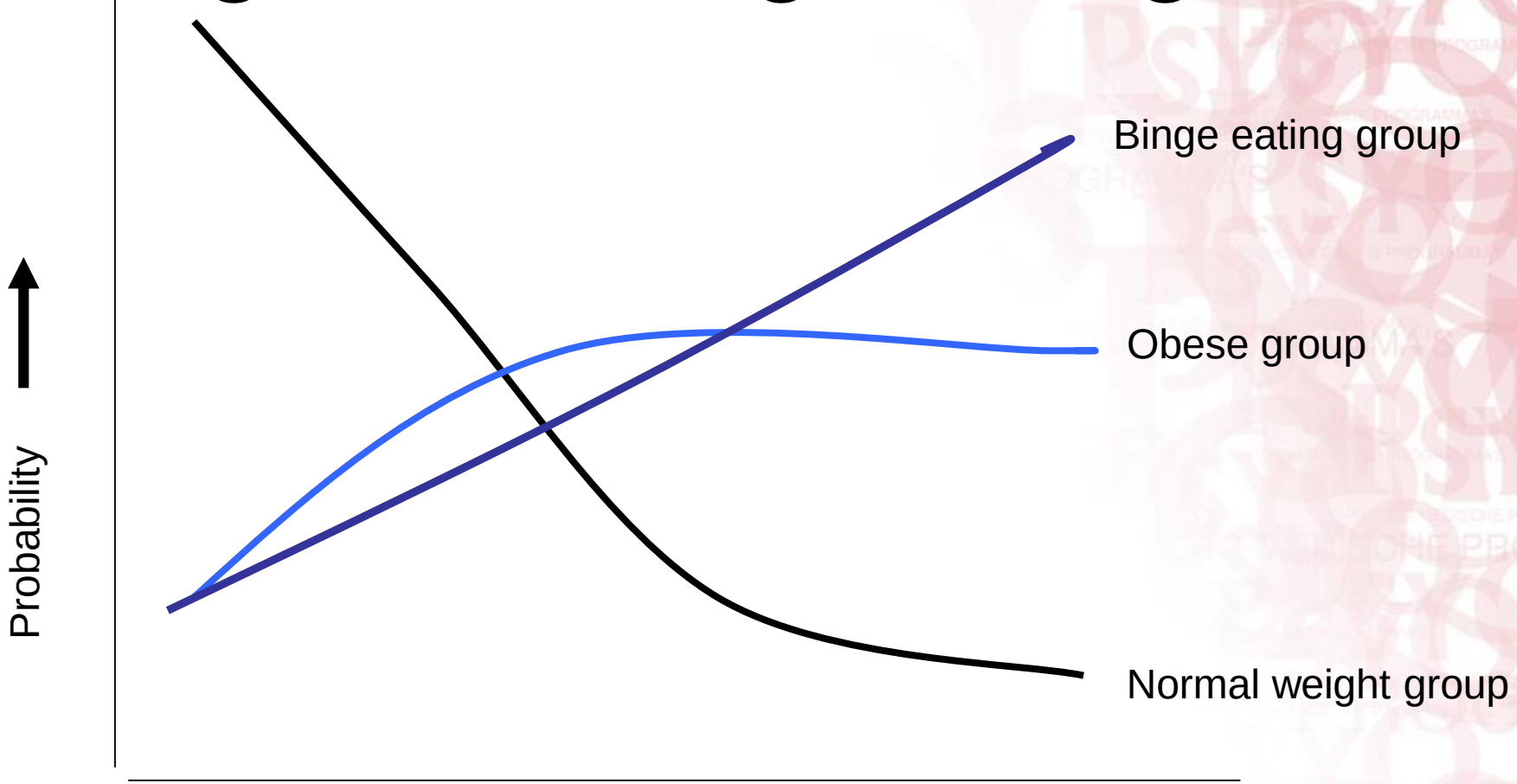
ADHD index predicts weight and binge eating

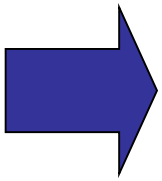


Davis 2009, J Psychiatr Res;43(7):687-96

Circadian disturbance, ADHD and health

- ADHD is associated with chronic DSPS
- ADHD patients often work in night shifts or are active at night
- May be gene-environment interaction: circadian preference based on (clock)genes and dopaminergic pathways

- But: chronic work (>30 yrs) in night shifts is associated with higher risk of (breast)cancer
- Melatonin acts as a *circadian anti-cancer signal* at night
- Among others (light at night), chronic low melatonin levels may protect less well against development of cancer



is ADHD a high riskgroup for cancer?

Schernhammer 2001, J Natl Cancer Inst;93(20):1563-8; Schernhammer 2005, Eur J Cancer;41(13):2023-32; Hansen 2001, J Natl Cancer Inst;93(20):1513-5; Blask 2005, Endocrine;27(2):179-88. Moser 2006, Conf Proc IEEE Eng Med Biol Soc;1:424-8; Verkasalo 2005, Cancer Res;65(20):9595-600.

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Relative risk of breastcancer

2.00

First degree relatives

Flight attendants

Hormone Replacement Therapy

Shiftwork

1.50

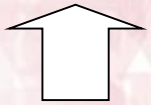
Alcohol > 45 g/day

BMI> 30

First birth > 35

Current use of contraceptives

Nulliparous

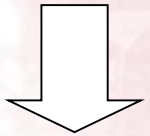


Increased risk

1.00

Physical activity

1 full time pregnancy



Decreased risk

First birth <20

Breastfeeding

0.50

>7 children

Moser 2006, Conf Proc IEEE Eng Med Biol Soc;1:424-8

Does cancer risk cluster in ADHD?

Several lifestyle risk factors may cluster in ADHD individuals:

- Night shift work
- High BMI
- Alcohol/drug abuse
- Smoking
- Low melatonin levels?

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Short sleep and cancer risk

- Shift work is considered carcinogenic in the long term (IARC 2007)
- Sleep loss by shiftwork is associated with higher incidence of breast- and prostate cancer
- Short sleep → short exposure to and/or low levels of melatonin
- Melatonin has anti-oxidative properties and protects against cancer growth
- Animal research shows inhibiting effects of melatonin on cancer growth and increased survival
- In humans, first studies with melatonin in cancer patients ongoing

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Schernhammer 2004, 2006; Parent ea 2012; Sigurdardottir ea 2012; Anisimov ea 2012

Cancer risk and exposure to light@night

- Use of artificial light at night stops melatonin production through the eyes, 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
- Women with total visual blindness have less cancer than sighted women

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Flynn-Evans ea, 2009

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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 Brimer**[2], **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]

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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

ASESA: a case- control study

- To explore the sleep/wake patterns, psychiatric and somatic comorbidity, 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**

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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**

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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)

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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 issues
- This is also apparent within the control group
- *Shorter sleep is related to a higher BMI*

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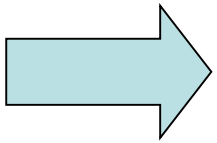
Late sleep = short sleep



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 associated with increased BMI
- Obesity is associated with diabetes, cardiovascular disease and cancer

Kooij 2012, book Adult ADHD;
Dubois 2009, Public Health Nutr;12(1):19-28;
Boere 2008, NTG;152(6):324-30;
Davis 2009, J Psychiatr Res;43(7):687-96;
Mota 2008, Ann.Hum.Biology;35(1)1-10;
Copinschi 2000, Novartis Found Symp;227:143-57
Spiegel 2005, J Appl Physiol;99(5):2008-19

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Sleep loss causes loss of control over appetite

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

- Reducing sleep duration by 2 hours already lowers levels of leptin, the satiety ("fullness") signal
- Sleep restriction study (n=12): 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;

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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

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Cortese 2016; Kooij 2016

Melatonin treatment

- To fall sleep: 3 mg at 22:00 in order to sleep at 23:00
- To reset the clock: 0.1 mg - 0.5 mg between 16:00 and 19:00, *in steps of 1.5 hour/wk from the normal sleep time to the desired bedtime*
- Circadin 2 mg for those who wake up nevertheless at 03:00 am
- No light exposure of tablets of melatonin! (tablets are photosensitive)

Lewy 2005, 2006, continued; Kooij 2012 Boek ADHD bij volwassenen

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Light therapy in the morning: for mood and 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 sunlight in summer

- Melatonin is reduced through closed eyelids by light, which is our natural wake up call
- Light box of 500 W, or Light therapy device of 10.000 lux 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

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Vrouwen humeuren & hormonen

- Vrouwen i.h.a. vaker depressie dan mannen (3-8%)
- PMDD bij 20-30%
- Postnatale depressie bij 13-19%
- Perimenopauzaal weer verhoogde kans

Hylan 1999

Stemming bij ADHD vrouwen

- ADHD vrouwen: 55% lifetime depressie,

  w.v. 60% in de winter
- Dagelijkse stemmingswisselingen (4-5x) bij 90%
- Vraag: vaker PMDD /PPD/ perimenopauzale depressie bij ADHD vrouwen? ⇨ geen onderzoek!

Amons 2006; Kooij 2001;

ADHD humeuren & hormonen

- N=138 vrouwen met ADHD op congres ADHDVrouw, mrt 2015
- 62% PMDD (met of zonder OAC) vs normgroep 29%
- 67% PPD vs 16%
- Geen relatie PMDD en PPD
- Meer angst/depressie perimenopauzaal ook, maar kleine groep (n=30)
- Relatie PMDD en perimenopauzale depressie bijna significant

- Vervolgonderzoek gaande, met controle voor lifetime depressie bij PsyQ

Hylan ea 1999; Kooij ea submitted

Treatment of ADHD and concurrent disorders

1. Psycho- education
2. Discontinue alcohol/drugs
3. Medication for ADHD and concurrent disorders
4. Light Therapy for late sleep and winter depression
5. Coaching
6. Cognitive Behaviour Therapy
7. Relationship therapy
8. Support or Advocacy Groups

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Safren 2005, Weiss 2003; Kooij 2012

BESCHIKBARE MEDICATIE voor ADHD

Bewezen effectief in gecontroleerd onderzoek

Volgorde obv effectsize in Richtlijn NVvP (2015)

Stimulantia:

1. Methylfenidaat (Ritalin, Equasym, Medikinet, Concerta, Mph retard Sandoz, Mylan, Regenboog)®: alleen registratie voor ADHD bij kinderen, adolescenten, en jong volwassenen die doorgaan na adolescentie
1. Dextro-amfetamine (Retard Regenboog): registratie Amfexa (5 mg kortwerkend)

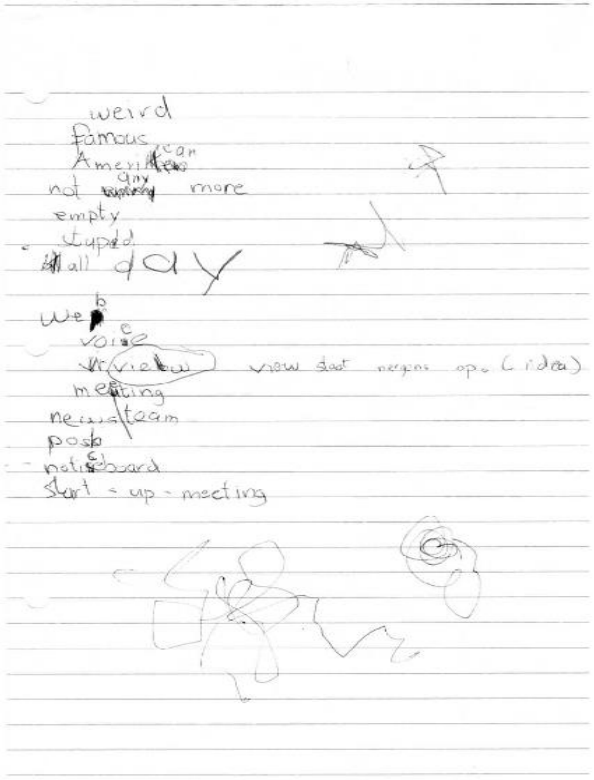
Niet-stimulantia:

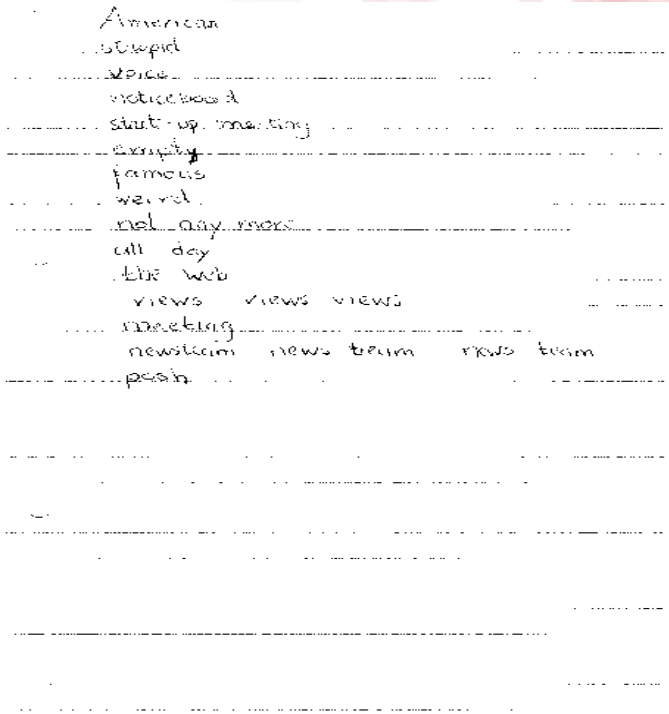
2. Atomoxetine (Strattera): registratie voor kinderen en volwassenen met ADHD
3. Bupropion (Wellbutrin XR): registratie voor depressie en stoppen met roken

Living room before treatment with mph

Living room after treatment with mph

Homework before and after mph





10 year Anniversary of (the 28) PsyQ Programs Adult ADHD in the Netherlands, October 2013

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ADHDFUND

online crowdfunding

- Patient empowerment: patienten bepalen onderzoeksagenda via online voorkeurslijst
- Top 4 voorkeuren (n=538): ADHD en stemming, gezondheid, autisme en slaap

- Nu online: EYEADHD: ADHD, slaap en het oog
- Draag je ook bij?

PsyQ
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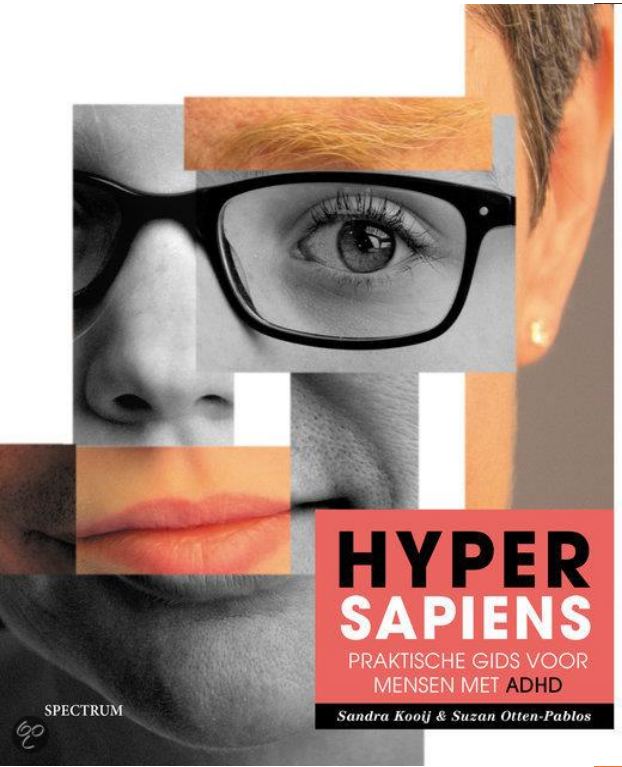
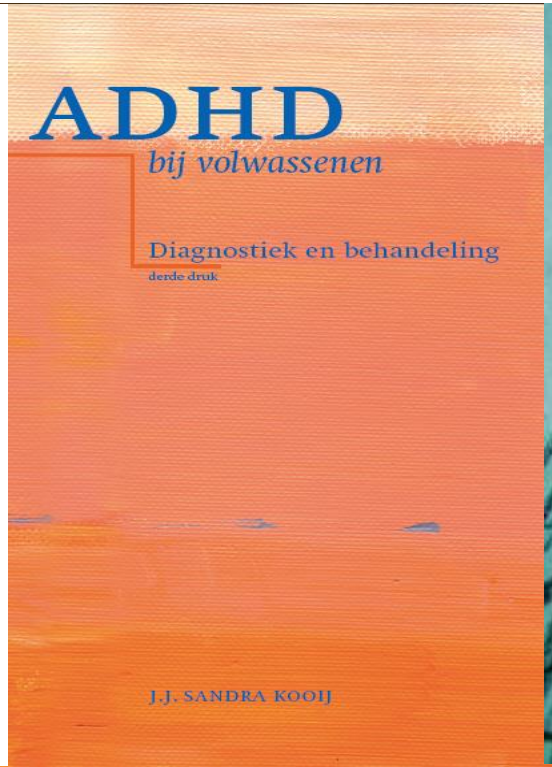
www.adhdfund.com

Meer info


HYPER
SAPIENS
PRAKTISCHE GIDS VOOR
MENSEN MET ADHD
Sandra Kooij & Suzan Otten-Pablos
SPECTRUM


ADHD
bij volwassenen
Diagnostiek en behandeling
derde druk
J.J. SANDRA KOOIJ


Over
Medicatie
voor volwassenen met ADHD