The role of sleep in healthy brain ageing

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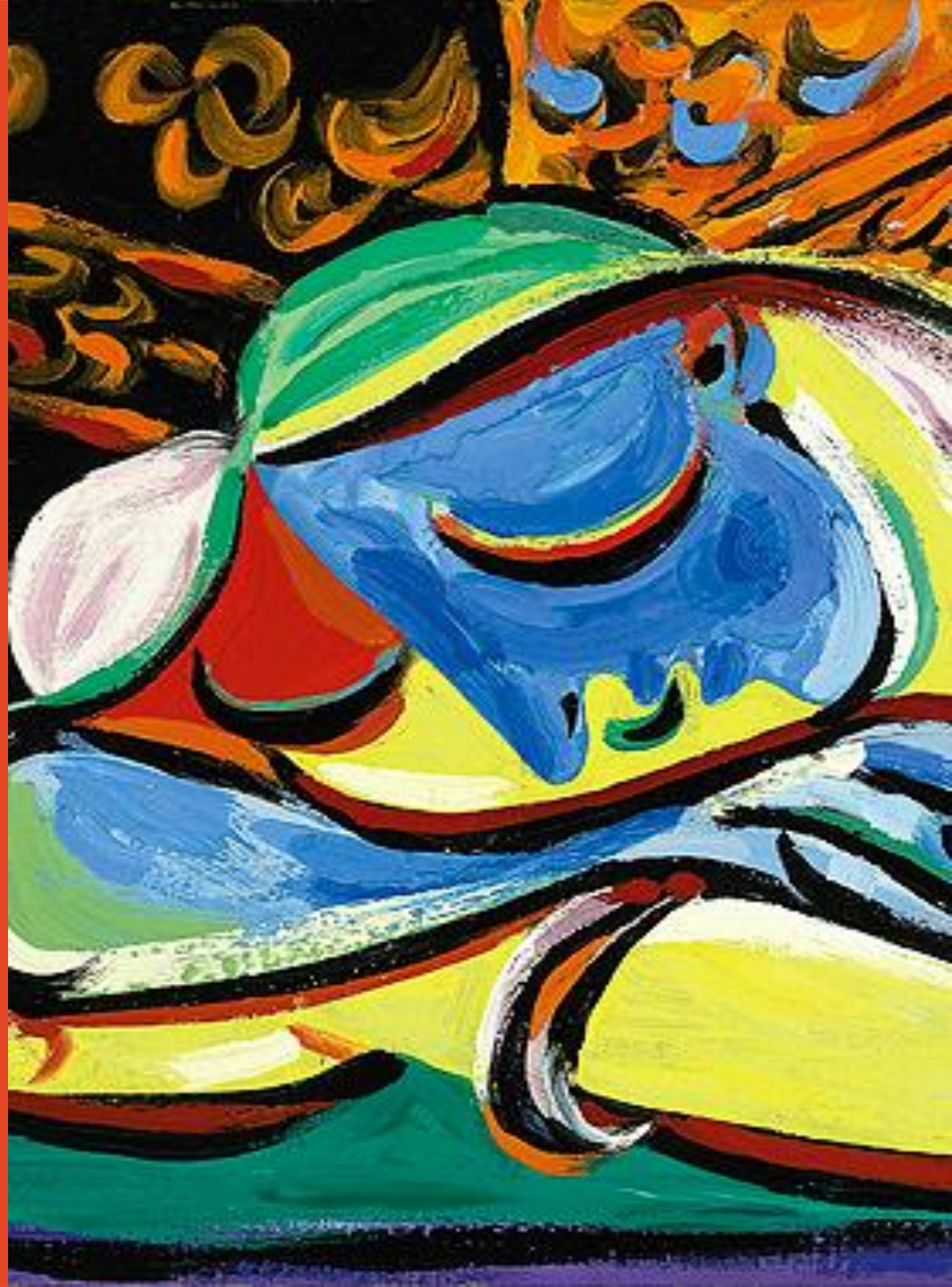


Overview

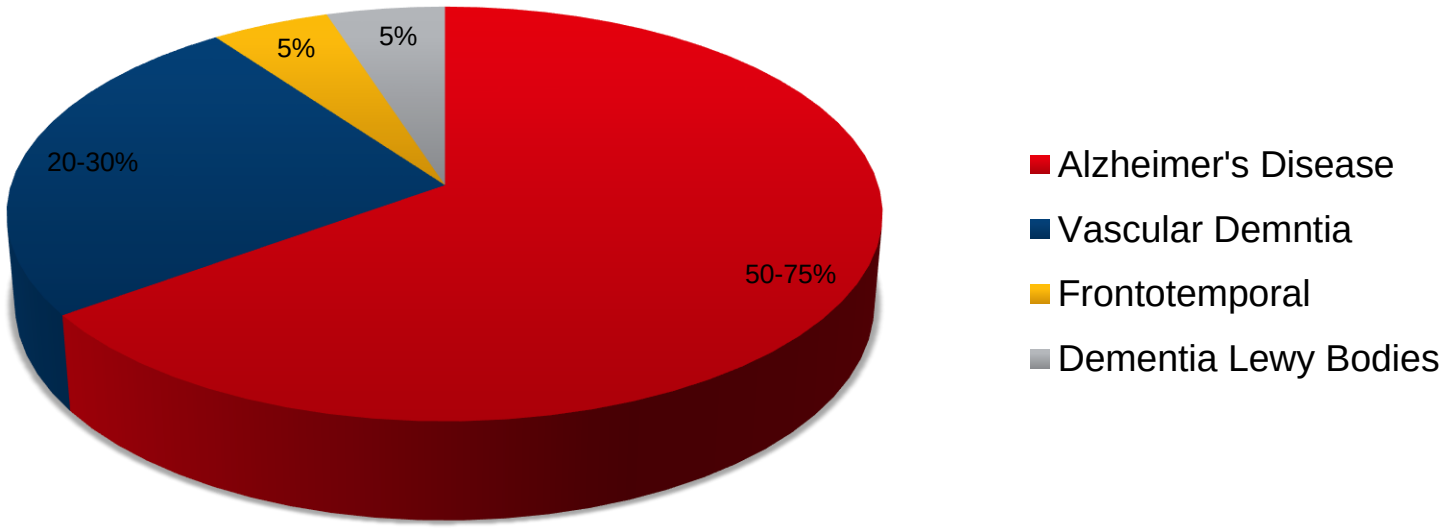
- Dementia background
- A few sleep fundamentals
- Evidence linking sleep and dementia
- Assessment of sleep disturbances in older people
- What treatments are available?
- Top ten tips for patients

What is dementia?

- Impairment of brain functions such as memory, language, executive functioning, personality, attention, processing speed
- Two key principals underlie the concept of dementia:

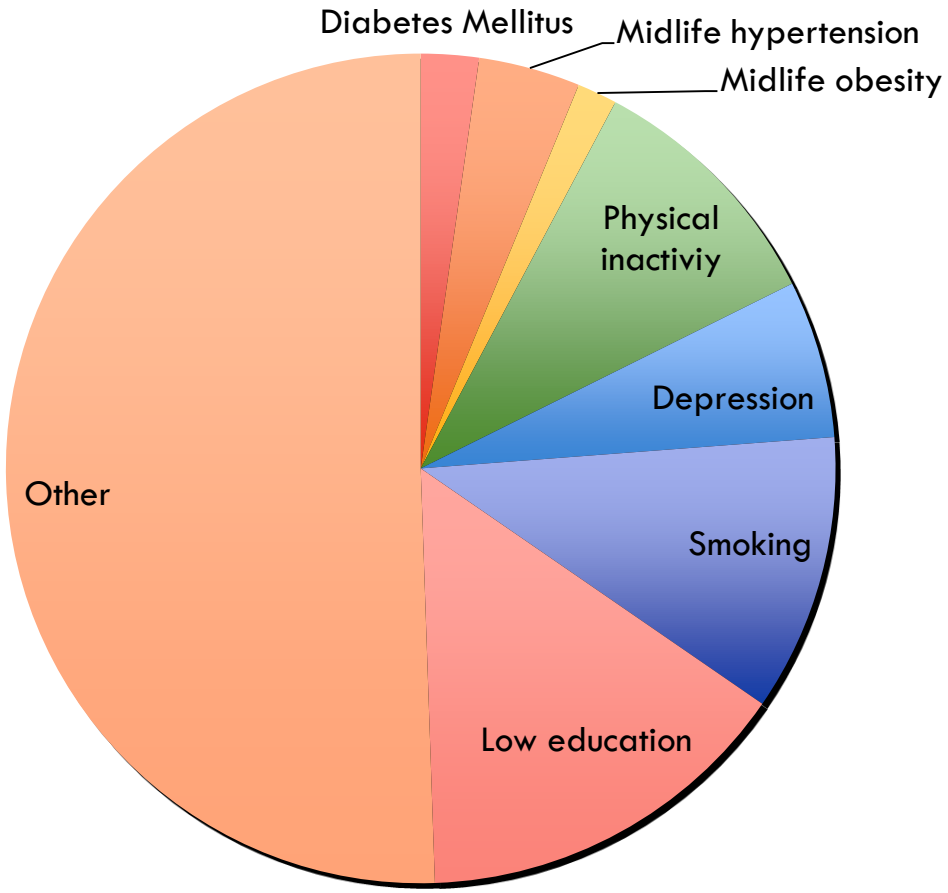
1) Person has experienced decline from a previously higher level of functioning
2) Significantly impaired ability to function at work or usual activities.

- Many different types of neurodegenerative dementia:
  - Alzheimer's disease (AD)
  - Vascular dementia (VaD)
  - Mixed dementia
  - Frontotemporal dementia (FTD)
  - Lewy Body dementia
  - Parkinson's disease dementia
  - .....amongst others.....

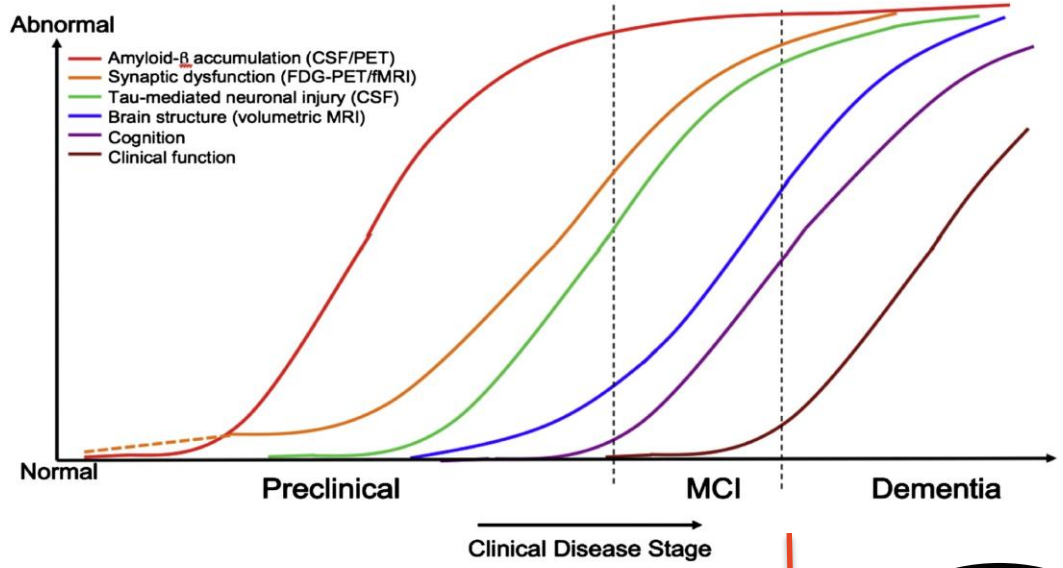


Rationale for Dementia Risk Reduction

Around 50% of the risk for Alzheimer's disease is due to modifiable risk factors



Sperling et al., 2011; Dubois et al., 2007; Norton et al, 2014



Pathology in the brain leading to dementia occurs 10-20 years before symptoms emerge

Sleep disturbance is a key feature of all the major dementias

A few sleep fundamentals

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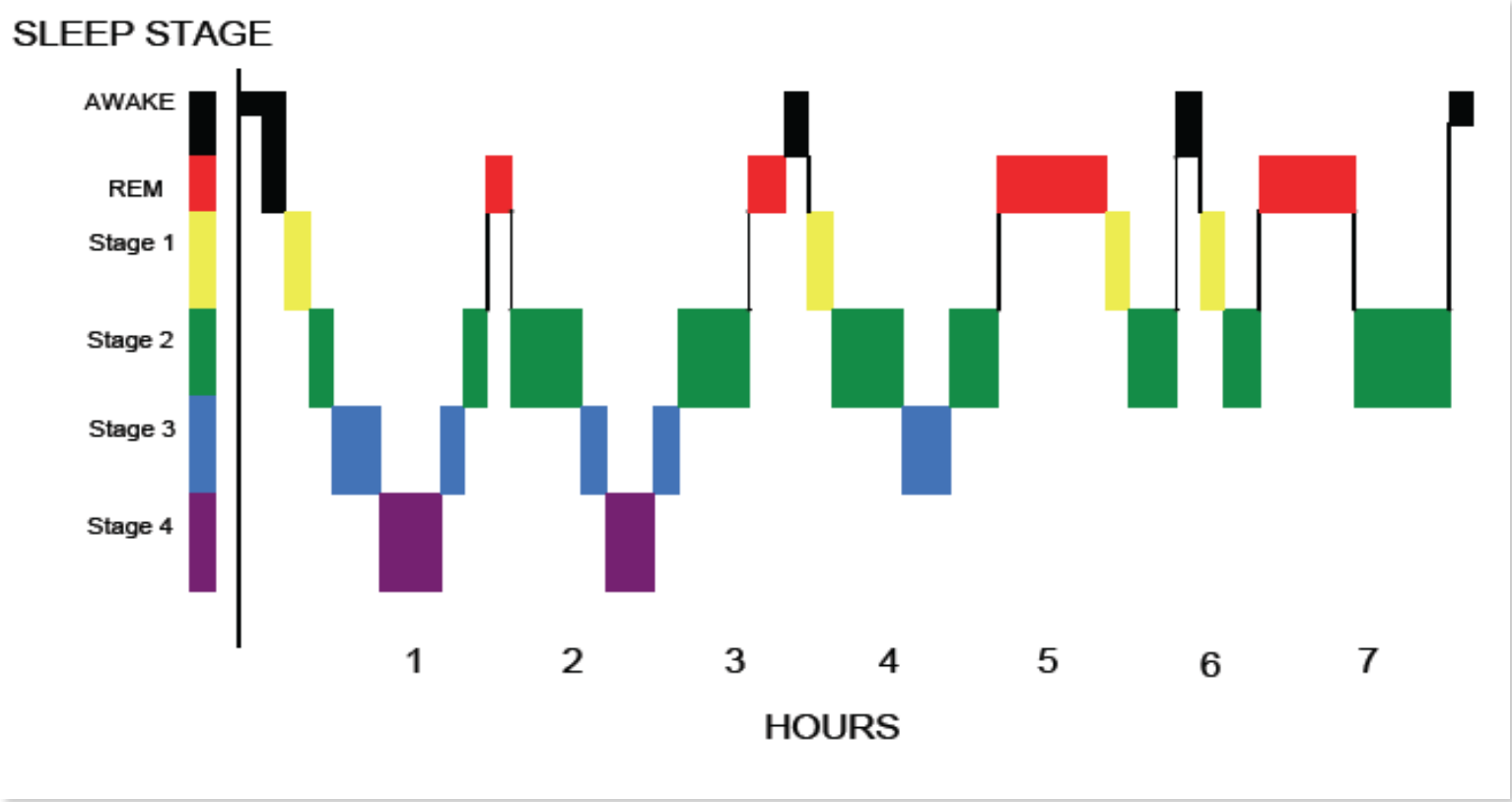
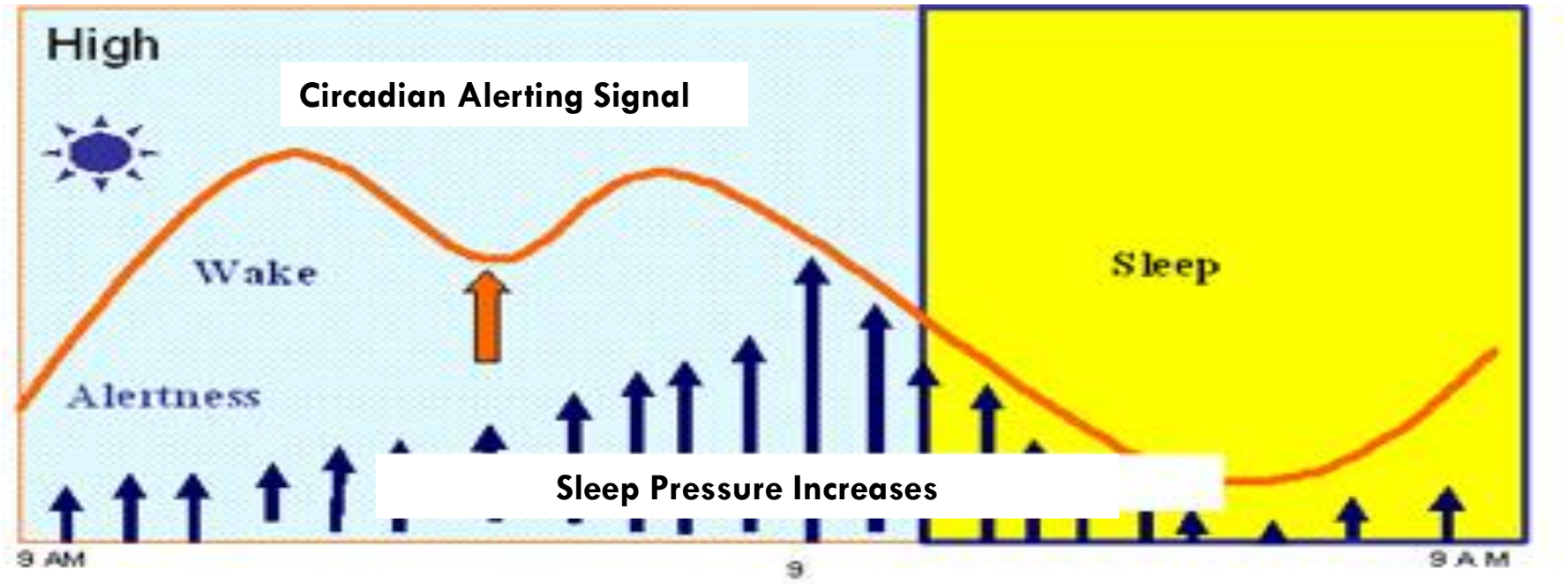
The structure of nocturnal sleep

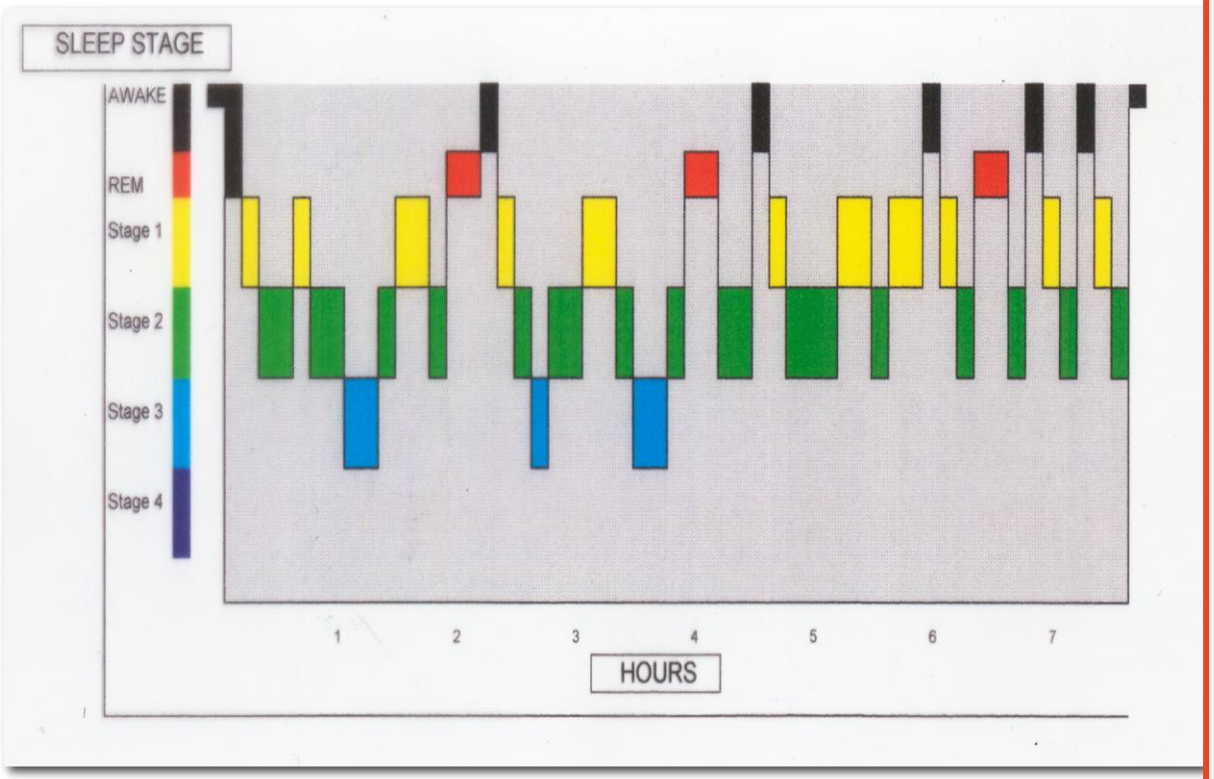


- Sleep is divided into 2 main types:
  - Non Rapid Eye Movement (NREM)
    -divided into 4 stages
    stage 1 (light sleep), 2, 3, 4
  - Rapid Eye Movement (REM)
- 90 min cycles

Sleep-wake activity is a balance between sleep pressure and circadian alerting signal



How does the sleep-wake system change as we age?



- Shallow, fragmented
- Decreased slow wave sleep (deep sleep)
- Decreased Rapid eye movement (REM; dreaming) in second half
- Decreased sleep duration
- Daytime sleepiness
- Longer to recover from lack of sleep
- Circadian: decreased amplitude, advanced timing

Ohayon et al, 2004, 2005; Ancoli-Israel, 2008, 2005;

The benefits of sleep

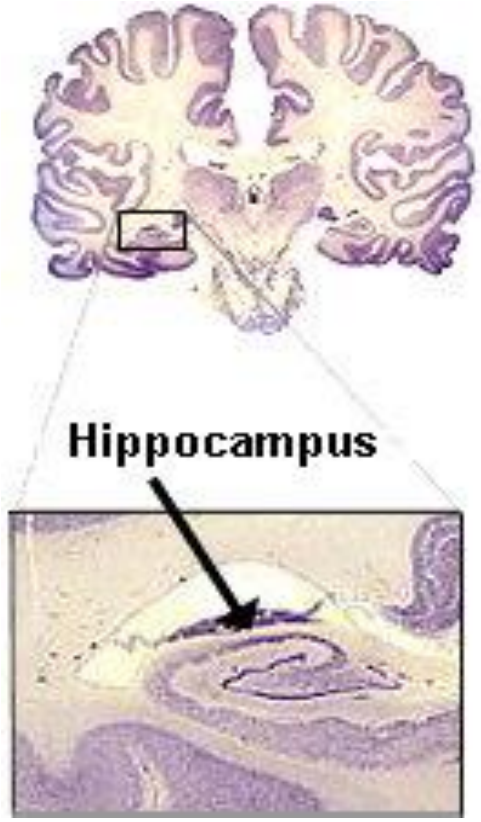
- Mood, alertness, wellbeing
- Regulation of immune responses and pro-inflammatory cytokines including IL-6, CRP, TNF-alpha
- Health effects (restriction = ⇡ glucose sensitivity and ⇡insulin resistance, ⇡ BP and heart rate)
- Synaptic density/strength/efficiency

What are the functions of sleep?

Hippocampal neurogenesis

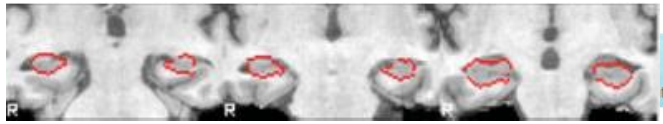
Prolonged sleep loss/disruption may effect hippocampal neurogenesis

- Supports the production of new cells and their development into neurons
  - 1 day loss, little effect
  - Prolonged disruption leads to major decreases in hippocampal cell proliferation
  - REM - cell proliferation
  - NREM + REM - the *number* of cells that subsequently develop into adult neurons



Human studies:

- Sleep restriction and poor sleep quality are associated with smaller hippocampi



Journal of Alzheimer's Disease 44 (2015) 1279–1290
DOI 10.3233/JAD-142016
IOS Press

Hippocampal Volume in Older Adults at Risk of Cognitive Decline: The Role of Sleep, Vascular Risk, and Depression

Emma L. Elcombe[a], Jim Lagopoulos[b], Shantel L. Duffy[a], Simon J.G. Lewis[a,b], Louisa Norrie[a,b], Ian B. Hickie[a,b] and Sharon L. Naismith[a,b,*]
[a]*Healthy Brain Ageing Program, University of Sydney, NSW, Australia*
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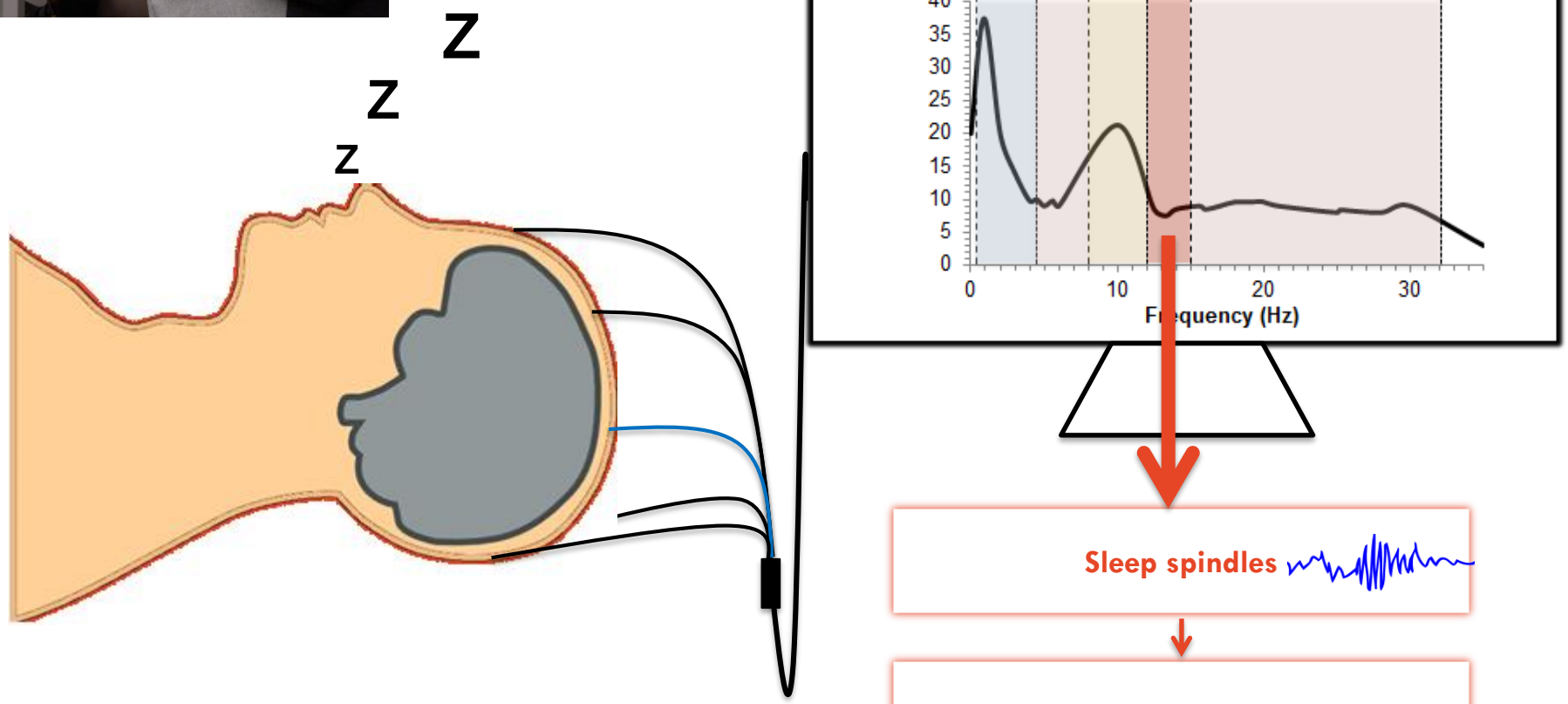
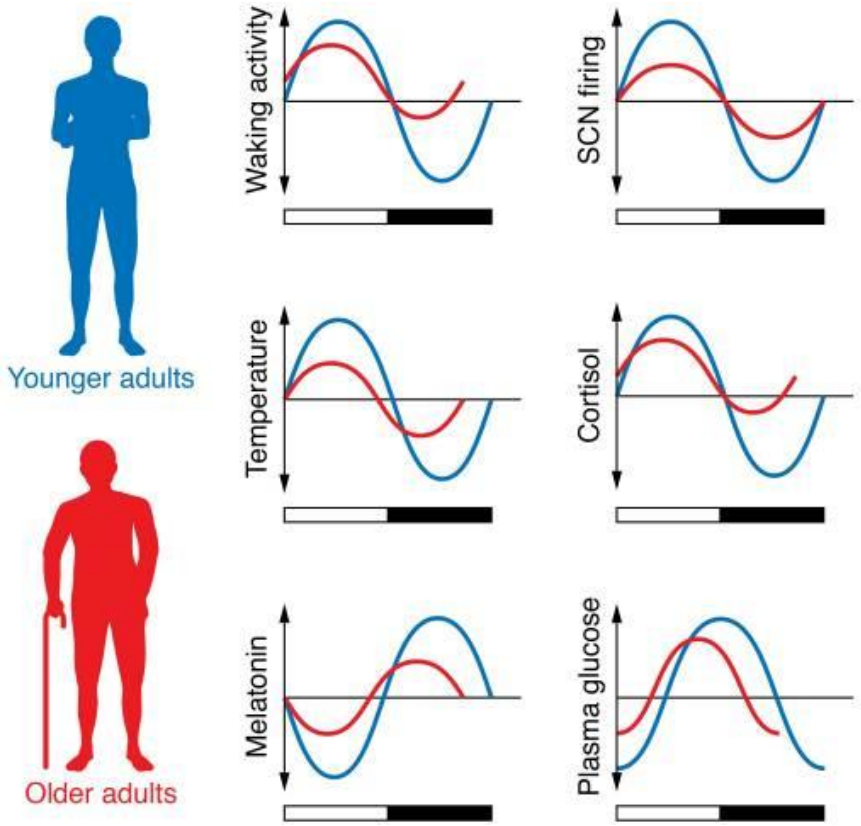
New neurons in the adult brain: The role of sleep and consequences of sleep loss

Peter Meerlo, Ralph E. Mistlberger, [...], and Dennis McGinty

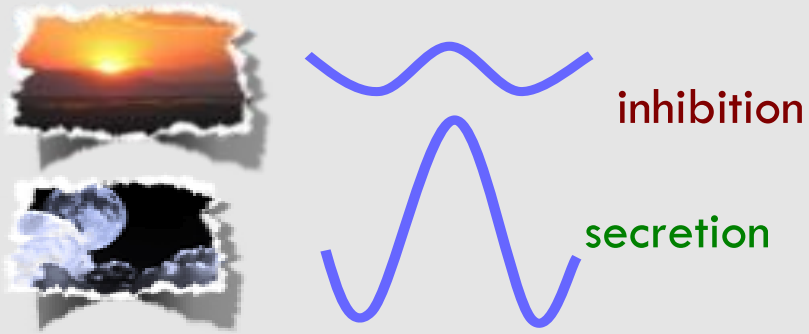
What are the functions of sleep?
Sleep Dependent Memory



What about circadian rhythms?



- Co-regulates timing, structure and consolidation of sleep
- Generated by the suprachiasmatic nucleus (SCN) of the hypothalamus ('Master clock')
  - Regulated by environmental signals
  - Exerts circadian influence via many signals particularly melatonin, a hormone produced by the pineal gland



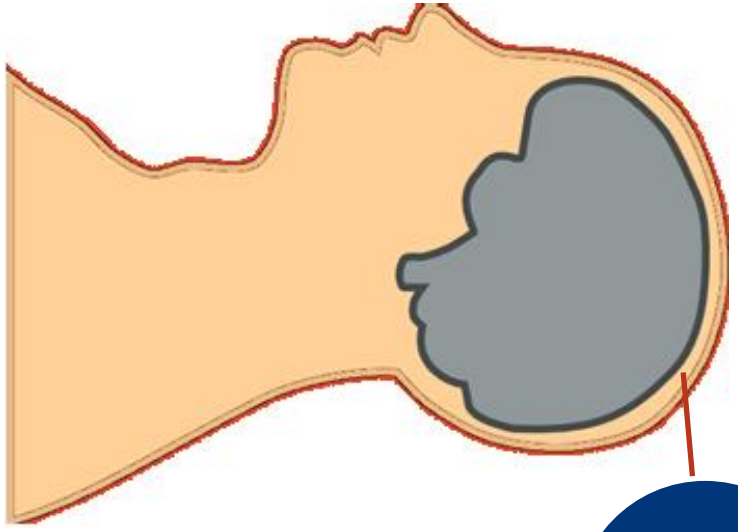
- Multiple age related changes

Sleep-wake problems in older adults

- 50% of older adults have chronic sleep complaints
  - Prevalence range 9-69%
- Insomnia: Most frequent complaint in later-life (rates 30-60% or 12-25% using more stringent criteria)
- Older adults twice as likely to be prescribed a sedative or hypnotic than younger adults

Ancoli-Israel S. JAGS 2005.

How is sleep disturbance linked to cognitive decline?



Role of overnight sleep

- Glymphatic system – clearance of toxins, waste and b-amyloid
- Immune/inflammatory regulation
- Neurogenesis
- Synaptic plasticity

Impaired sleep quality

- Sleep duration, insomnia
- Night-time awakenings
- ?Epigenetic mechanisms

Obstructive sleep apnoea

- Fragmented sleep
- Hypoxemia
- Oxidative stress/cardiovascular mechanisms

?Consequence of brain degeneration

Obstructive sleep apnoea (OSA) is an emerging risk factor for dementia, increasing the risk of MCI and dementia AND at an earlier age.

Evidence linking sleep and dementia

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Why are we concerned about sleep and brain degeneration?

- Alzheimer's Disease:
  - Predictive of more rapid decline and shorter survival
  - Prospective studies: Poor self-reported sleep & PSG sleep quality increases risk
- Parkinson's Disease
  - Prodromal feature
  - Linked to poor quality of life and depression
- Dementia with Lewy Bodies
  - REM Sleep Behaviour Disorder

Naismith, Rogers & Lewis 2011; Weldemichael & Gorssman, 2010; see Wu & Swaab, 2007

Is self-reported sleep quality a predictor of dementia?

- 18 longitudinal studies (n= 246,786) subjects at baseline and n=25,847 dementia cases after an average 9.49 y of follow-up.
- Subjects who reported sleep disturbances had a higher risk of incident all-cause dementia, AD, and vascular dementia, RR = 1.19.

Sleep Medicine Reviews 40 (2018) 4–16

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journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis

Le Shi [a, b], Si-Jing Chen [b], Meng-Ying Ma [c], Yan-Ping Bao [a], Ying Han [a], Yu-Mei Wang [d], Jie Shi [a], Michael V. Vitiello [e], Lin Lu [b, a, *]

Is sleep duration a predictor of dementia?

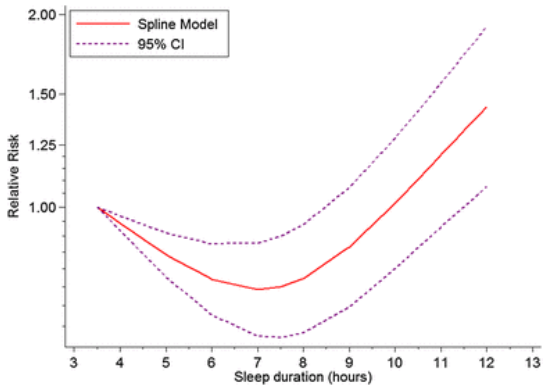
6 studies examined risk of MMSE cognitive decline (n = 46,068 subjects)

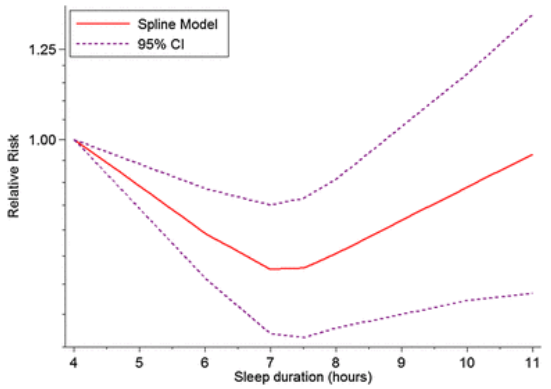
Pooled RR per 1 h increases in sleep duration was 0.99 (95% CI 0.97–1.01)

"U" shaped curve with lowest point located at 7 h was detected

4 studies examined risk for MCI/dementia (n = 24305, 2718 cases)

The "J" shaped dose–response association between sleep duration and the risk of MCI/dementia was found (combined RR for per 1 h increases in sleep duration = 0.98, 95% CI 0.97–1.00)





Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-018-1005-y

REVIEW

Non-linear associations between sleep duration and the risks of mild cognitive impairment/dementia and cognitive decline: a dose–response meta-analysis of observational studies

Ying Liang[1] · Ling-Bo Qu[2] · Hao Liu[1]

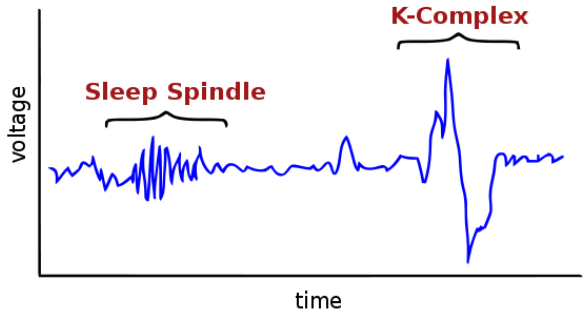
What is the nature of the sleep-wake changes in Alzheimer's?

- 40-50% - sleep disturbance
- Daytime agitation, nocturnal insomnia, restlessness - 'Sundowning'
- Hypersomnia
- Up to 40% of nocturnal time awake
- Daytime napping
- Predictive of more severe cognitive decline
- In early AD, linked to working memory, verbal fluency, memory change and executive functioning
- Linked to carer burden and institutional care

Bonanni et al, 2005; Cooke et al, 2006

AD: sleep architecture and circadian change

- Amplification of usual ageing changes
- More stage 1 sleep, fragmented sleep
- Predictive of more pronounced cognitive decline
- Sleep apnoea 35-63%
  - 33-70% have sleep disordered breathing
  - 70-80% of patients with dementia with AHI>5
  - 48% with AHI>20
- Reduced and poorly formed sleep spindles:
  - Related to memory consolidation
- Prominent circadian change
- Degeneration in SCN ⇒ decreased melatonin
- Neuropathological studies – decreased melatonin in pineal gland



Weldemichael & Gorssman, 2010; see Wu & Swaab, 2007

Systematic review and meta-analysis of prevalence and associates of sleep problems in people with dementia living in care homes

Lucy Webster[1], Sergi Costafreda[1], Aisling Stringer[1], Amy Lineham[2], Jessica Budgett[1], Simon Kyle[3], Julie Barber[4], Rossana Horley[5], Gill Livingston[1]

[1]Division of Psychiatry, UCL; [2]Medical School, UCL; [3]Sleep and Circadian Neuroscience Institute, University of Oxford; [4]Department of Statistical Science, UCL; [5]Alzheimer's Society Research Network, UK

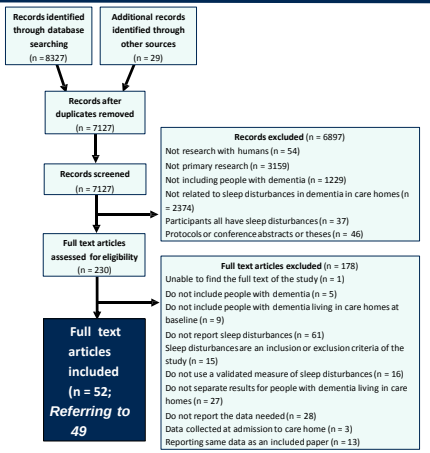
Background

- Sleep problems are common in people living with dementia
- They include:
  - difficulty falling asleep
  - night-time awakenings
  - waking too early
  - excessive daytime sleepiness
- They affect individuals and families
- May cause people with dementia to move to care homes
- So sleep problems may be more common in people with dementia living in care homes
- There are no systematic reviews or meta-analyses on this topic

Method

- We searched electronic databases to November 2017
- Included: studies reporting prevalence or associates of sleep problems on validated questionnaires or actigraphy in people with dementia living in care homes
- Excluded: studies reporting sleep apnoea, rest-activity rhythms or circadian rhythms
- Two researchers independently decided if studies fulfilled inclusion criteria
- Two raters independently rated study quality according to criteria and reached consensus

Studies



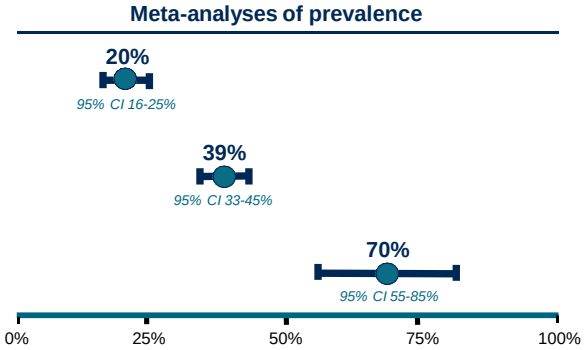
- 52/7127 papers included
  - 45 on prevalence & 19 on associates
- We emailed authors for further papers and data
  - Additional data received from 16 studies
- Most studies from Europe (35)
  - Others from Australia (4), China (3), Japan (3), South Korea (2), USA (1), and Brazil (1)
- We meta-analysed pooled estimates of prevalence
- Synthesised reports of associated factors
- We divided sleep problems into:
  a) Clinically significant cases on validated questionnaires
  b) Any symptoms on validated questionnaires
  c) Night-time sleep problems measured on actigraphy

How prevalent are sleep problems?

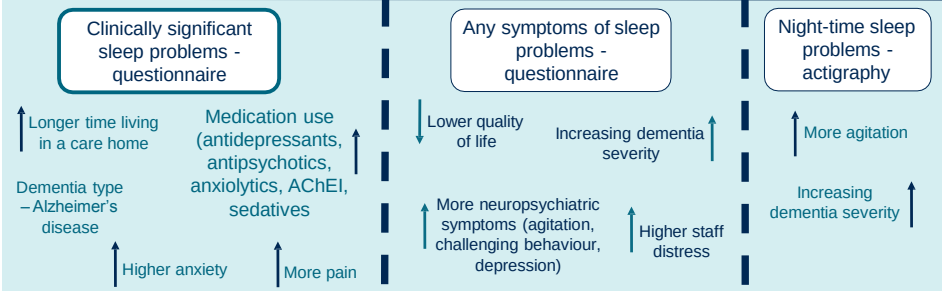
Measured on questionnaires
Clinically significant sleep problems
17 studies; n=6860

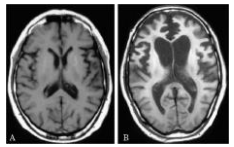
Any symptoms of sleep problems
27 studies; n=14,184

Measured on actigraphy
Sleep efficiency <85%
5 studies; n=240



What is associated with sleep problems?





CT scans showing brain atrophy in the same individual with frontotemporal dementia 3 years apart.
DOI: https://doi.org/10.1212/WNL.55.8.1224

Conclusions

- 20% of people with dementia living in care homes have clinically significant sleep problems
- Actigraphy (sleep efficiency <85%) may overestimate how many people have sleep problems as measuring movement
- However staff may not realise that residents are awake at night
- Both agitation and increasing dementia severity are associated with sleep problems on questionnaires and actigraphy

Contact
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Funding
PhD funded by the Economic and Social Research Council (UK) through the UCL, Bloomsbury and East London Doctoral Training Partnership

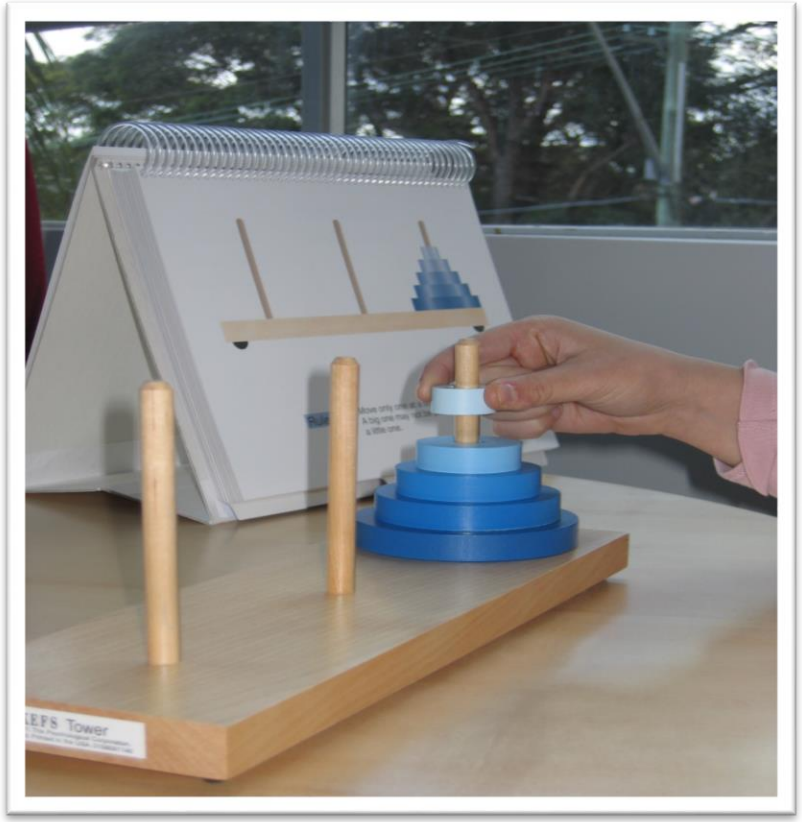
Are sleep-wake changes evident in Mild Cognitive Impairment (MCI)?

PSQI sleep disturbance: 63% of MCI and 44% of controls

	Unique R2, %
Antidepressant use	ns
Time spent exercising	ns
Disability rating	ns
Age	0.9
Depression	14.6
Alcohol	4.3
Education	3.4
MMSE	1.9
Shared predictor variance	10.4

Full model: R2 = 35.5, n = 158 MCI

Method: 1) Forced entry, age; 2) Stepwise entry, all significant univariate predictors.
Non-signiifcant univariate predictors include: Vascular risk factors (heart disease, diabetes, cholesterol, smoking history, hypertension), Body Mass Index, Medical burden, Anxiety



McKinnon et al 2014

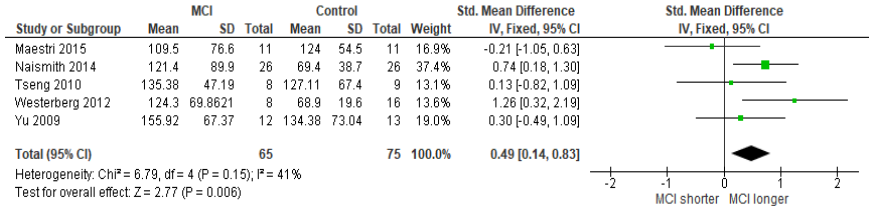
Is sleep macroarchitecture altered in MCI?

Unpublished data,

Meta-analysis: 14 studies

- REM Latency (+31mins)
- Total sleep time (-27mins)
- Sleep efficiency -5%
- WASO (+18mins)
- Latency (+6mins)
- ODI (+10.8)
- Not SWS or AHI

REM latency (standardised mean difference)

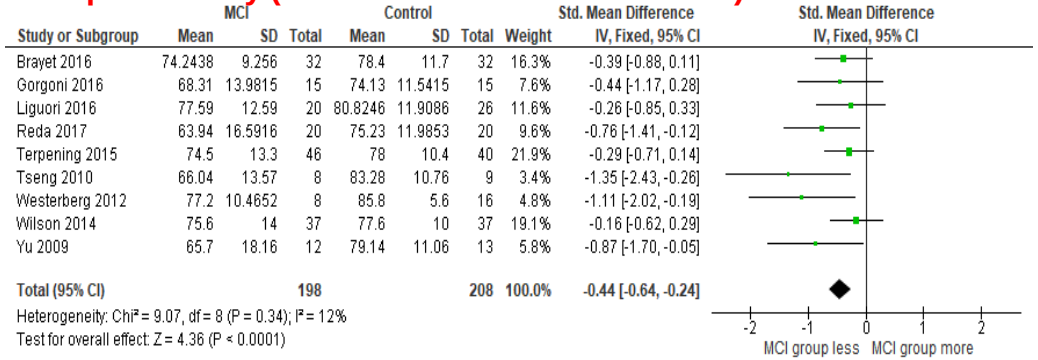


Study or Subgroup	MCI Mean	MCI SD	MCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Maestri 2015	109.5	76.6	11	124	54.5	11	16.9%	-0.21 [-1.05, 0.63]
Naismith 2014	121.4	89.9	26	69.4	38.7	26	37.4%	0.74 [0.18, 1.30]
Tseng 2010	135.38	47.19	8	127.11	67.4	9	13.1%	0.13 [-0.82, 1.09]
Westerberg 2012	124.3	69.8621	8	68.9	19.6	16	13.6%	1.26 [0.32, 2.19]
Yu 2009	155.92	67.37	12	134.38	73.04	13	19.0%	0.30 [-0.49, 1.09]
Total (95% CI)			**65**			**75**	**100.0%**	**0.49 [0.14, 0.83]**

Heterogeneity: Chi² = 6.79, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 2.77 (P = 0.006)

Std. Mean Difference IV, Fixed, 95% CI
-2 -1 0 1 2
MCI shorter MCI longer

Sleep efficiency (standardised mean difference)

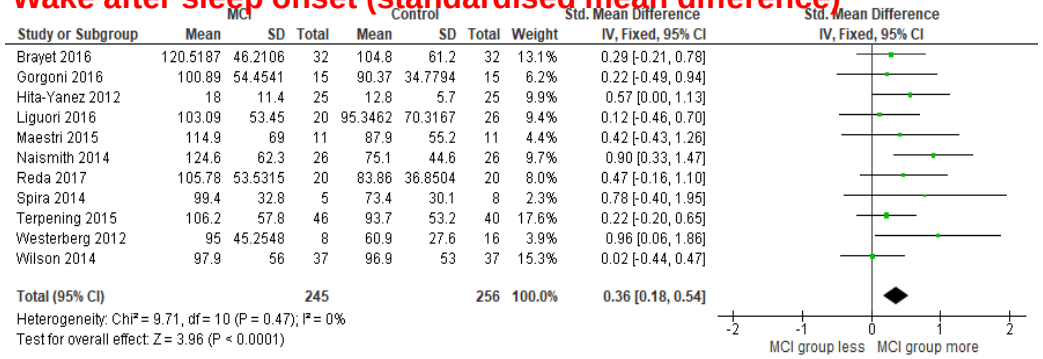


Study or Subgroup	MCI Mean	MCI SD	MCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Brayet 2016	74.2438	9.256	32	78.4	11.7	32	16.3%	-0.39 [-0.88, 0.11]
Gorgoni 2016	68.31	13.9815	15	74.13	11.5415	15	7.6%	-0.44 [-1.17, 0.28]
Liguori 2016	77.59	12.59	20	80.8246	11.9086	26	11.6%	-0.26 [-0.85, 0.33]
Reda 2017	63.94	16.5916	20	75.23	11.9853	20	9.6%	-0.76 [-1.41, -0.12]
Terpening 2015	74.5	13.3	46	78	10.4	40	21.9%	-0.29 [-0.71, 0.14]
Tseng 2010	66.04	13.57	8	83.28	10.76	9	3.4%	-1.35 [-2.43, -0.26]
Westerberg 2012	77.2	10.4652	8	85.8	5.6	16	4.8%	-1.11 [-2.02, -0.19]
Wilson 2014	75.6	14	37	77.6	10	37	19.1%	-0.16 [-0.62, 0.29]
Yu 2009	65.7	18.16	12	79.14	11.06	13	5.8%	-0.87 [-1.70, -0.05]
Total (95% CI)			**198**			**208**	**100.0%**	**-0.44 [-0.64, -0.24]**

Heterogeneity: Chi² = 9.07, df = 8 (P = 0.34); I² = 12%
Test for overall effect: Z = 4.36 (P < 0.0001)

Std. Mean Difference IV, Fixed, 95% CI
-2 -1 0 1 2
MCI group less MCI group more

Wake after sleep onset (standardised mean difference)

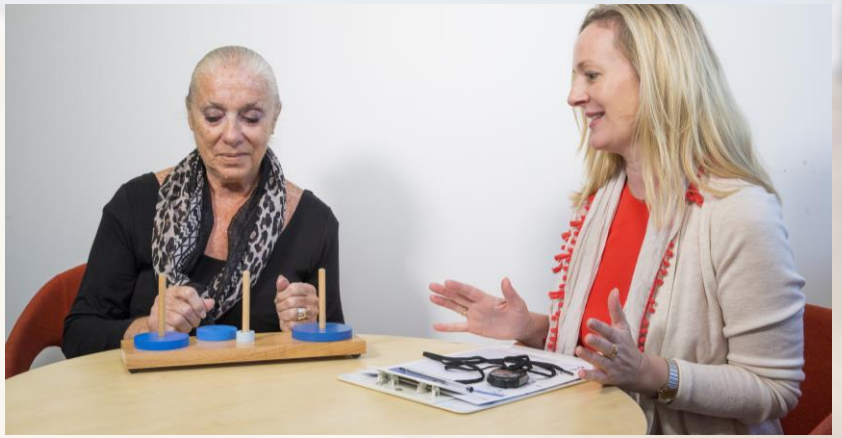


Study or Subgroup	MCI Mean	MCI SD	MCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Brayet 2016	120.5187	46.2106	32	104.8	61.2	32	13.1%	0.29 [-0.21, 0.78]
Gorgoni 2016	100.89	54.4541	15	90.37	34.7794	15	6.2%	0.22 [-0.49, 0.94]
Hita-Yanez 2012	18	11.4	25	12.8	5.7	25	9.9%	0.57 [0.00, 1.13]
Liguori 2016	103.09	53.45	20	95.3462	70.3167	26	9.4%	0.12 [-0.46, 0.70]
Maestri 2015	114.9	69	11	87.9	55.2	11	4.4%	0.42 [-0.43, 1.26]
Naismith 2014	124.6	62.3	26	75.1	44.6	26	9.7%	0.90 [0.33, 1.47]
Reda 2017	105.78	53.5315	20	83.86	36.8504	20	8.0%	0.47 [-0.16, 1.10]
Spira 2014	99.4	32.8	5	73.4	30.1	8	2.3%	0.78 [-0.40, 1.95]
Terpening 2015	106.2	57.8	46	93.7	53.2	40	17.6%	0.22 [-0.20, 0.65]
Westerberg 2012	95	45.2548	8	60.9	27.6	16	3.9%	0.96 [0.06, 1.86]
Wilson 2014	97.9	56	37	96.9	53	37	15.3%	0.02 [-0.44, 0.47]
Total (95% CI)			**245**			**256**	**100.0%**	**0.36 [0.18, 0.54]**

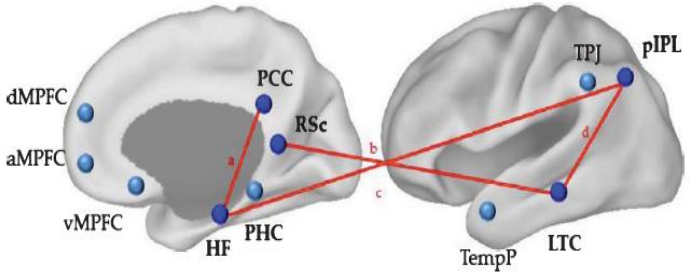
Heterogeneity: Chi² = 9.71, df = 10 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)

Std. Mean Difference IV, Fixed, 95% CI
-2 -1 0 1 2
MCI group less MCI group more

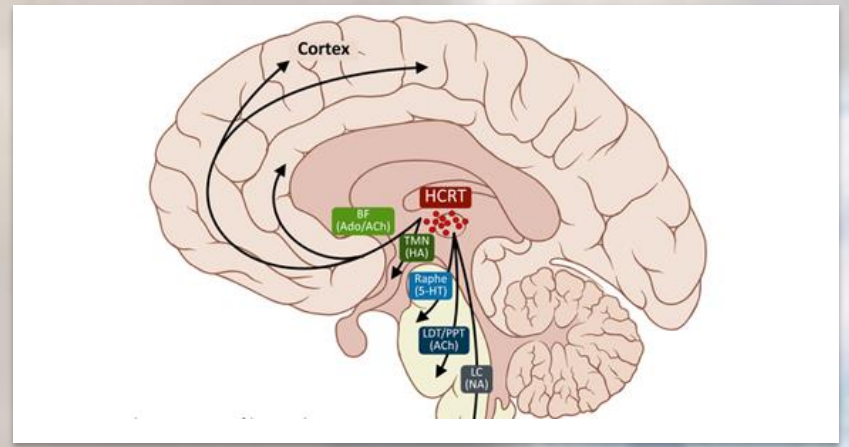
How do sleep changes relate to brain integrity in Mild Cognitive Impairment?



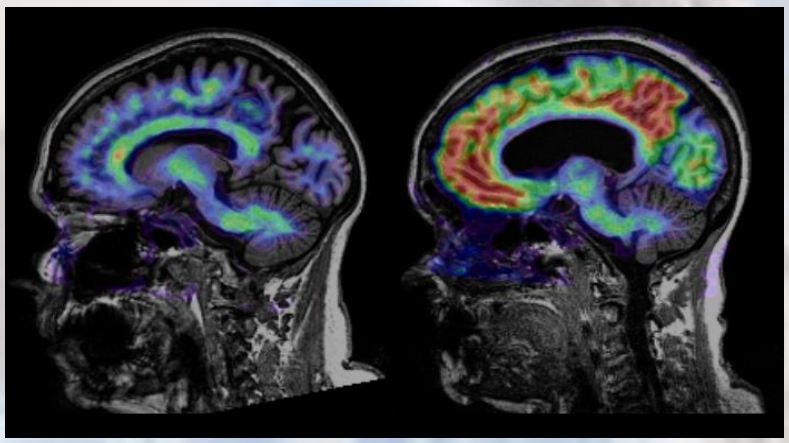
Self-report and actigraphic sleep relates to executive and memory performance



Self-report and actigraphic sleep relates to decreased connectivity between temporal and parietal networks



Increases in the wake promoting hormone orexin

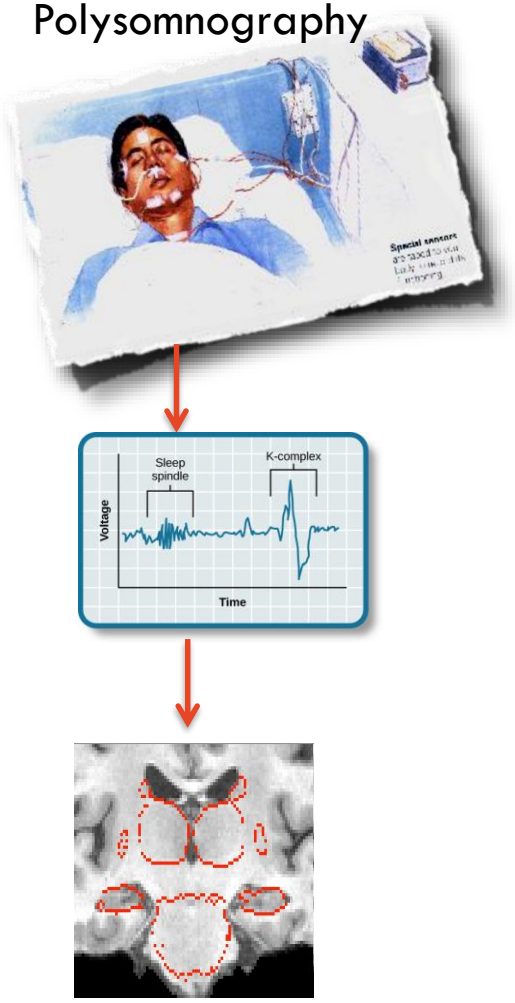


Self-report sleep relates to PET and CSF amyloid levels in healthy and MCI

Naismith et al, 2010; McKinnon et al, 2014, Ligouri et al, 2016 , Mander et al, 2014

Delving deeper: sleep microarchitecture in MCI

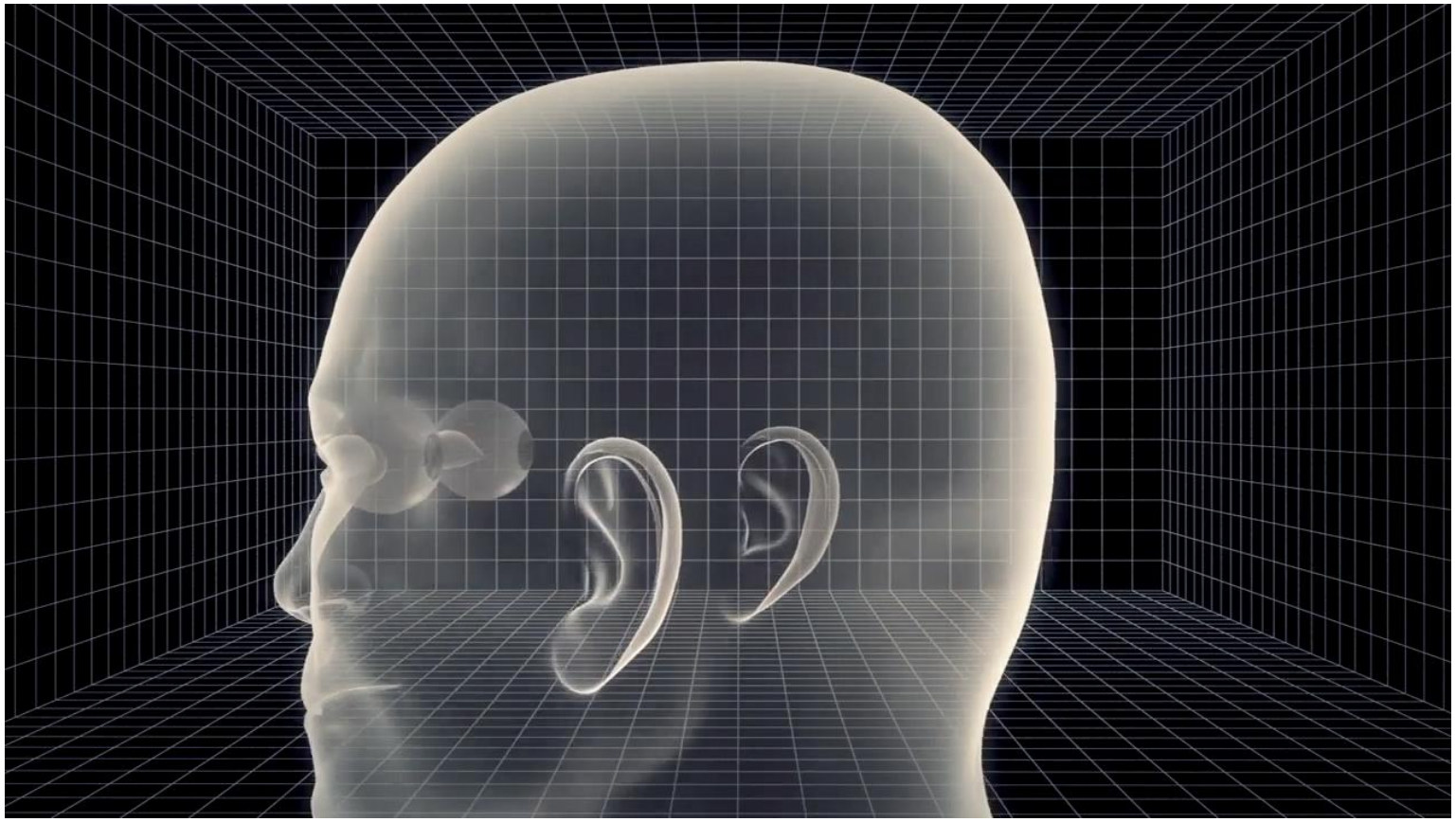
Polysomnography



	Controls N=40	MCI N=60	p
Total sleep time, mins	363.4 (68.4)	352.7 (100.7)	ns
Sleep efficiency/100	76.1 (10.6)	73.8 (14.7)	ns
Lowest O2 desaturation, %	87.1 (5.1)	85.9 (5.2)	ns
Sigma power (C3-M2), 12-15Hz	**0.73 (.2)**	**0.64 (.2)**	* **d=0.46**
Slow spindle range	**0.72 (.19)**	**0.64 (0.21)**	**
Fast spindle range	**0.49 (.19)**	**0.42 (.21)**	**ns**
Delta, 1-4.5Hz	2.6 (.2)	2.5 (0.2)	*
Alpha, 8-12Hz	1.27 (.2)	1.16 (.2)	*

Naismith et al isubmitted

Mechanisms by which sleep may promote brain integrity: The Glymphatic system



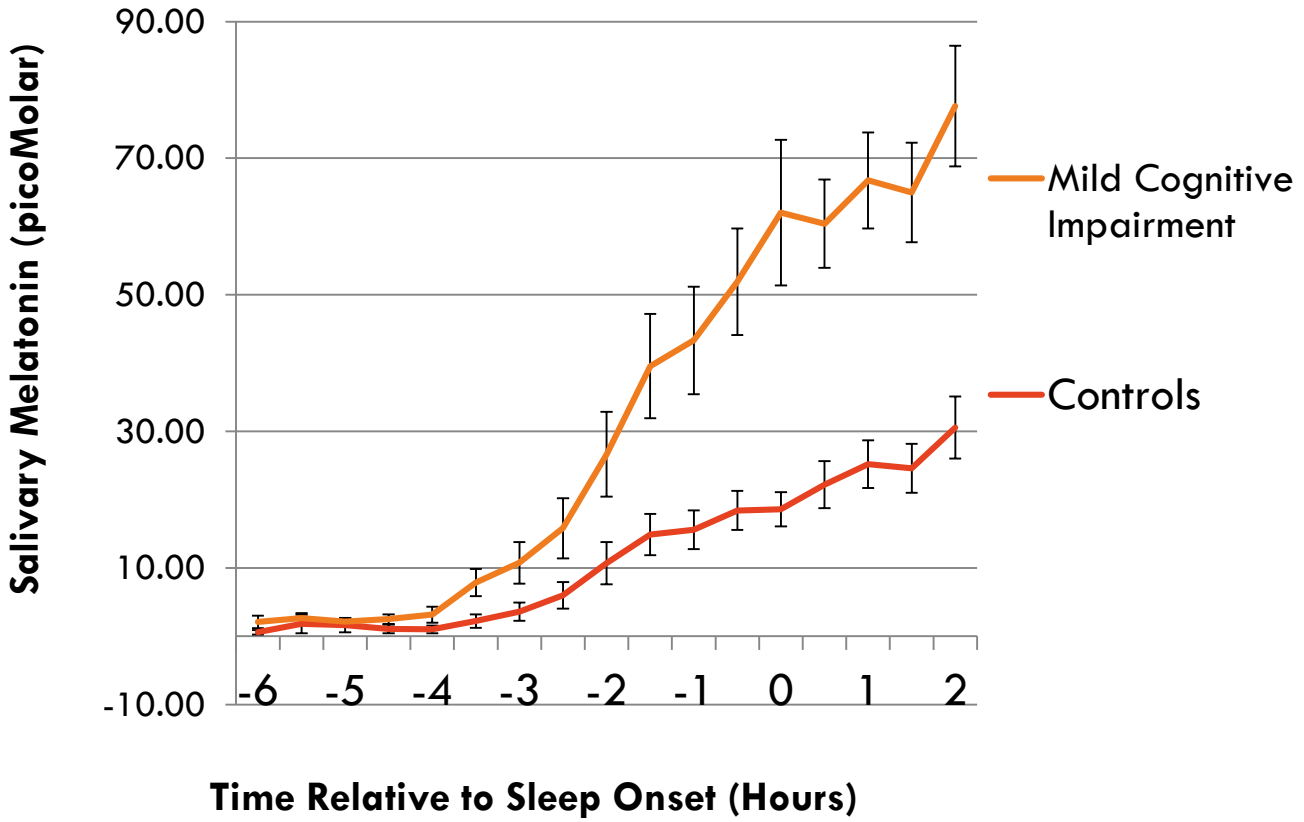
- The interstitial/extracellular concentration of b-amyloid has circadian oscillation - higher in the wake (even in states of darkness) state than the sleep state
- Xie et al in Science (2013) showed that sleep clears B-amyloid via the glymphatic system, particularly in slow wave sleep
- Sleep deprivation accelerates amyloid plaque deposition, whilst promoting sleep with orexin antagonists inhibits plaque formation

Are circadian rhythms linked to cognitive decline?

Brain effects of circadian misalignment:

- Astrogliosis, oxidative stress damage, synaptic degeneration, altered gene expression, functional brain connectivity, learning/memory, hippocampal neurogenesis & seizure threshold.

Altered timing of melatonin onset in MCI: associations with memory performance



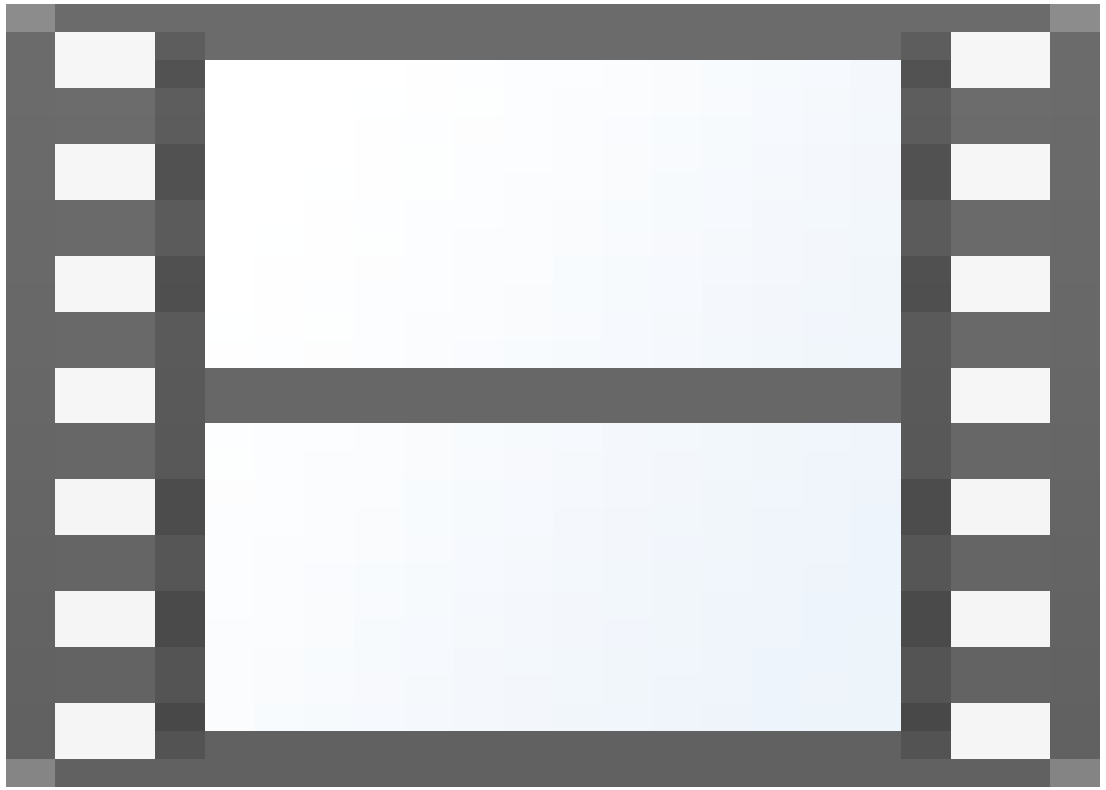
Naismith et al, 2014

Sleep-Wake Disturbances in Parkinson's Disease

- Sleep fragmentation
  - Insomnia (early, mid & late)
  - Discomfort (Wearing Off, Dystonia, Nocturia)
- Daytime somnolence
- Rapid Eye Movement sleep behaviour disorder (RBD)
- Restless legs syndrome (RLS)
- Sleep-disordered breathing

Look out for REM Sleep Behaviour Disorder

- Prodromal feature of Parkinson's disease and Dementia with Lewy Bodies (80% of RSBD cases progress to DLB)
- Loss of normal muscle atonia during REM sleep
- Dream enactment behaviour
- Congruent motor activity
  - Punching or shouting
- Injury
  - Self & bed partner 33%



Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study

Alex Iranzo, Eduard Tolosa, Ellen Gelpi, José Luis Molinuevo, Francesc Valldeoriola, Mónica Serradell, Raquel Sanchez-Valle, Isabel Vilaseca, Francisco Lomeña, Dolores Vilas, Albert LLadó, Carles Gaig, Joan Santamaria

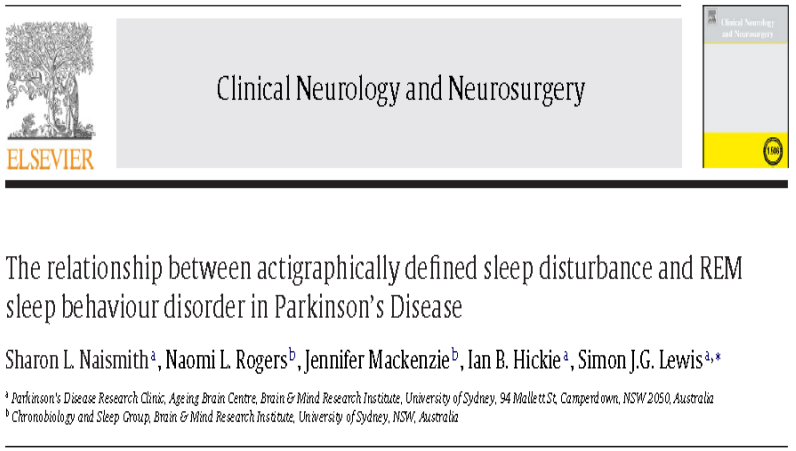
People with RSBD 120 more likely to develop these neurodegenerative diseases up to 20 years later

Diagnostic Criteria

- International Classification of Sleep Disorders (ICSD) – 2
  - REM without atonia during a sleep study
  - Abnormal REM behaviour on a sleep study
  - History of sleep related injury
  - Absence of REM related epileptiform activity
  - Absence of other potential etiology such as drug related, OSA

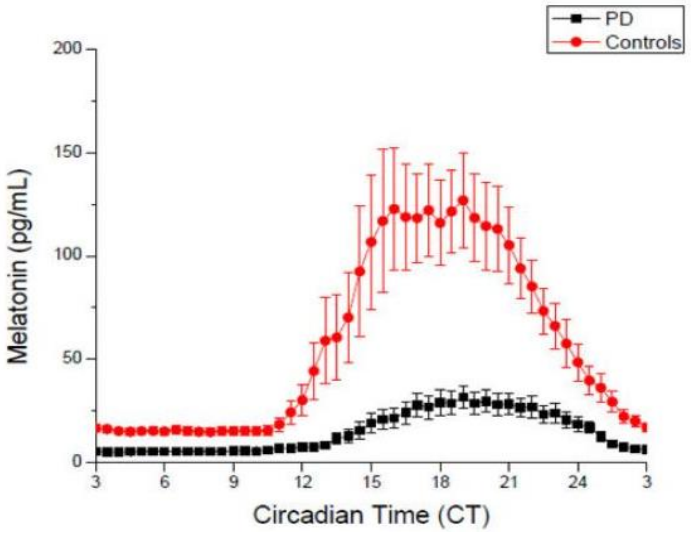
Limitations

- Scoring of REM sleep difficult in PD
  - Multiple arousals
- Subjective interpretation of RWA
  - Can be highly variable
- Limited access to PSG
  - Actigraphy
  - Questionnaires



Melatonin secretion in PD

- Early stage but treated PD & Controls
- Plasma melatonin (every 30 mins)
- No phase differences (advance or delay)
- Lower Area UC



Videnovic et al JAMA Neurol 2014

Contents lists available at ScienceDirect

Sleep Medicine

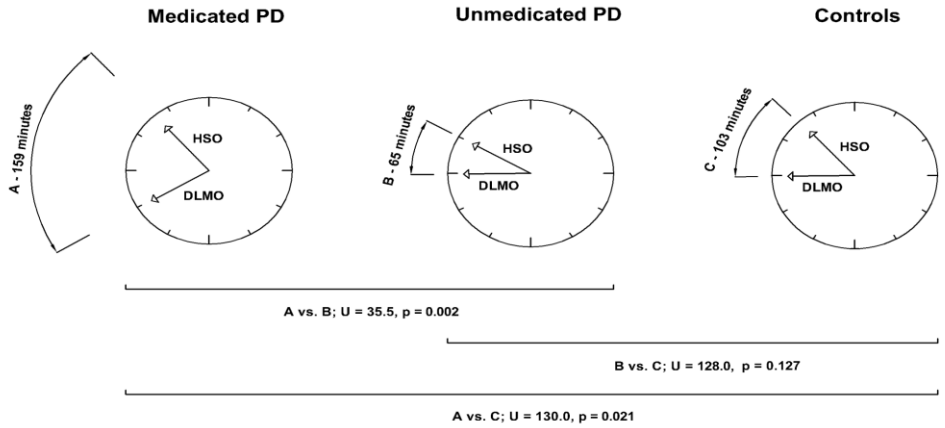
journal homepage: www.elsevier.com/locate/sleep

Original Article

Disturbances in melatonin secretion and circadian sleep–wake regulation in Parkinson disease

S.J. Bolitho [a], S.L. Naismith [b], S.M.W. Rajaratnam [c], R.R. Grunstein [d], J.R. Hodges [e], Z. Terpening [b] N. Rogers [f], S.J.G. Lewis [a,*]

- Does dopaminergic treatment influence circadian disturbance?
- 27 healthy controls
- Patient groups (matched)
  - 13 unmedicated patients
  - 16 medicated patients



How is sleep disordered breathing linked?

Journal of Clinical and Experimental Neuropsychology
2004, Vol. 26, No. 1, pp. 43–54
1380-3395/04/2601-043$16.00

Neurobehavioral Functioning in Obstructive
Sleep Apnea: Di
Hypoxem
S. Naismith[1,2], V. W

Sleep-Disordered Breathing, Hypoxia,
and Risk of Mild
and Dementia in

Kristine Yaffe, MD

Association between Sleep-Disordered
Breathing and Neuropsycl
Performance in Older Adu
Cognitive Impairment

Zoe Terpening[a,*], Simon J.G. Lewis[a], Brendon J. Yee[b,c], R
and Sharon L. Naismith[a]

Featured Article

Sleep characteristics and risk of dementia and Alzheimer's disease:
The Atherosclerosis Risk in Communities Study

Rebe

JAMA Neurology | Original Investigation

Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment
A Systematic Review Meta-analysis

Yue Leng, PhD; Claire T. McEvoy, PhD; Isabel E. Allen, PhD; Kristine Yaffe, MD

Sleep disordered breathing is associated with:

- Cognitive impairment on fronto-subcortical tasks (Naismith et al 2014)
- MCI + dementia 5 years later (Yaffe et al 2011)
- Neuropsychological dysfunction in MCI (Terpening et al 2014)
- Increased dementia risk at 15-year follow-up n=1081, part. Severe OSA (AHI>30) OR = 2.35 (Lutsey et al 2017)
- Meta-analysis, n>4million, SDB 26% more likely to develop cognitive impairment (Leng et al 2017)

How is sleep disordered breathing linked?

Is Obstructive Sleep Apnoea Related to Neuropsychological Function in Healthy Older Adults? A Systematic Review and Meta-Analysis

Neuropsychol Rev
DOI 10.1007/s11065-017-9344-6

Nathan Cross[1,2,3,4,5] · Amit Lampit[1,4] · Jonathon Pye[1,4] · Ronald R. Grunstein[2,5,6] · Nathaniel Marshall[2,5,7] · Sharon L. Naismith[1,3,4,5]

Participants: Healthy participants with a mean age > 50 years.

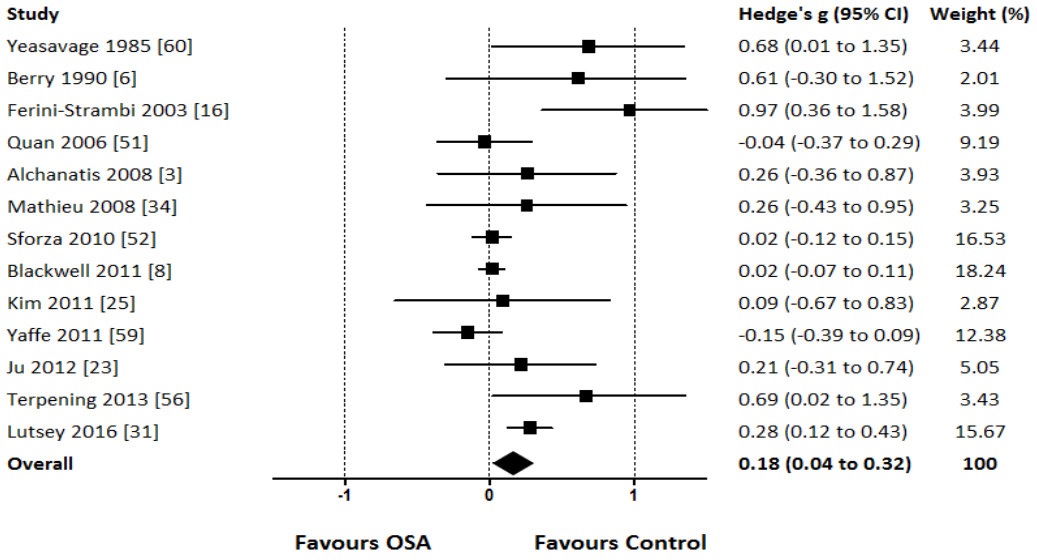
Diagnosis: Only objectively defined OSA as measured by a validated sleep apnoea diagnostic device.

Comparisons: Matched controls with AHI < 5.

Outcome measures: Scores on standardised neuropsychological tests

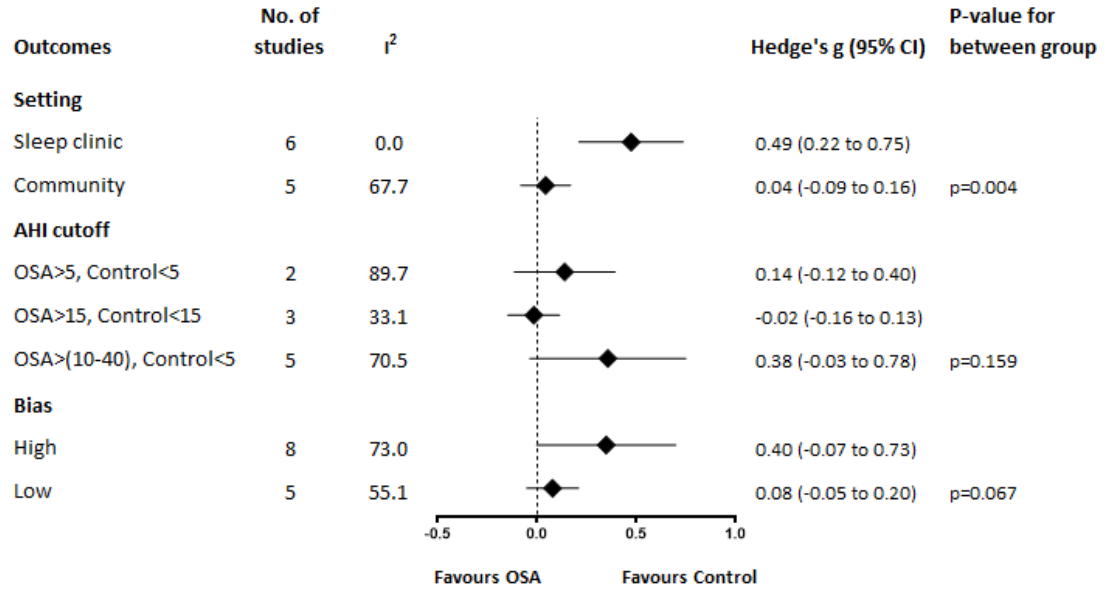
Study design: Cross-sectional or case-control data. Correlations between cognitive outcomes and measure of OSA severity (i.e. AHI) were included.

13 studies



Test for heterogeneity: Q = 29.4, df=12, I^2=69.2 (0.04 to 0.32)
Test for overall random effect: Z=2.25 p=0.009

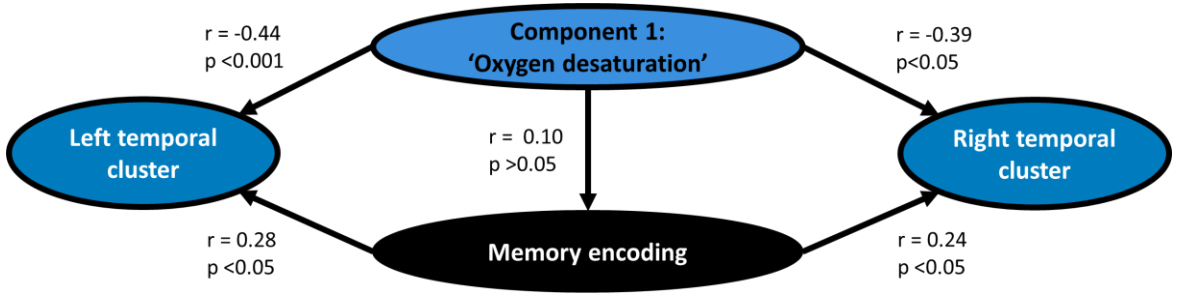
Forest plot of individual mean and weighted effect sizes across all cognitive domains. Effect size estimates are based on a random-effects model.



Subgroup analyses of moderators of the association between neuropsychological performance and OSA. Q-test was performed for between-group heterogeneity, using a mixed effects model.

Oxygen desaturation particularly problematic

Linked with reduced cortical thickness in temporal lobes bilaterally, which in turn is associated with poorer memory

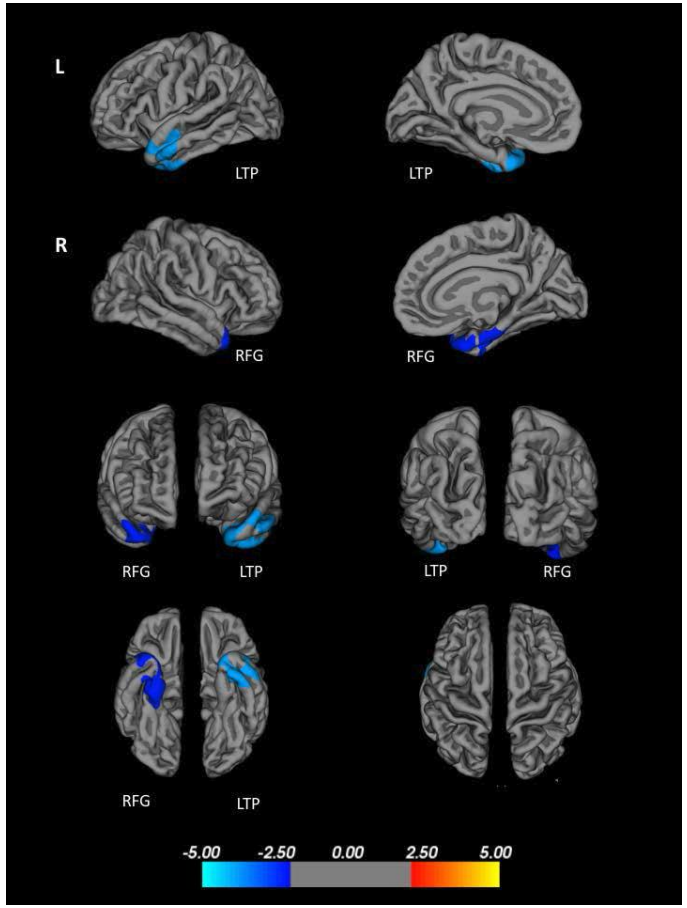


N = 83 'at risk' of dementia

Variables included in analysis	Component	
	'Oxygen desaturation'	'Sleep disturbance'
Apnoea-Hypopnea Index	0.774	0.489
Oxygen Desaturation Index	0.856	0.311
%TST Saturation O_2 below 90%	0.842	0.154
Lowest saturation O_2 (inverted)	0.855	-0.115
Sleep Efficiency (inverted)	0.001	0.768
Awakening Index (n/hr)	0.115	0.780
Arousal Index (n/hr)	0.454	0.734
Variance explained	42.8%	30.1%

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.

Shaded cells represent the variables contributing to each component (loading > 0.5)



Cross et al, Eur R Journal, 2018

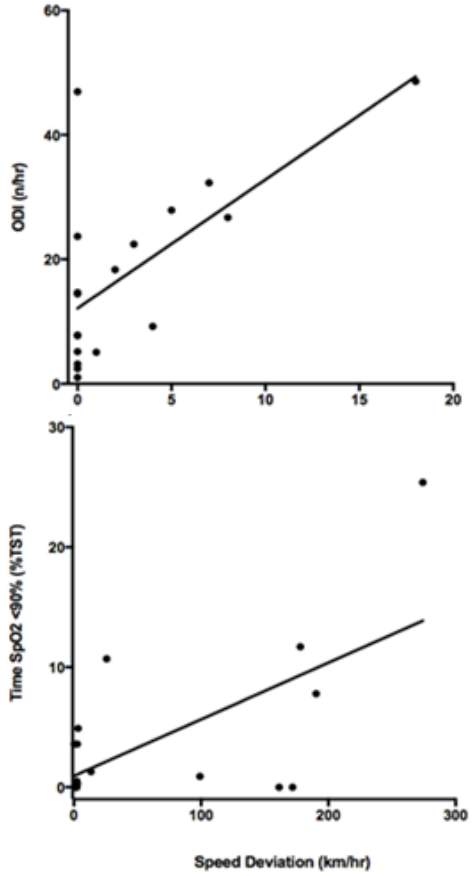
Functional significance

- 19 MCI (50–79; mean 67.8 years)
- 23 Controls (51–78; mean 63.3 years)
- Neuropsychological, medical assessment
- Sleep lab at Brain and Mind Centre
- No difference in demographic or sleep architecture
- AusEd™ driving simulator

Journal of the International Neuropsychological Society (2017), **23**, 1–9.
Copyright © INS. Published by Cambridge University Press, 2017.
doi:10.1017/S1355617717000273

Association between Sleep Disordered Breathing and Nighttime Driving Performance in Mild Cognitive Impairment

Nathan Cross,[1,2,3] Zoe Terpening,[1] Shantel L. Duffy,[1,2,3,4] Simon J.G. Lewis,[1,2,3,5] Ron Grunstein,[2,3,5] Keith Wong,[2,3,5] AND Sharon L. Naismith[1,3,4]



In MCI, driving crashes, steering and speed deviations relate to having oxygen desaturation during sleep

Assessment of sleep disturbances in older people

THE UNIVERSITY OF SYDNEY

Ways to assess sleep

1. Questionnaires and clinical interview

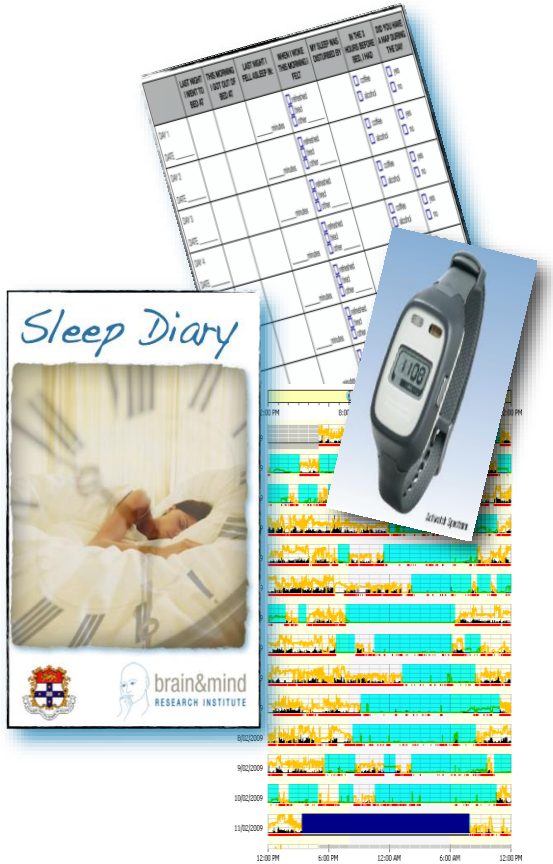
The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

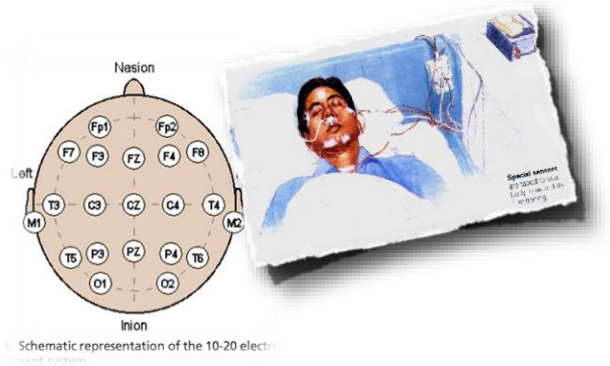
1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

2. Diary and Actigraphy

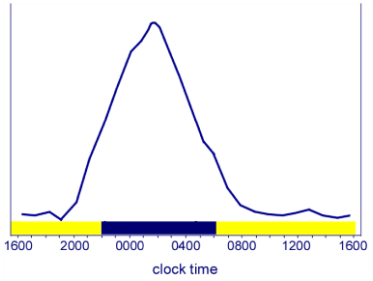


3. PSG



Schematic representation of the 10-20 electr

4. Melatonin



How to assess for sleep disturbance in community dwelling older people

Polysomnography	Sleep efficiency, duration, oxygen desaturation, apnoea-hyopnoea index in REM and Non-REM sleep **Pros: detects sleep disorders undetected by other means** **Cons: costly, waiting lists, artificial envirobment**
Actigraphy, with sleep diary	Sleep latency (from diary), Sleep efficiency (from software), Nighttime behavior (visual), Sleep duration (from software), Circadian rhythmicity (wake time from software and visual inspection), Sleep behaviours (from diary) **Pros: Ecological validity, gives markers of circadian rhythmicity** **Cons: Some specialized knowledge/training to score**
Self-report	Pittsburgh Sleep Quality Index (>5) Insomnia Severity Index (>7) Multivariate Apnoea Index Berlin Questionnaire Epworth Sleepiness Scale **Pros: Quick, easy to administer, clinical cutoffs** **Cons: Sometimes poor correlation with polysomnography, may be hindered by poor recall in those with cognitive impairment, may be linked to depressive symptoms**

Pittsburgh Sleep Quality Index (cognitively intact, ?MCI)

Add items:
Score of ≥5 – sleep disturbance

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 1 9-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ *Global PSQI* _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

Epworth Sleepiness Scale

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Add items:

Score of $\geq$8 ⇢ refer for PSG

Screening for Sleep Apnoea

Berlin Questionnaire

1. Complete the following:

Height: _____ Weight: _____

Age: _____ Gender: ____M ____F

2. Do you snore?
_____Yes
_____No
_____Don't know

If you snore:

3. Your snoring is…
_____ Slightly louder than breathing
_____ As loud as talking
_____ Louder than talking
_____ Very loud, can be heard in adjacent rooms

4. How often do you snore?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

5. Has your snoring ever bothered other people?
_____ Yes
_____ No

6. Has anyone noticed that you quit breathing during your sleep?
_____ Nearly every day.
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

7. How often do you feel tired or fatigued after your sleep?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

8. During your wake time, do you feel tired, fatigued, or not up to par?
_____ Nearly every day
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

9. Have you ever nodded off or fallen asleep while driving a vehicle?
_____ Yes
_____ No
_____ If yes, how often does it occur?
_____ Nearly every day.
_____ 3-4 times a week
_____ 1-2 times a week
_____ 1-2 times a month
_____ never or nearly never

10. Do you have high blood pressure?
_____ Yes
_____ No
_____ Don't know

BMI (Body mass index) = _____

(see next page for scoring instructions)

Scoring the Berlin Questionnaire
The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

Categories and Scoring:

Category 1: items 2, 3, 4, 5, and 6;
Item 2: if '**Yes'**, assign **1 point**
Item 3: if either of the last two options is the response, assign **1 point**
Item 4: if either of the first two options is the response, assign **1 point**
Item 5: if **'Yes'** is the response, assign **1 point**
Item 6: if either of the first two options is the response, assign **2 points**
Add points. Category 1 is positive if the total score is 2 or more points.

Category 2: items 7, 8, and 9.
Item 7: if either of the first two options is the response, assign **1 point**
Item 8: if either of the first two options is the response, assign **1 point**
Item 9: if **'Yes'** is the response, assign **1 point**
Add points. Category 2 is positive if the total score is 2 or more points.

Category 3 is positive if the answer to item 10 is 'Yes' or if the BMI of the patient is greater than 30kg/m2. (BMI is defined as weight (kg) divided by height (m) squared, i.e.., kg/m2).

High Risk: if there are 2 or more categories where the score is positive.
Low Risk: if there is only 1 or no categories where the score is positive.

Additional Question: item 9 should be noted separately.

If 'high risk' refer for sleep study
Others: MAP, STOP, STOP_BANG
Note: not validated for older people with cognitive impairment

Sleep Disorders Inventory

- Frequency, severity and caregiver burden of sleep disturbances 2-weeks prior
- Prevalences of sleep symptoms 3 (waking up during the night thinking its daytime) to 82% (getting up during the night)
- 7 items
- Score = average of frequency ratings x average of severity ratings (range – 12).

The Sleep Disorders Inventory: an instrument for studies of sleep disturbance in persons with Alzheimer's disease

ROCHELLE E. TRACTENBERG[1], CLIFFORD M. SINGER[2], JEFFREY L. CUMMINGS[3], and LEON J. THAL[4]

	Symptom
1	Difficulty falling asleep
2	Getting up during the night (do not count if the subject gets up once or twice per night to go to the bathroom and quickly falls back to sleep)
3	Wandering, pacing or getting involved in inappropriate activities at night
4	Awakening you during the night
5	Awakening at night, dressing, and planning to go out, thinking that it is morning and time to start the day
6	Awakening too early in the morning (earlier than is his/her habit)
7	Sleeping excessively during the day
8	Other night-time behaviors that bother you

Frequency

0: Not present in the last 2 weeks

1: Less than once per week

2: One to two times per week

3: Several times per week but less than every day

4: Once or more per day (every night)

Severity

0: Not present

1: Mild: night-time behaviors occur but are not particularly disruptive

2: Moderate: night-time behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of night-time behavior may be present

3: Marked: night-time behaviors occur; several types of night-time behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed

Caregiver Distress: How emotionally distressing do you find this behavior?

0: Not at all

1: Minimally

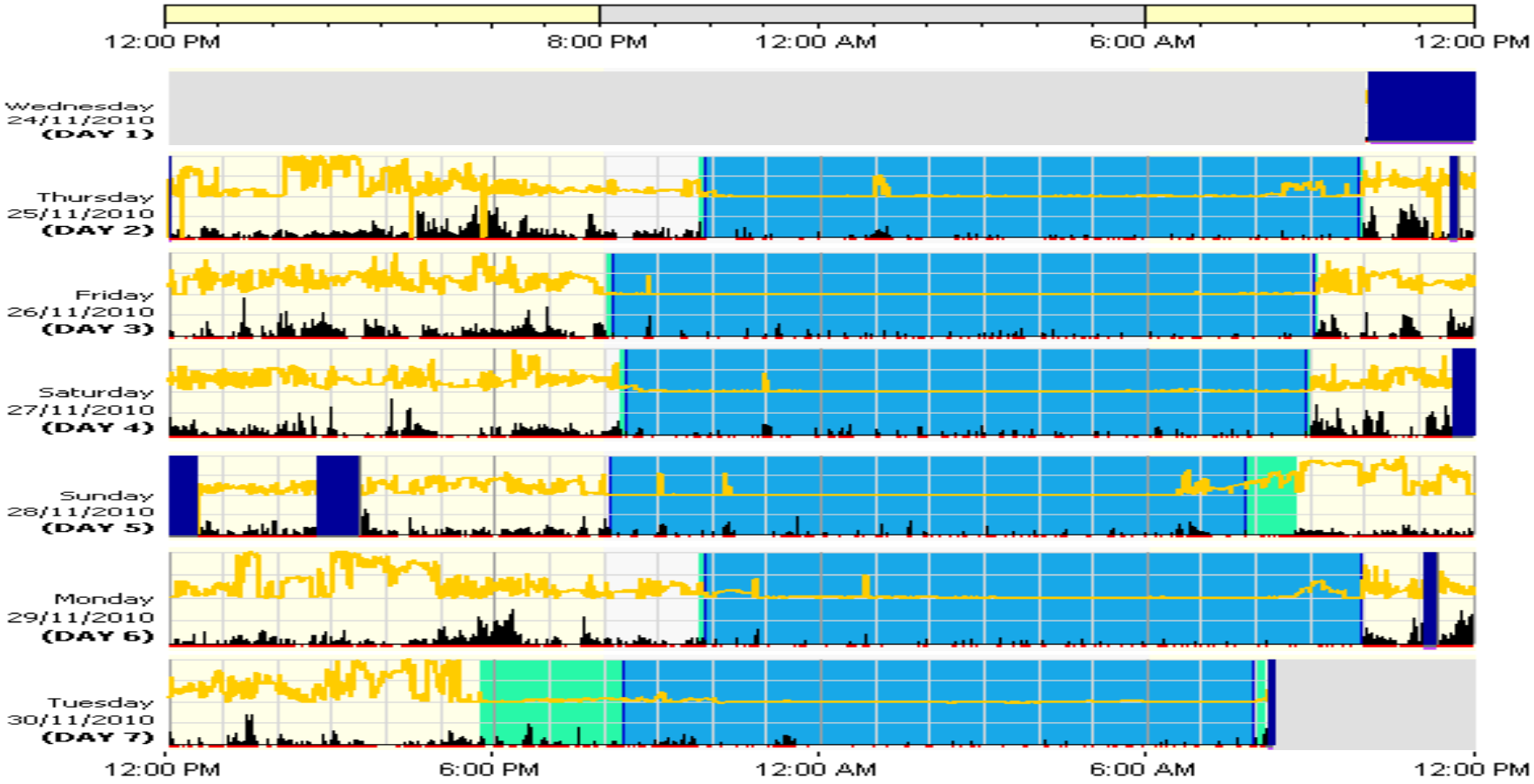
2: Mildly

3: Moderately

4: Severely

5: Very severely/extremely

Actigraphy



1. Look at sleep-wake patterns across 7-14 days
2. Look at activity levels during waking and sleep periods
3. Can detect delayed timing, advanced timing, irregular timing of sleep
4. Sleep onset, wake times, light, daytime naps, getting up at night

Sleep diary

DATE	LAST NIGHT I WENT TO BED AT	THIS MORNING I WOKE UP AT	LAST NIGHT I FELL ASLEEP IN	WHEN I WOKE I FELT	MY SLEEP WAS DISTURBED BY	DID YOU HAVE A NAP YESTERDAY?	IN THE 3 HOURS BEFORE BED, I HAD	DID YOU EXERCISE YESTERDAY?	
								DURATION	INTENSITY (1 - 10)
DAY 1 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 2 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 3 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 4 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 5 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 6 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	
DAY 7 Date:			_____ mins	☐ Refreshed ☐ Tired ☐ _____		_____ am/pm for _____mins _____ am/pm for _____mins	☐ Alcohol ☐ Caffeine	_____ mins _____ mins _____ mins	

REM sleep Behaviour Disorder

- ❑ Vivid dreams?
- ❑ Dreams have an action-packed content?
- ❑ Dream contents match behaviour?
- ❑ Limbs move while sleeping?
- ❑ Hurt/almost hurt bed partner?
- ❑ Speaking/shouting/swearing
- ❑ Kicking/waving/saluting?
- ❑ Things fall down?
- ❑ Awoken by own movements?
- ❑ Remember dream contents well?
- ❑ Disturbed sleep?

Score>5 suggestive of RBD?

The REM Sleep Behavior Disorder Screening Questionnaire—A New Diagnostic Instrument

Movement Disorders
Vol. 22, No. 16, 2007, pp. 2386–2393

Karin Stiasny-Kolster, MD,[1] Geert Mayer, MD,[2] Sylvia Schäfer, MD,[1] Jens Carsten Möller, MD,[1] Monika Heinzel-Gutenbrunner, PhD,[3] and Wolfgang H. Oertel, MD[1]

[1]*Department of Neurology, Center of Nervous Diseases, Philipps-University, Marburg, Germany*
[2]*Department of Neurology, Hephata-Klinik, Schwalmstadt-Treysa, Germany*
[3]*Department of Child and Adolescent Psychiatry and Psychotherapy, Philipps-University, Marburg, Germany*

- Mostly widely used screening questionnaire
- Validated against the current diagnostic guideline
  - 84% sensitivity, 96% specificity

A Single-Question Screen for Rapid Eye Movement Sleep Behavior Disorder: A Multicenter Validation Study

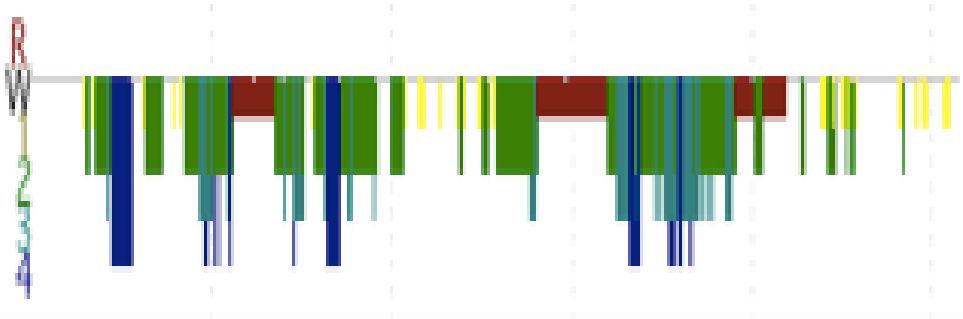
Ronald B. Postuma, MD, MSc,[1,2*] Isabelle Arnulf, MD, PhD,[3] Birgit Hogl, MD,[4] Alex Iranzo, MD,[5] Tomoyuki Miyamoto, MD, PhD,[6] Yves Dauvilliers, MD, PhD,[7] Wolfgang Oertel, MD,[8] Yo-El Ju, MD,[9] Monica Puligheddu, MD,[10] Poul Jennum, MD,[11] Amelie Pelletier, PhD,[1,13] Christina Wolfson, PhD,[12,13] Smaranda Leu-Semenescu, MD,[3] Birgit Frauscher, MD,[4] Masayuki Miyamoto, MD, PhD,[14] Valerie Cochen De Cock, MD, PhD,[7] Marcus M. Unger, MD,[8] Karin Stiasny-Kolster, MD,[8] Maria Livia Fantini, MD, MSc,[10,15] and Jacques Y. Montplaisir, MD, PhD[2,16]

Have you ever been told, or suspected yourself that you seem to 'act out your dreams' while asleep for example, punching, flailing your arms in the air, making running movements?

Movement Disorders, Vol. 27, No. 7, 2012

Compared to current guideline
- 94% sensitivity
- 87% specificity

Polysomnography



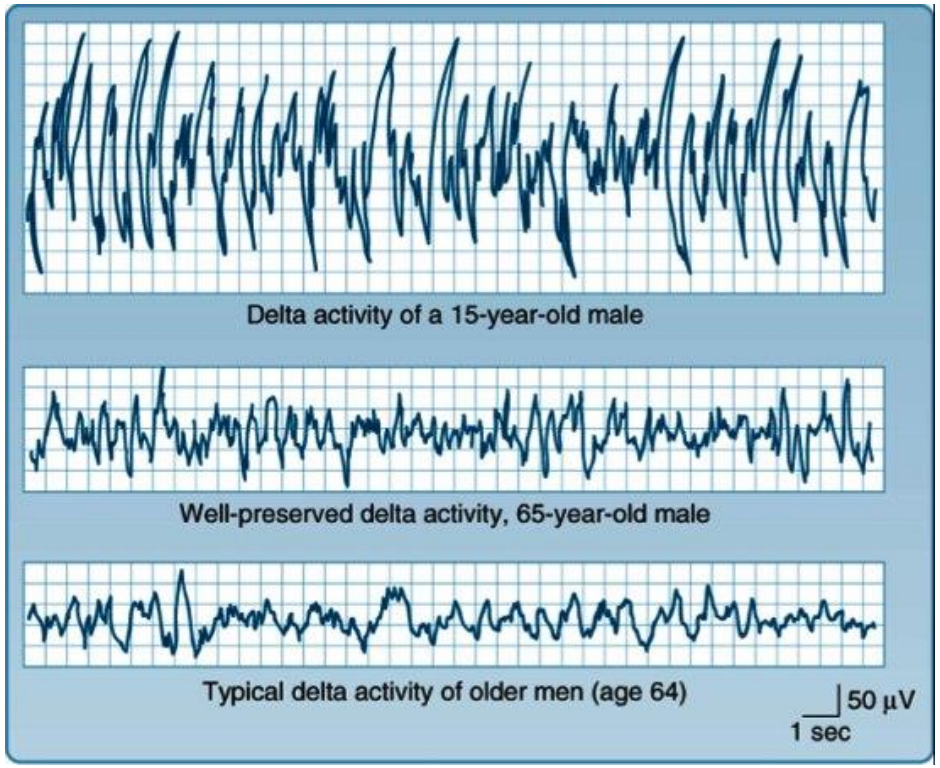
Summary
Sleep Architecture

Total sleep period (min)	= 443.0	Sleep latency (min)	= 4.5
Total sleep time (min)	= 423.5	REM latency (min)	= 86.0
Wake after sleep onset (min)	= 25.0	NREM sleep (min)	= 326.0
Sleep efficiency (%)	= 92.6	REM sleep (min)	= 97.5

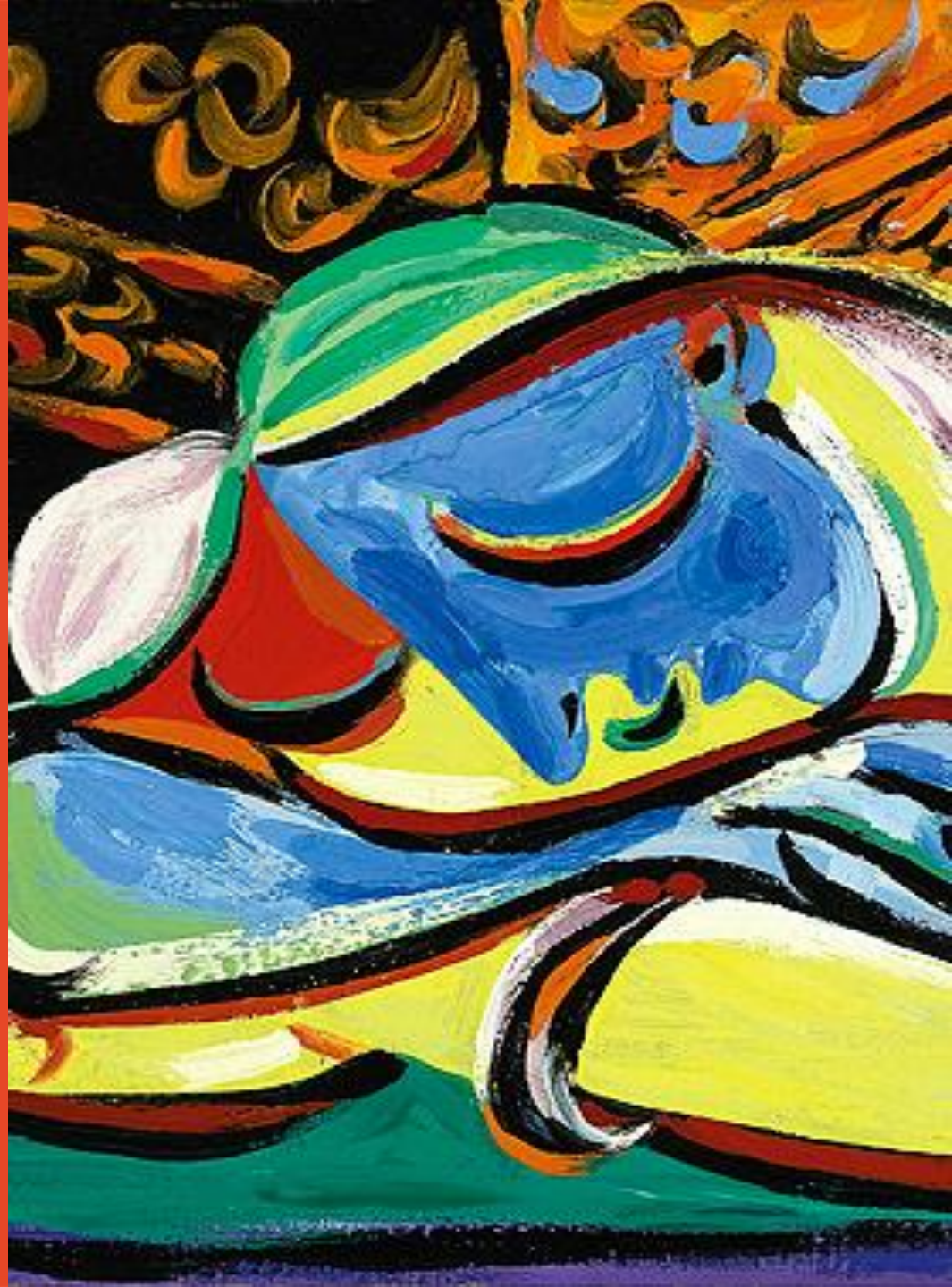
Respiratory*, Movement and arousal events

Total AHI (events/hr)	= 0.7	Total RDI (events/hr)	= 0.7
RERA index	= 0.0	RDI in NREM (events/hr)	= 0.2
RDI in REM (events/hr)	= 2.5		
Minimum SpO_2 during sleep (%)	= 93	ODI (desat/hr)	= 0.7
PLM Index (PLM/hr)	= 0.3	Limb Movement (Movement/hr)	= 6.5
Total arousal index (arousals/hr)	= 6.1	Limb arousal index (arousals/hr)	= 0.1

(*Respiratory events = see page 4 for definition of apneas, hypopneas and RERA)



What treatments are available?



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Things to considering when assessing and considering treatment options for sleep

- **Depression**
- **Sleep disordered breathing**
- Sleep expectations
- Medical conditions
- Medications
- Body mass index
- Sleep apnoea
- Exercise (not enough, wrong times)
- Raised core body temperature
- Lighting
- Nocturia, pain, discomfort
- Alcohol use
- Thyroid, menopause
- Circadian misalignment
- PLMS, Restless legs

Non-drug treatments for sleep in dementia

The management of sleep disorders in dementia: an update.
Kinnunen, Kirsi; Vikhanova, Anastasia; Livingston, Gill

Current Opinion in Psychiatry. 30(6):491-497, November 2017.
DOI: 10.1097/YCO.0000000000000370

Table 1. Results of trials testing nonpharmacological treatments

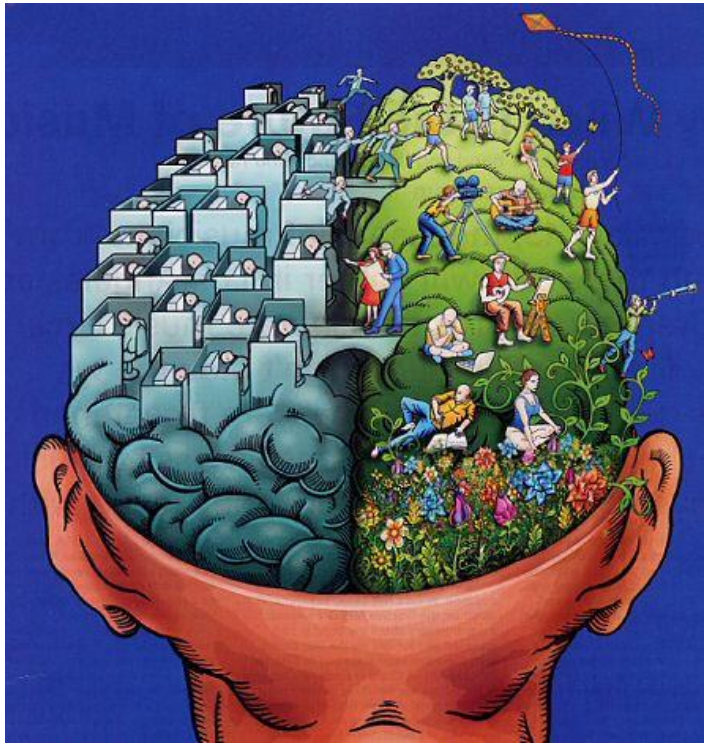
Study	Strategy	Control group	Participants	Outcomes
Gibson *et al.* [17]	Mixed (light therapy, exercise, sleep education)	None	Fifteen community-dwelling dyads of carers and people with dementia	40% Dropout Six participants improved
Tewary *et al.* [18]	Sleep education program for caregivers	None	Fourteen people with dementia (and carers)	50% Dropout Improved sleep problems
Sekiguchi *et al.* [19]	Bright light therapy 1 h daily for 2 weeks	None	Seventeen people with dementia (people with Alzheimer's disease, 8; people with vascular dementia, 4; DLB, 5)	Improved sleep disturbance in 4/17 mild-to-moderate patients with Alzheimer's disease
Lai *et al.* [20]	Music with movement	Not applicable	Results not available	Not known
Krolak-Salmon *et al.* [21]	Multidisciplinary team intervention	None	424 people with dementia	Overall neuropsychiatric symptoms reduced in 329 people with data
Lazarou *et al.* [22]	Smart home/assistive technology	None	Four people with dementia	Improved sleep
Kodama *et al.* [23]	Physical activity reference values for a good sleep–wake pattern	None	117 older community-dwelling participants; 52 with dementia	51–55 min activity per day needed

DLB, people with dementia with Lewy bodies.

Studies: 2015-2017

Brief behavioural therapy for cognitively intact older adults

- 4 sessions of (brief behavior therapy for insomnia) BBTi vs. self-monitoring control
- Improvements in sleep onset latency, wake after sleep onset, sleep efficiency, sleep quality, post-treatment and at 3-months follow-up
- Mood improvements in both groups
- No cognitive improvements on neuropsychological measures



McCrae et al, 2018

Cognitive Behaviour Therapy for MCI: "Sleep-well, think well" CBTi

- 8-week (4 session) pilot group intervention for MCI
  - 16 active treatment, 12 received information only
- Large effect size improvements:
  - Self-reported sleep quality, daytime sleepiness
  - Small to moderate (but non-significant) improvements in actigraphy (WASO, efficiency) and executive functioning.

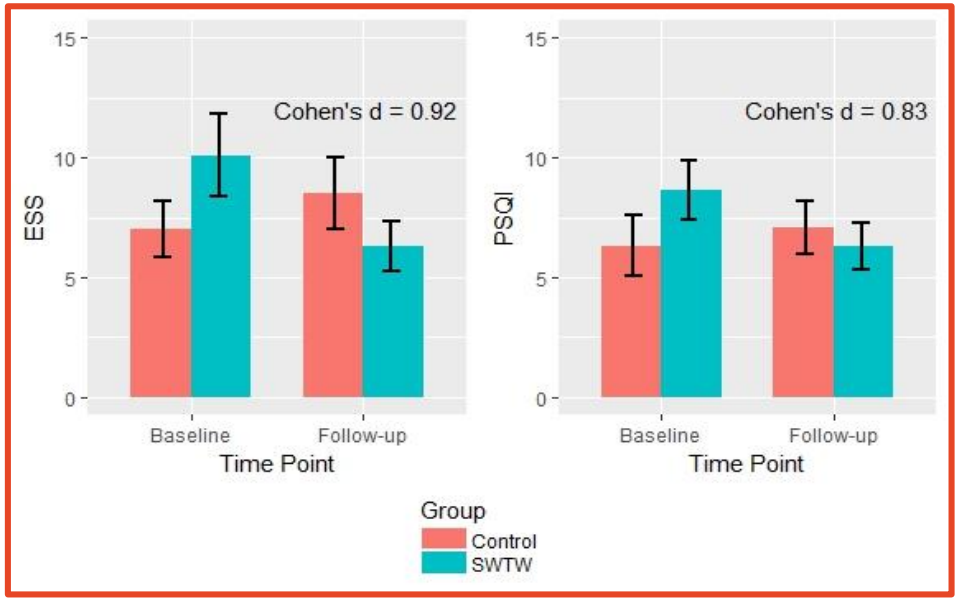


Table 1
Original SRT method as described by Spielman et al. (1987) [1].

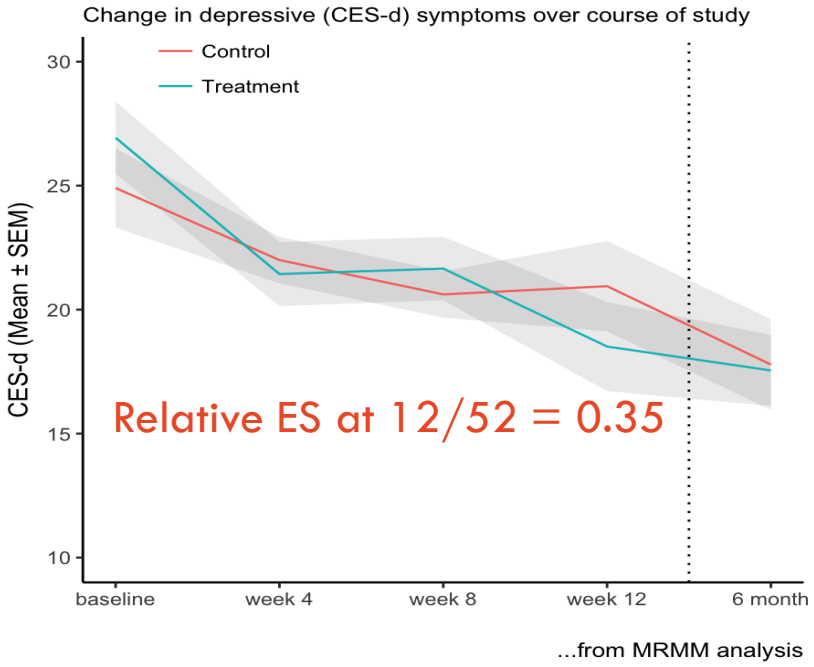
Sleep window generation:	Average TST based on two week sleep diary
Minimum TIB:	Minimum TST not less than 4.5 h
Sleep window position:	Fixed rise-time to suit daytime schedule
Sleep efficiency criterion:	≥90% over five days increase TIB by 15 min; <85% over five days decrease TIB by 15 min; no TIB change if 85–89.
Daytime sleep:	Napping prohibited

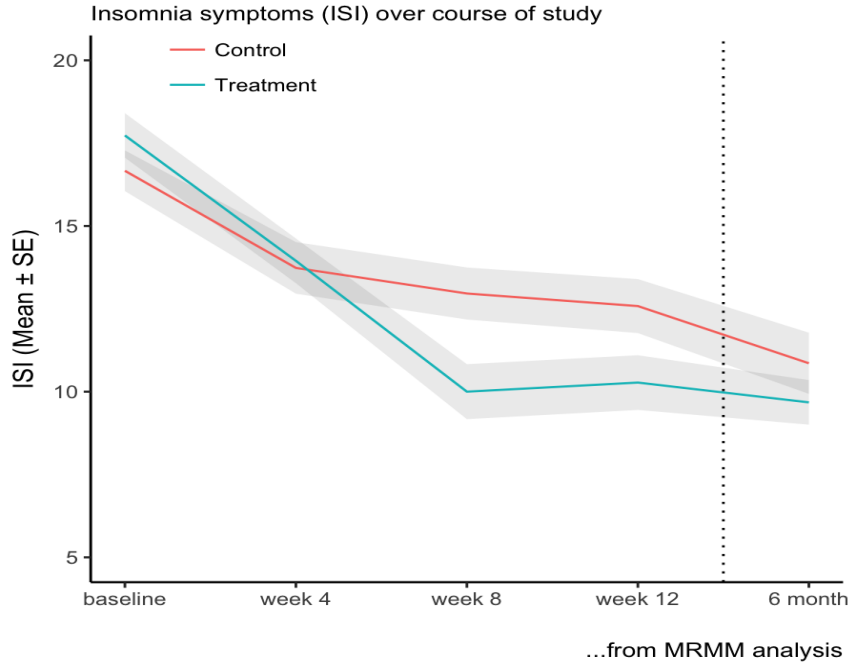
TST = total sleep time; TIB = time-in-bed.

Naismith, Pye, Terpening, Lewis, Bartlett, in press

eCBTi in older men with depression - SOMI

- RCT, n = 87 males, MDD





group X time difference in the MMRM analysis p=0.15
mean difference PHQ-9 4.3 (95% CI -1.2 to 9.8)

Glozier et al in press, ANZJP

Sleep interventions for carers

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doi: 10.1017/S1041610218000753

DREAMS-START (Dementia RElAted Manual for Sleep; STrAtegies for RelaTives) for people with dementia and sleep disturbances: a single-blind feasibility and acceptability randomized controlled trial

Gill Livingston,[1,2] Julie A. Barber,[3] Kirsi M. Kinnunen,[1] Lucy Webster,[1] Simon D. Kyle,[4] Claudia Cooper,[1,2] Colin A. Espie,[4] Brendan Hallam,[1] Rossana Horsley,[5] James Pickett[6] and Penny Rapaport[1]

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[6] *Alzheimer's Society, London, UK*

ABSTRACT

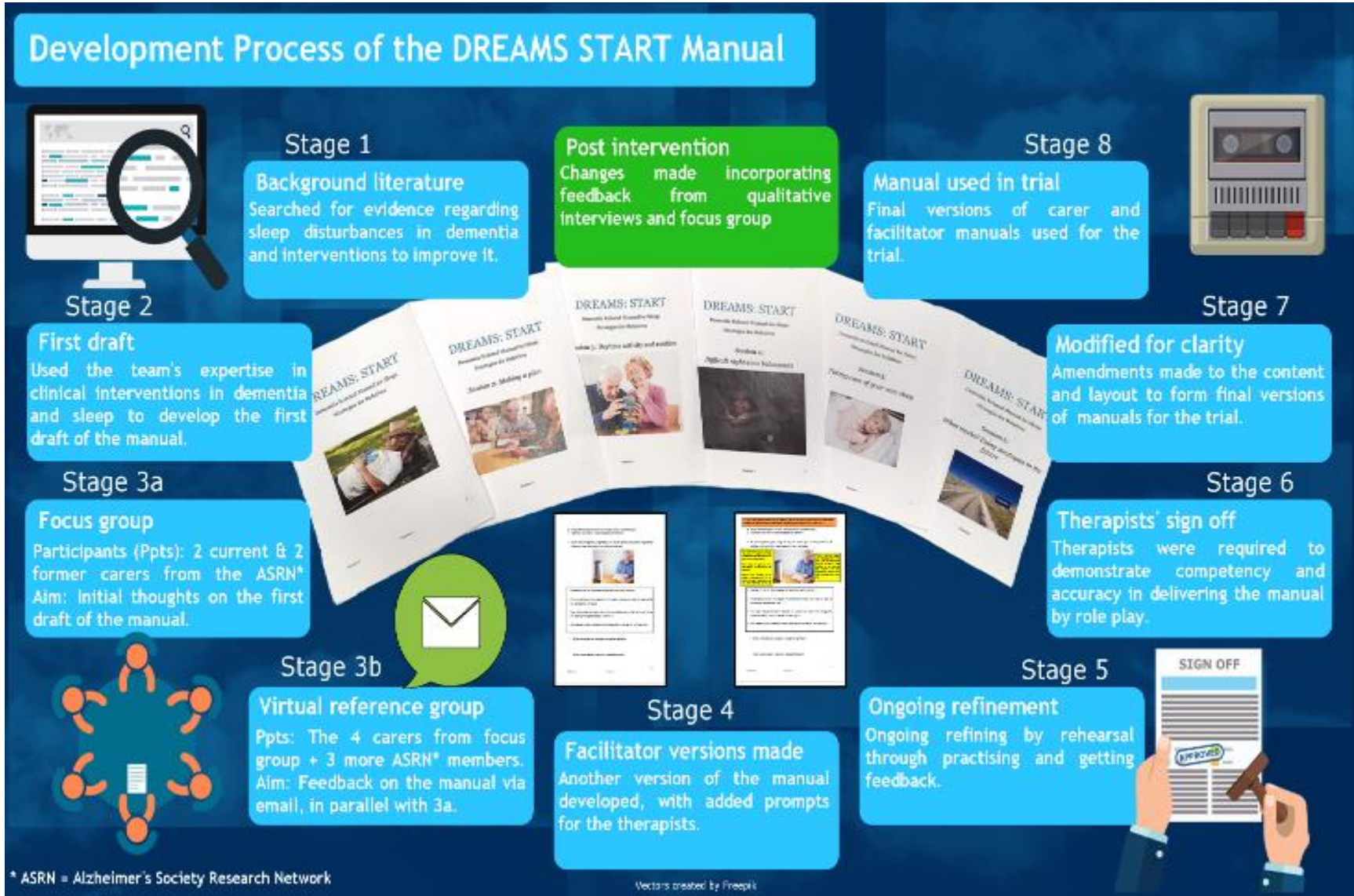
Background: 40% of people with dementia have disturbed sleep but there are currently no known effective treatments. Studies of sleep hygiene and light therapy have not been powered to indicate feasibility and acceptability and have shown 40–50% retention. We tested the feasibility and acceptability of a six-session manualized evidence-based non-pharmacological therapy; Dementia RElAted Manual for Sleep; STrAtegies for RelaTives (DREAMS-START) for sleep disturbance in people with dementia.

Methods: We conducted a parallel, two-armed, single-blind randomized trial and randomized 2:1 to intervention: Treatment as Usual. Eligible participants had dementia and sleep disturbances (scoring ≥4 on one Sleep Disorders Inventory item) and a family carer and were recruited from two London memory services and Join Dementia Research. Participants wore an actiwatch for two weeks pre-randomization. Trained, clinically supervised psychology graduates delivered DREAMS-START to carers randomized to intervention; covering Understanding sleep and dementia; Making a plan (incorporating actiwatch information, light exposure using a light box); Daytime activity and routine; Difficult night-time behaviors; Taking care of your own (carer's) sleep; and What works? Strategies for the future. Carers kept their manual, light box, and relaxation recordings post-intervention. Outcome assessment was masked to allocation. The co-primary outcomes were feasibility (≥50% eligible people consenting to the study) and acceptability (≥75% of intervention group attending ≥4 intervention sessions).

Results: In total, 63out of 95 (66%; 95% CI: 56–76%) eligible referrals consented between 04/08/2016 and 24/03/2017; 62 (65%; 95% CI: 55–75%) were randomized, and 37 out of 42 (88%; 95% CI: 75–96%) adhered to the intervention.

Conclusions: DREAM-START for sleep disorders in dementia is feasible and acceptable.

6 session DREAMS-START (Dementia RElAted Manual for Sleep; STrAtegies for RelaTives)



Sleep disturbing psychotropic medications

Drug Interventions	
Cholinesterase Inhibitors (e.g. Aricept)	Benefits to REM sleep, some studies, Donepezil – more Stage 2 and less Stage 1 sleep
	Can cause insomnia, disturbing dreams, REM Sleep Behaviour Dis.
	No studies examine effects on memory, but beneficial effects in healthy or young samples
Antidepressants (e.g. Zoloft)	May suppress REM, insomnia
Antipsychotics (e.g. Seroquel)	May exacerbate sleep-wake disturbance in AD
Sedative hypnotics (e.g. Stillnox)	Less disruption to sleep architecture No known data on cognitive effects
Benzodiazepines (e.g. Valium)	Decrease SWS & REM, reduce latency & awakenings
	Associated with EDS, falls, cognitive side-effects, confusion, Short-term use only
	Clonazepam often effective for REM Sleep Behaviour Disorder

Naismith, Rogers, Lewis 2010; Cooke et al, 2006

Other sleep disturbing medications

	Example of use
Diuretics	Blood pressure, glaucoma
Anticholinergics	COPD
Antihypertensives	High blood pressure
Corticosteroids (Prednisone)	Rheumatoid arthritis
H2 blockers (Zantac, Tagamet)	Gastroesophageal reflux or peptic ulcers
Levodopa, dopamine agonists	Parkinson's disease
Adrenergic drugs	For life threatening events – e.g. asthma, cardiac arrest

Benzos do not seem to help sleep in AD..

REVIEW

Use of Benzodiazepines in Alzheimer's Disease: A Systematic Review of Literature

Michaela Defrancesco, MD, PhD, MSc; Josef Marksteiner, MD; W. Wolfgang Fleischhacker, MD; Imrich Blasko, MD, MSc

Memory Clinic (Dr Defrancesco), and Division of General and Social Psychiatry (Drs Fleischhacker and Blasko), Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Innsbruck, Austria; Department of Psychiatry and Psychotherapy A, Landeskrankenhaus Hall, Hall, Austria (Dr Marksteiner); Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Innsbruck, Austria (Dr Fleischhacker).

Correspondence: Michaela Defrancesco, MD, PhD, MSc, Department of Psychiatry and Psychotherapy, Division of General and Social Psychiatry, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria (Michaela.Defrancesco@i-med.ac.at).

Abstract

Background: Benzodiazepines are frequently prescribed in patients with Alzheimer's disease. Unfortunately, studies evaluating their benefits and risks in these patients are limited.

Methods: Clinical trials focusing on the effect of benzodiazepines on cognitive functions, disease progression, behavioral symptoms, sleep disturbances, and the general frequency of benzodiazepine use were included in this review. Published articles from January 1983 to January 2015 were identified using specific search terms in MEDLINE and PubMed Library according to the recommendations of The Strengthening the Reporting of Observational Studies in Epidemiology initiative.

Results: Of the 657 articles found, 18 articles met predefined selection criteria and were included in this review (8 on frequency, 5 on cognitive functions, 5 on behavioral and sleep disturbances). The frequency of benzodiazepine use ranged from 8.5% to 20%. Five studies reported accelerated cognitive deterioration in association with benzodiazepine use. Two studies reported clinical efficacy for lorazepam and alprazolam to reduce agitation in Alzheimer's disease patients. No evidence was found for an improvement of sleep quality using benzodiazepines.

Conclusion: This systematic review shows a relatively high prevalence of benzodiazepine use but limited evidence for clinical efficacy in Alzheimer's disease patients. However, there is a paucity of methodologically high quality controlled clinical trials. Our results underscore a need for randomized controlled trials in this area.

International Journal of Neuropsychopharmcology, 2015

Drug treatments for dementia

- "A Cochrane review on pharmacotherapies: No definitive randomised controlled trial (RCT) evidence of improvements in actigraphy measures for melatonin, trazodone or ramelteon. Trazodone 50mg at night showed some potential for increased nocturnal sleep time and sleep efficiency in Alzheimer's disease, but confirmation awaits a larger trial. Notably, no RCTs were found of medications such as hypnotics that are widely prescribed for sleep problems in dementia"

Study	Treatment	Control group	Participants	Outcomes
Wang *et al.* [28]	Melatonin	Placebo-controlled randomised trials (meta-analysis)	453 with dementia (305 with Alzheimer's disease; 287 with primary outcome)	Negative primary outcome sleep efficiency ($N = 287$), but improved nocturnal sleep time ($N = 305$)
Macías Saint-Gerons *et al.* [29]	Trazodone	Naturalistic study of Spanish population	11 766 individuals aged over 65 years	Increased use of trazodone for dementia and sleep problems
Iaboni *et al.* [30]	Dispensing of drugs with sedative properties (benzodiazepines, trazodone, quetiapine)	Naturalistic study of Canadian population	1 181 469–1 603 809 individuals Aged over 66 years with drug benefit 2002–2013	Increased use of trazodone and decreased use of benzodiazepines over time, especially in those with dementia
Scoralick *et al.* [31]	Mirtazapine, 15 mg	Placebo-controlled randomised trial	24 with Alzheimer's disease	Increased daytime sleepiness Did not increase sleep efficiency or nocturnal sleep time
Leonpacher *et al.* [32▪]	Citalopram, 30 mg (secondary analysis)	Placebo-controlled randomised trial	186 with Alzheimer's disease	Increase in the severity of sleep disturbances in those with these present at week 9
Altınyazar *et al.* [33]	Agomelatine, 25 mg	No control, case study	A 91-year-old woman with Alzheimer's disease	Improved both insomnia and depression
Kazui *et al.* [34]	Donepezil, 5 mg	24 healthy controls	16 DLB (8 with sleep disturbances at baseline)	Inconclusive but tendency towards decreased sleep disturbances in DLB at 14 weeks
Ishikawa *et al.* [35]	Memantine, 20 mg	None	12 with Alzheimer's disease	Improved sleep and was well tolerated

DLB, people with dementia with Lewy bodies.

The management of sleep disorders in dementia: an update.
Kinnunen, Kirsi; Vikhanova, Anastasia; Livingston, Gill

Current Opinion in Psychiatry. 30(6):491-497, November 2017.
DOI: 10.1097/YCO.0000000000000370

Light therapy

- General principles:
  - Evening exposure delays sleep
  - Morning exposure advances sleep
  - Magnitude of circadian shifts depends on intensity and duration - brighter and longer duration produces larger shifts
  - Short wavelength light (blue light) has greatest effects
- Efficacy:
  - Reduction in nighttime awakenings in dementia
  - Benefits best for morning light and if sleep complaints (latency, efficiency, awakenings, total sleep time)
  - May have broader effects on cognition and mood in AD
  - Combination of light and melatonin may have superior effects

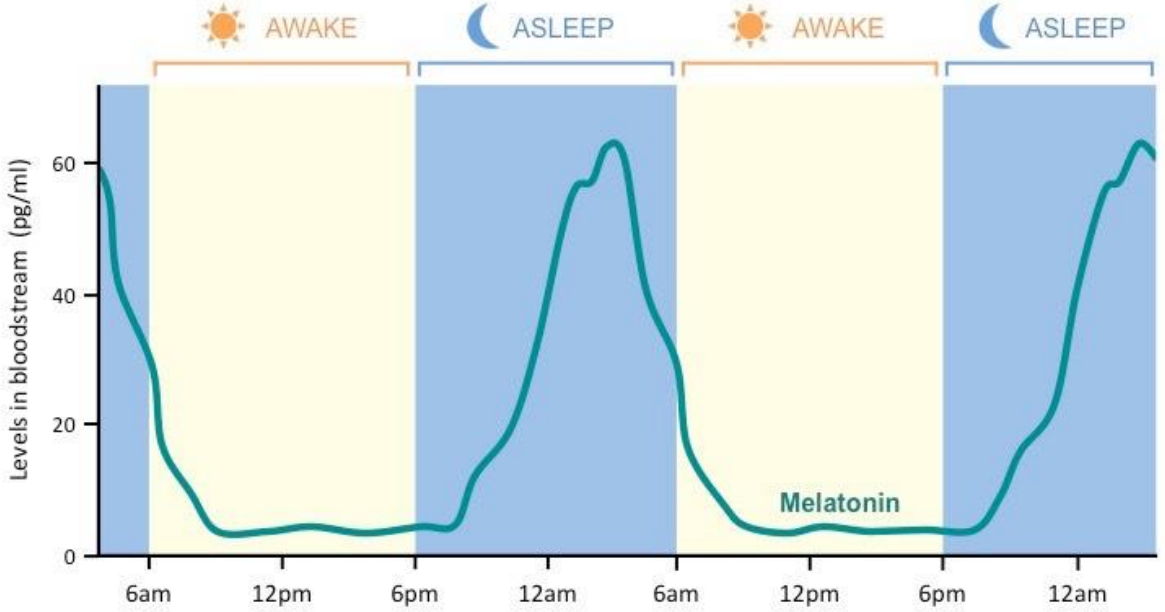
Studies of light therapy

- Healthy older people:
  - *Munch et al: 2011: n = 10 older individuals*
  - 2-hours of blue-enriched polychromatic light per day over 13 days delayed circadian timing by nearly 2-hours
- Nursing home residents:
  - *Alessi: RCT, n = 118 nursing home residents*
    - >30minutes exposure to sunlight (10,000lx)
    - Decreased daytime sleep and less nocturnal awakenings, increase in social activities
- People with dementia:
  - *Riemersma RCT: n = 189 residents, most of whom had dementia*
  - 4-weeks bright light (1000lx) all day (09:00-18:00) *vs.* dim (300lx) light. 19% reduction in depressive symptoms, 53% improvement in functioning and 5% improvements in cognition similar to found with cholinesterase inhibitors.

See review by Hanford and Figueiro, 2013

Melatonin

- Chronobiotic
- A powerful antioxidant & free radical scavenger
- Helps to clear harmful reactive oxygen species and reduce oxidative stress levels in brain tissue, as well as beta-amyloid in animal studies

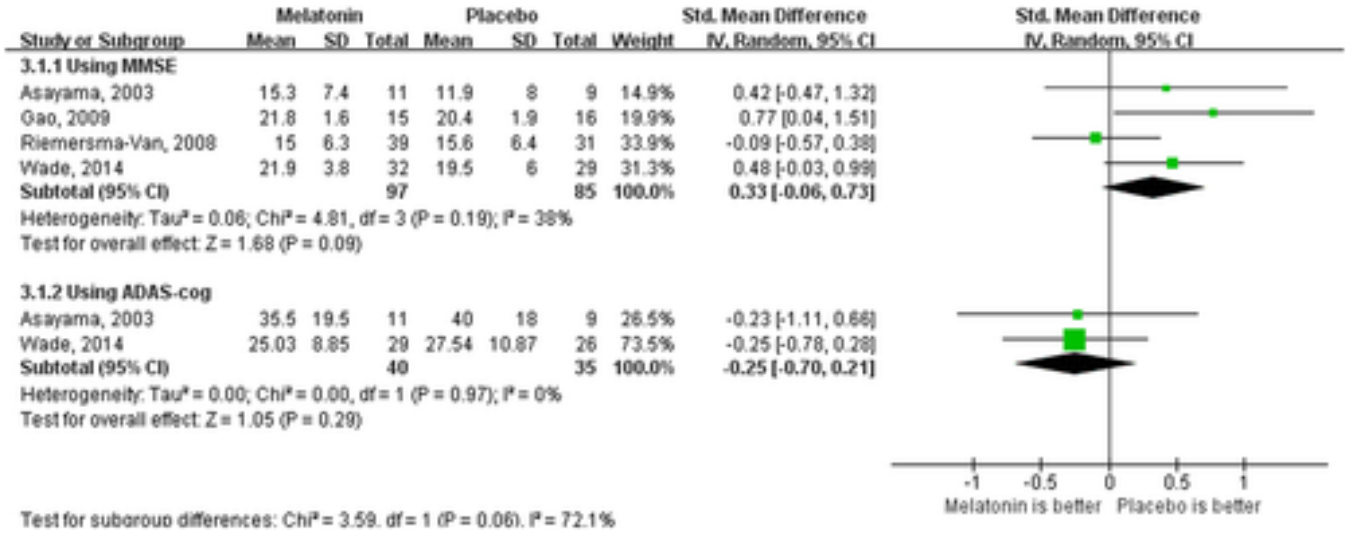


- **6 melatonin administration studies in MCI**
  - 5 double-blind, 1 open-label retrospective (n=651)
  - Doses: 1-9mg administered evening or bedtime
  - Duration 10 days to 3.5 years
  - Improvements in sleep quality and cognition, including psychomotor speed, set-shifting, memory

Cardinali et al, 2010; Dowling et al, 2008; Riemersma et al, 2007

Meta-analysis of melatonin trials in AD

- 7 studies (n = 462), duration 10 days to 24 weeks.
- AD subjects receiving melatonin treatment showed prolonged total sleep time at night (n = 305; SMD: 0.26).
- No improvements in cognition (MMSE or ADAS-Cog).
- The discontinuation rate was similar between the melatonin and placebo groups



Wang et al. Int J Ger Psychiatry, 2016

Treatment for REM Sleep Behaviour Disorder in PD

Melatonin 3-12mg at bedtime

- REM sleep most strongly regulated or modulated by the circadian timing system
- 31/38 patients reported improvements: 1 case report, 2 open-label prospective case series (iRBD), 2 retrospective case series
- Successfully treated patients include DLB, PD and MSA, Memory problems, sleep-disordered breathing
- Side effects - headache, sleepiness (AM), delusions/hallucinations
- Follow-up: effective and safe 2y

Clonazepam 0.25mg to 2mg, 30 minutes at bedtime

- Long acting benzodiazepine
  - Elimination half-life of 30-40 hours
- Partial or full response >80 %
- Adverse events: daytime sleepiness, confusion, cognitive
- Relative contraindications: sleep apnoea, dementia, falls history

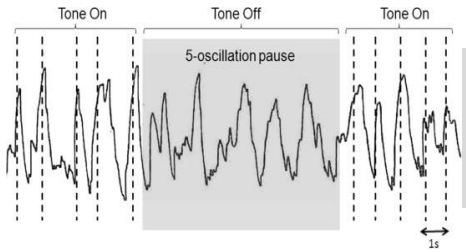
Anderson & Shneerson 2009; Boeve et al 2003; Olson et al 2000, Schenck et al 1993, Sforza et al 1997

Managing Sleep Fragmentation in Parkinson's Disease

- Nocturia
  - Voiding ≥2 times per night
  - >60% of patients
- Depression
- Avoid alerting events
  - Computer, i-pad, phone (blue light)
- Non-pharmacological
- PD medications
  - Selegiline, Amantadine, Anticholinergic therapy
- Non-PD medications
  - Alpha-blockers (Reduced REM sleep)
  - Beta-blockers (Inhibit Melatonin secretion)
  - Corticosteroids (Cortisol stimulation)
- Uncontrolled motor symptoms, pain, wearing off

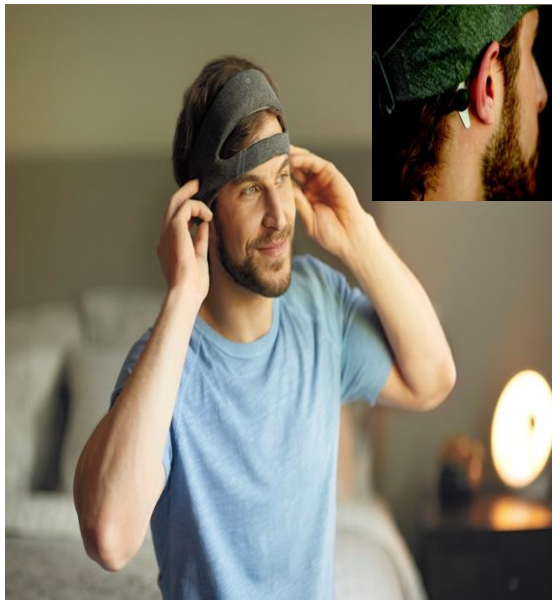
The future..

Sound waves to improve sleep



Increase slow waves

Sleep quality not quantity



PHILIPS

Slide courtesy of A/Prof Chris Gordon, Sydney Nursing School

Top ten sleep tips for patients

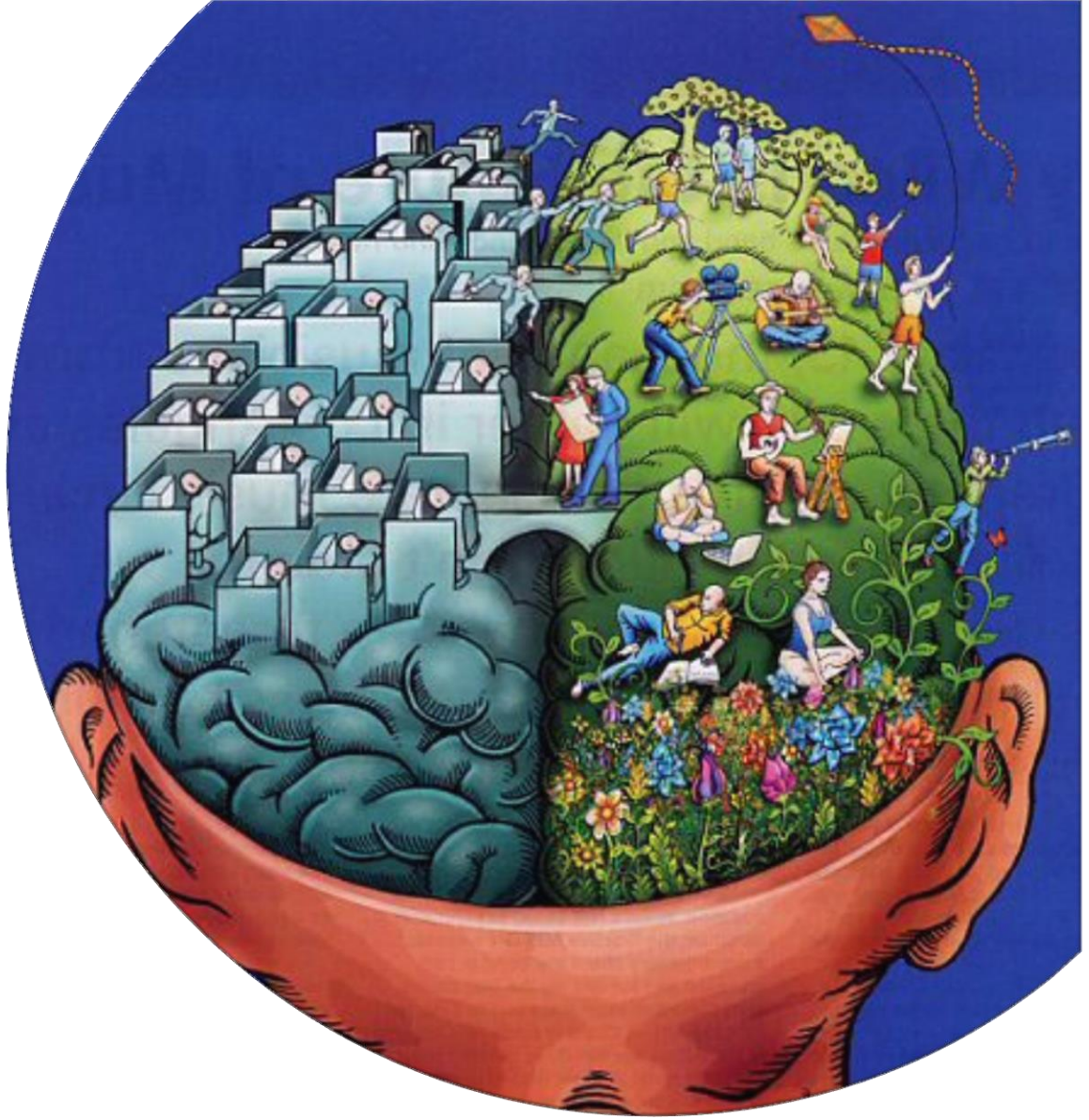
THE UNIVERSITY OF SYDNEY

1. Mind your mind: depression

Depression is one of the biggest predictors of poor sleep quality

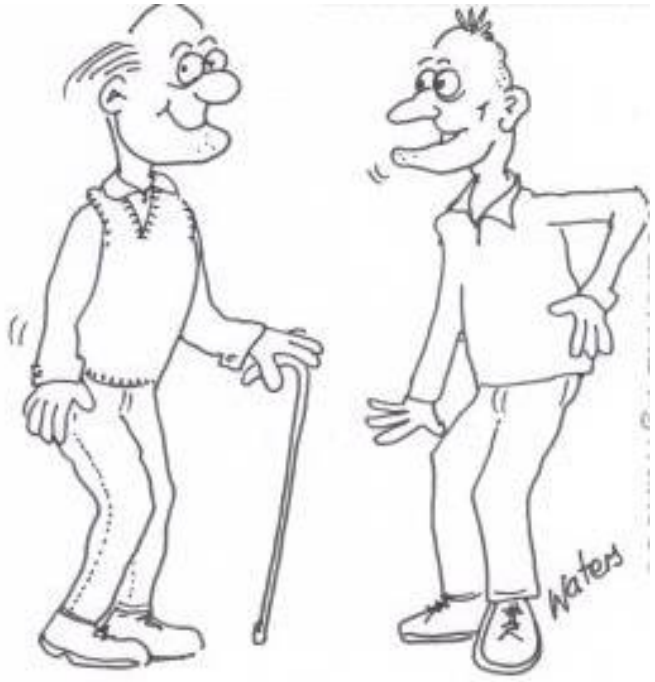
Depression may even be linked to the onset and recurrence of sleep disorders

Need to deal with both sleep and mood problems not just one



2. Mind your mind: stress and anxiety

- Some anxiety is useful
- Too much is unhelpful
- Have "worry time" before bed
  - Write down those worries on paper
  - Place them in a worry box (container)
  - Check them out in the morning
- Were they worth worrying about at night?



"When you get older everything hurts. and what doesen't hurt doesn't work!

- Mindfulness and relaxation techniques (e.g. progressive muscle relaxation, yoga) can help

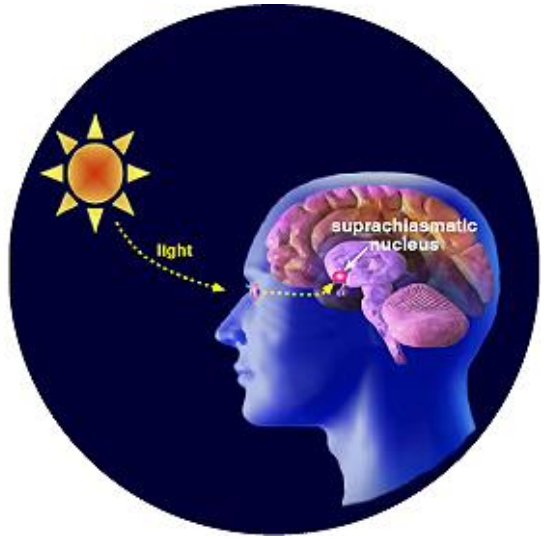
3. Keep physically active

- Increases deep sleep
- Reduces light sleep
- Improves circadian rhythms
- Reduces sleep fragmentation
- Optimal results if in morning or early afternoon
- Reduces time to fall asleep particularly with aerobic exercise
- Resistance training also beneficial
- Try not to do vigorous exercise too close to bedtime

4. Keep cognitively active

- There is a strong link between cognitive decline and sleep problems
- Emerging evidence that cognitive training can improve sleep
- Cognitive activity in the hours prior to sleep can also increase deep sleep stages

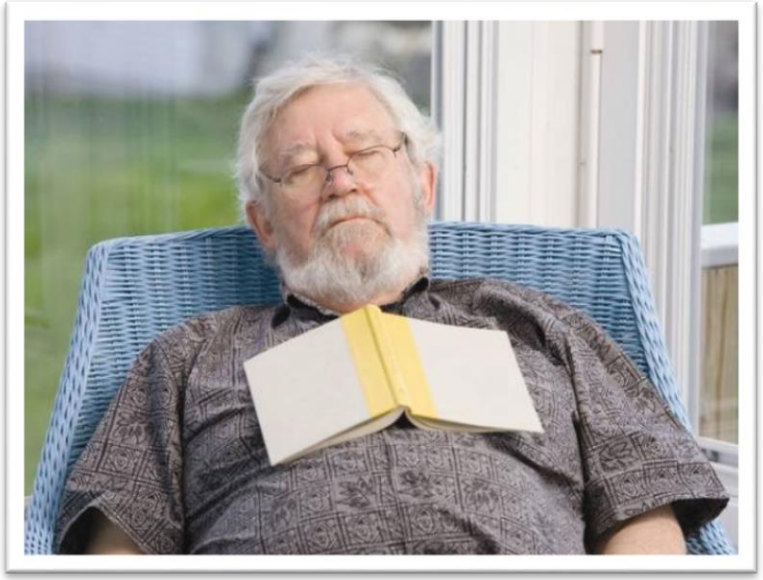
5. Keep your body clock ticking in time..



- Behaviours
  - Get up at the same time everyday
  - Avoid heavy meals prior to bedtime
  - Avoid raising body temperature at night
    - hot baths, heavy exercise
- Light
  - Light bright in morning and dim at night
  - Consider bright light therapy
    - Evening light = delayed sleep
    - Morning light = advances sleep
  - Blue light has greatest effects
- Melatonin, prescribed by GP
  - A powerful antioxidant & free radical scavenger
  - Helps sleep to occur within 2 hours

6. Use Naps wisely

- Prescribed ‘controlled napping’
  - Duration is important!
  - Nap less than 30minutes
  - Nap earlier in day, not in evening
  - Counts in your total sleep count



- May improve alertness, cognition, mood
- Can be associated with sleep inertia (feeling ‘groggy’) if nap for too long
- Consider effects on night-time sleep

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Napping in older people ‘at risk’ of dementia: relationships with depression, cognition, medical burden and sleep quality

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Keywords
ageing, cognitive decline, mood disorder, morbidity, nap, objective sleep quality

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SUMMARY
Sleep disturbance is prevalent in older adults, particularly so in those at a greater risk of dementia. However, so far the clinical, medical and neuropsychological correlates of daytime sleep have not been examined. The aims of this study were to investigate the characteristics and effects of napping using actigraphy in older people, particularly in those ‘at risk’ of dementia. The study used actigraphy and sleep diaries to measure napping habits in 133 older adults ‘at risk’ of dementia (mean age = 65.5 years, SD = 8.4 years), who also underwent comprehensive medical, psychiatric and neuropsychological assessment. When defined by actigraphy, napping was present in 83.5% (111/133) of participants; however, duration and timing varied significantly among subjects. Nappers had significantly greater medical burden and body mass index, and higher rates of mild cognitive impairment. Longer and more frequent naps were associated with poorer cognitive functioning, as well as higher levels of depressive symptoms, while the timing of naps was associated with poorer nocturnal sleep quality (i.e. sleep latency and wake after sleep onset). This study highlights that in older adults ‘at risk’ of dementia, napping is associated with underlying neurobiological changes such as depression and cognition. Napping characteristics should be more routinely monitored in older individuals to elucidate their relationship with psychological and cognitive outcomes.

7. Beware substances and medications!

- Avoid caffeine
  - Decreases slow wave 'deep' sleep
  - Increases awakenings
  - Increases time to fall asleep
  - Can be helpful if wish to delay sleep
- Avoid alcohol
  - Sedative but disruptive
- Consider medications
  - sleeping medications are only effective for short-term use (<2 weeks)
  - Increase risk of falls, dizziness, nausea, drowsiness, headaches
- Limit liquid before bed
- Eating 3-4 hours before bedtime

8. Consider assessment and treatment for sleep apnoea!

- San Diego CPAP study, n = 39-52
  - Less light sleep and awakenings, more deep sleep
  - Reductions in excessive daytime sleepiness
  - Improvements in memory

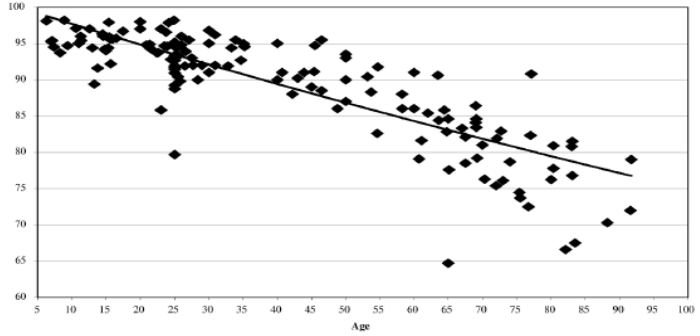
- Sustained effects of CPAP (MMSE 18-30)
  - Cooke *et al*, 2009: n = 10, 1-year follow-up (CPAP n = 5 *vs.* no CPAP)
  - Medium to large effect size improvements in executive functions, psychomotor speed, mood, daytime sleepiness

Ancoli-Israel et al., 2008; Chong et al, 2006; Cooke et al, 2009

9. Re-align sleep expectations

- Do not focus on the ‘perceived negative’ effects of poor sleep
- Set boundaries around thinking, worrying and planning
- It is normal to be alert when waking at the beginning or end of a dream
  - Drowsiness will soon follow
  - Usually takes 15-20 minutes

“Acceptance of good nights and bad nights – sleep problems will occur – it is what you do that matters”



Sleep efficiency

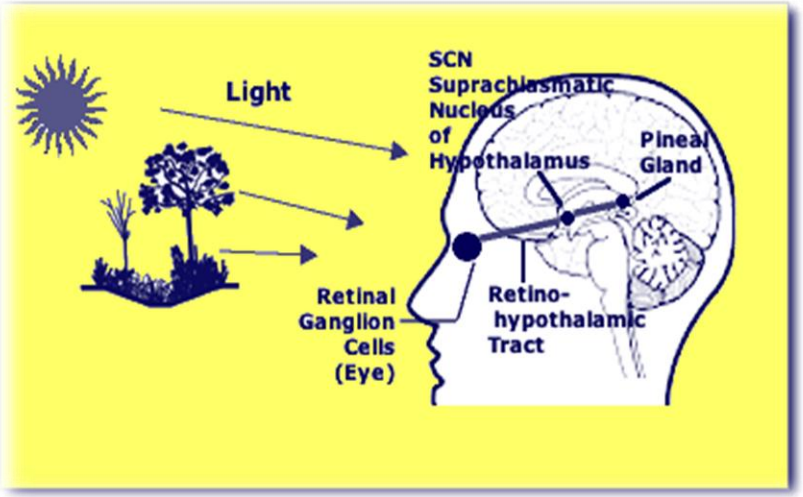
Courtesy of Delwyn Bartlett, Woolcock

10. After you've tried everything….

- If you can't sleep
  - Get up! Do not stay in bed awake for more than 20 minutes
  - Relax in a different environment
    - Dim lighting
    - Do not stimulate the mind
- Do not try to make up for lost sleep
- Consider formal CBT-I / sleep restriction therapy
- Use a sleep diary
- Talk to your doctor

Dealing with daytime sleepiness

- Limit the number of demanding activities you perform each day
- Schedule activities that are cognitively and physically demanding for periods when you feel most alert
- Take regular rest breaks or brief nap
- Ensure adequate light exposure
- Consider substance and medication review



Summary

Sleep–wake disturbance

- A prodromal and key feature of Alzheimer's and synucleinopathies (PD, DLB)
- Long sleep duration, sleep-disordered breathing, circadian advance and changes to sleep architecture ⇢ problematic, as well as reports of poor sleep quality
- Bidirectional links, ? multiple mechanisms
- Non-pharmacological treatment methods (CBTi) current gold standard, but need more RCTs in MCI, AD, PD. Melatonin is likely to help MCI and AD.
- More screening is required and especially for sleep apnoea and REM Sleep Behaviour Disorder
- Now need to determine if treatment of sleep disturbance can slow disease

NHMRC Centre of Research Excellence to Optimise Sleep in Brain Ageing and Neurodegeneration (CogSleep)

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