DCRC
Dementia Centre for Research Collaboration

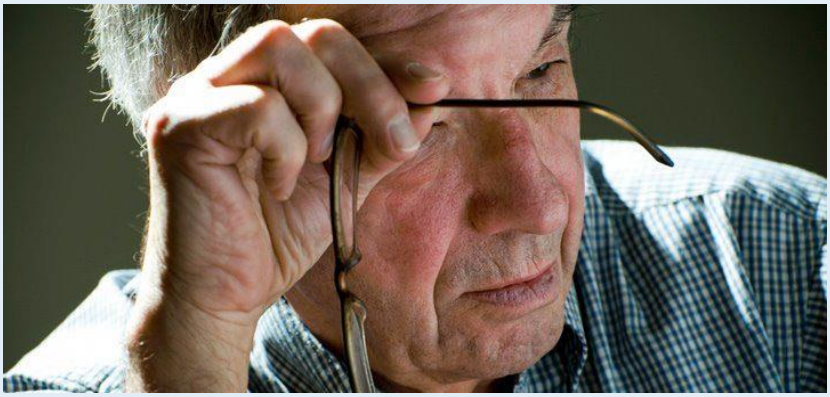
ONLINE SYMPOSIA 2
Friday 16th July 2021
10am – 12.30pm (AEST)

Dementia Training Australia

Sleep Disturbances and Dementia

WELCOME FROM

Professor Henry Brodaty
DCRC, UNSW Sydney



CHAIRS

Dr Claire Burley
DCRC, UNSW Sydney

Dr Nadeeka Dissanayaka
University of Queensland

SPEAKERS & EXPERT PANEL

John Thorpe
Dementia Advocate

Dr Melinda Jackson
Monash University

Dr Rosemary Gibson
Massey University

Professor Simon Lewis
University of Sydney

Event resources will be available on the DCRC website:
https://tinyurl.com/4kkjbyu5

For more information on DCRC visit www.dementiaresearch.org.au

Australian Government
National Health and Medical Research Council

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Changed Behaviours Special Interest Group (CB-SiG)
ONLINE SYMPOSIUM 2 PROGRAM
SLEEP DISTURBANCES IN DEMENTIA
Friday 16th July 2021, 10am – 12.30pm AEST

The symposia will be recorded for broad circulation.
Data or information that is not ready for wide circulation will be censored from the recording before distribution.
https://dementiaresearch.org.au/projects/sig-changed-behaviours/

Time	Action and speakers
10:00am – 10:05am (5 minutes)	**Claire Burley** - General housekeeping, introduce CB-SiG & Co-Chair
10:05am – 10:10am (5 minutes)	**Professor Henry Brodaty,** Director DCRC & Co-Director CHeBA, UNSW Sydney - Welcome
10:10am – 11:00am	**Session 1: Expert presentations part 1** SESSION CHAIR: Dr Claire Burley , UNSW Sydney
10:10am – 10:35am (20-min talk, 5-min Q&A)	Presenter 1: **John Thorpe** Dementia Advocate Talk Title: *Sleep before and after a dementia diagnosis*
10:35am – 11:00am (20-min talk, 5-min Q&A)	Presenter 2: **Dr Melinda Jackson**, Senior Lecturer and Psychologist Affiliation: Sleep, Cognition and Mood Lab, Monash University Talk Title: *Snoring to oblivion: the role of Obstructive Sleep Apnoea in the pathogenesis of cognitive impairment and dementia*
11:00am – 11:10am (10 minutes)	*Break for 10 minutes*
11:10am – 12:00pm	**Session 2: Expert presentations part 2** SESSION CHAIR: Dr Nadeeka Dissanayaka, University of Queensland
11:10am - 11:35am (20-min talk, 5-min Q&A)	Presenter 3: **Dr Rosemary Gibson,** Senior Lecturer Affiliation: Sleep/Wake Research Centre, Massey University, New Zealand Talk Title: *"Even my tired is tired": accounts of sleep disruptions from families living with dementia in New Zealand*

Australian Government
National Health and Medical Research Council

Email: c.burley@unsw.edu.au
Address: DCRC, UNSW Sydney, Level 3, AGSM Building, Gate 11, Botany Street, Kensington, NSW 2052, Australia

11:35am – 12:00pm (20-min talk, 5-min Q&A)	Presenter 4: **Professor Simon Lewis**, Professor of Cognitive Neuroscience Affiliation: Brain and Mind Centre, University of Sydney Talk Title: *Clinical aspects of sleep and dementia*
12:00pm – 12:20pm (20 minutes)	**EXPERT PANEL DISCUSSION & AUDIENCE Q&A (all speakers & chairs)** ***'Where do we need to go next with dementia care, research and policy focused on sleep disturbances in dementia?'*** *(suggested prompt question if necessary)* Moderated by Professor Henry Brodaty, DCRC Director, UNSW Sydney
12:20pm – 12:30pm (10 mins)	Professor Henry Brodaty – Summary and future directions Dr Claire Burley – Close symposium

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Botany Street, Kensington, NSW 2052, Australia

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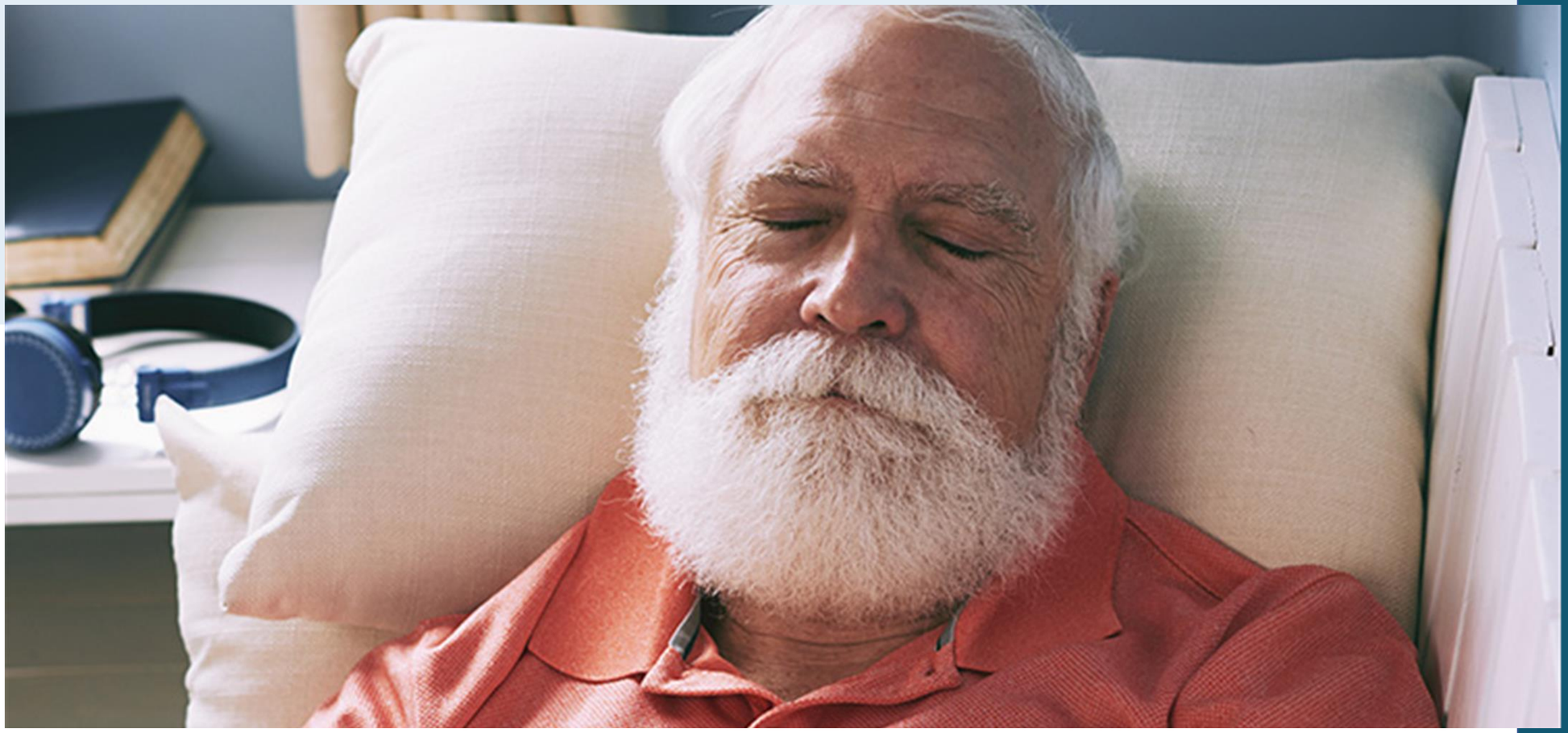
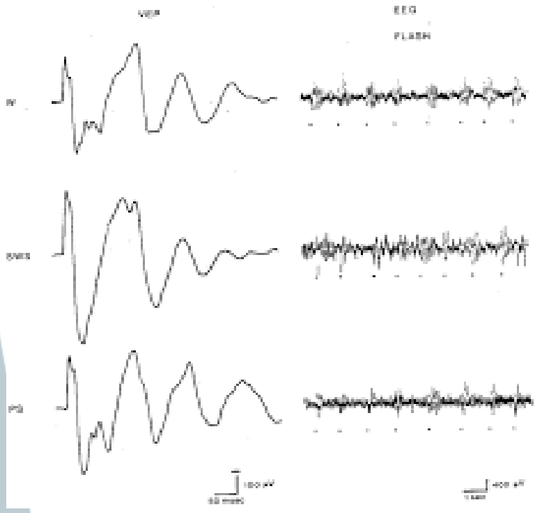


For more information on DCRC visit www.dementiaresearch.org.au or **DTA visit** www.DTA.com.au

Sleep and dementia

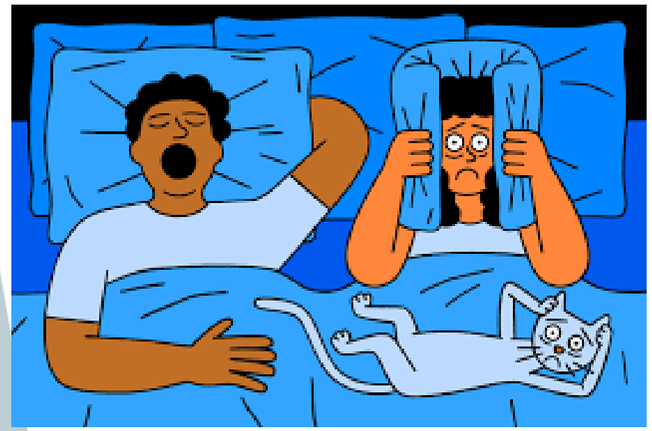
- About 1-in-2 older adults have regular insomnia
- About 1-in-2 older adults have sleep-disordered breathing
- Sleep-disordered breathing associated with poor sleep
- Poor sleep associated with worse cognition

Sleep and dementia



- Sleep disorders associated with dementia
- Are sleep disorders a risk factor for dementia?
- Slow wave sleep associated with amyloid-β protein clearance from brain in animal and human studies
- Does incipient dementia cause sleep disorders?

Sleep apnoea and dementia



Sleep apnoea → dementia?

Dementia → sleep apnoea?

Sleep and dementia

- **Can correcting insomnia and sleep-disordered breathing prevent or delay cognitive decline?**
- **Does incipient dementia cause sleep disorders?**
- **(Dementia may be associated with increased sleep too!)**

Sleep and dementia

As dementia progresses….

…..The architecture of sleep becomes disrupted

- **More broken sleep**
- **Less efficient sleep**
- **Diurnal rhythm lost**

Sleep and dementia

- Effects on family carers
  - Directly – disrupted sleep
  - Indirectly – depression → sleep Δ

Sleep and Lewy Body Dementia

- Often earliest symptom of LBD
  - Sleep movement disorder
    - restless legs
  - Vivid frightening dreams

Sleep and dementia: other factors

- Pain
- Noise
- Neighbours
- Incontinence
- Anxiety, fear
- Depression

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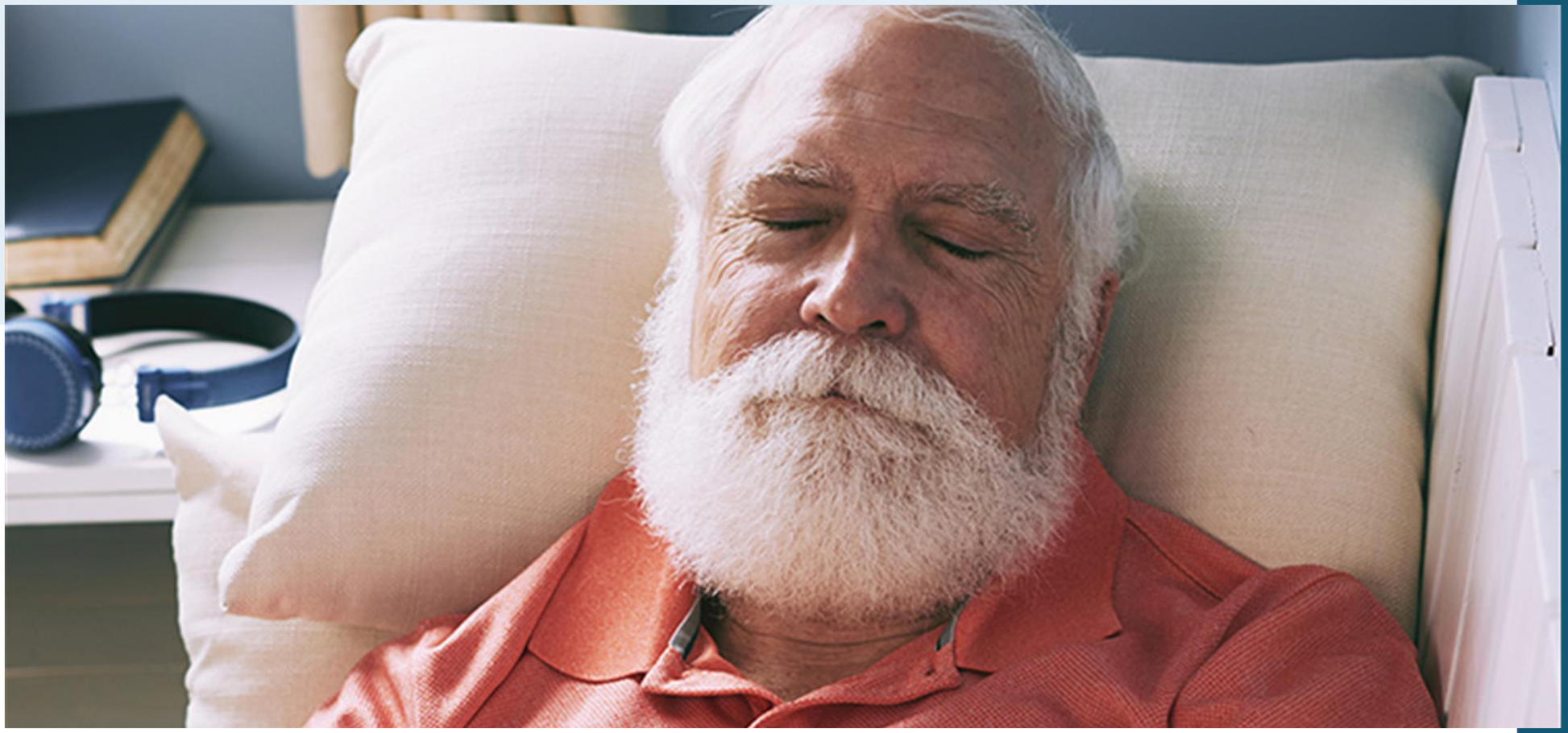

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Sleep : Before and After

Dementia diagnosis

I've slept for a quarter of my life but I am no expert

So…my early life
My adult years
Now.

Going to sleep…sleeping…other factors

- In bed for 2-4 weeks and had very strong pains in my legs. (Called growing pains)
- Could not sleep easily or for long periods so used to wake a lot.

- From the ages of 5-10 I had tonsillitis every year.
- No antibiotic (allergic to penicillin) so every year I had rheumatic fever.

- My mum bought me an old valve type radio (no transistors – this was 1950s). The radio helped to mask my pain. Used to listen to the music and it helped a lot.

- When I recovered each year I went to school, played every sport (a rubbish swimmer) and was normally in the top three in the class out of about 50-55 kids.

Early life

- I was a happy, positive kid in a great family.

Every person has a different story with Dementia

And every person has a different story with sleep

Going To Bed Vs Going to Sleep

Going to Bed was easy but falling asleep became very difficult so I used to Organise my dreams from about age 8

How dare my brain randomly select my topics/dreams!
I chose my dreams in advance

1. Where would I be in my dreams?
2. When would I be i.e. What time period/year?
3. Who would I see and be with?

- An example might be Ancient Rome with Julius Caesar in Alexandria with Cleopatra in about 45BC.
- Another – with Florence Nightingale in her rooms after her return to Britain from the Crimean war.
- Another – with Robin Hood in Nottingham in 1230. (Didn't have to be real events)

During the day I was encouraged to find out more (Real and fictional)

To sleep, perchance to dream

As I got older I continued this habit of falling to sleep constructively. Not every night but it did become a habit especially when I was having rheumatic fever or pain.

I continued this pattern of falling to sleep this way throughout my adult life.

TIAs and Strokes

From about 2003 I started having a series of TIAs. Initially I did not know that they were causing the problems I was having but I was often very tired as a result of them. About this time I started with CPAP for snoring and disturbed sleep

In 2009 I had heart surgery (double bypass) which was followed by a series of TIAs and then in 2019 I had my second bypass. At that point I had a massive number of strokes (Hundreds).

Later I found that my scans showed one third of my brain had suffered significant damage

When I was in hospital the medication before and after surgery sent me “loopy” (the “official term!).

I remember talking to the nurses about going to the “theatre”.

I asked to see the rehearsal area and discussed the performance! Was accompanied for a walk to see the props room. The nurses were lovely accommodating a crazy guy.

Immediately following the surgery I thought the medical staff were trying to kill me and other patients with tablets.

Drugs helped me sleep and reduced post operative pain but I was terrified.

Post operative

Pain and very poor sleep.
Exercise - Mainly walking.
Regular use of CPAP machine.
Sleeping 10+ hours a day
I was increasingly disorientated.

No diagnosis of dementia for about a year

No contact with anyone with or about dementia for 18 months

Now

Very difficult to get to sleep so process changed.

1. I listen to Audible story on my phone and then listen to relaxing music.
2. Set my alarm for morning but often don't fall to sleep for hours.
3. I still set my dream goals of:
    1. where will I be in the dream?
    2. Who will I meet in the dream?
    3. What event(s) will happen in the dream?

Dementia and Sleep.

Now…
Increasingly having difficulty with walking, reaching and grabbing objects, agitation and frustration.

I am more awake and alert at night and much less so during the day.

Thanks for listening

I will try to answer any question you have.

MONASH University

TURNER INSTITUTE FOR BRAIN AND MENTAL HEALTH

Snoring to oblivion: the role of obstructive sleep apnoea in the pathogenesis of cognitive impairment and dementia

Melinda L. Jackson, PhD

Turner Institute for Brain and Mental Health
Monash University

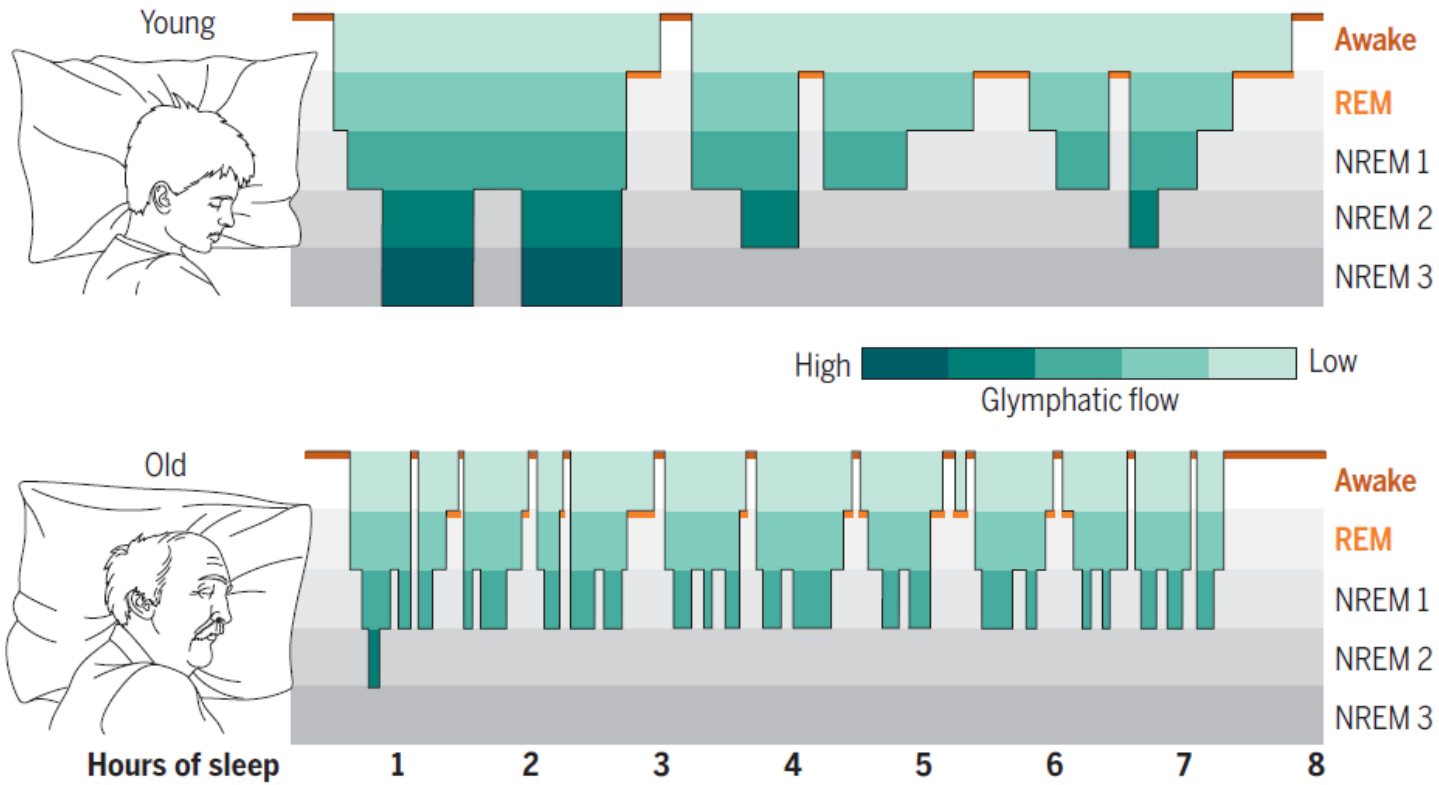
@ DrSleepPsych

Introduction

- Dementia affects around 400,000 Australians
- It is the second leading cause of death worldwide
- Estimated prevalence over 1 million by 2050
- Alzheimer's Disease (AD) is characterised by memory impairment and accumulation of beta-amyloid (Aβ) plaques in the brain
- Currently, there is no cure
- Identification and treatment of modifiable lifestyle, health and medical risk factors is the only available option

Sleep and ageing

- There is a natural change in structure, timing and quality of sleep as we age
- Sleep disorders, including insomnia, circadian rhythm disturbance and obstructive sleep apnoea are common in older adults and in persons with dementia



Nedergaard & Goldman, *Science* 2020

Sleep and the glymphatic hypothesis

- Sleep is an important process for the clearance of extracellular metabolites, including beta-amyloid, that accumulate during wakefulness.
- Sleep disruption (SWS) may increase Aβ deposition by:

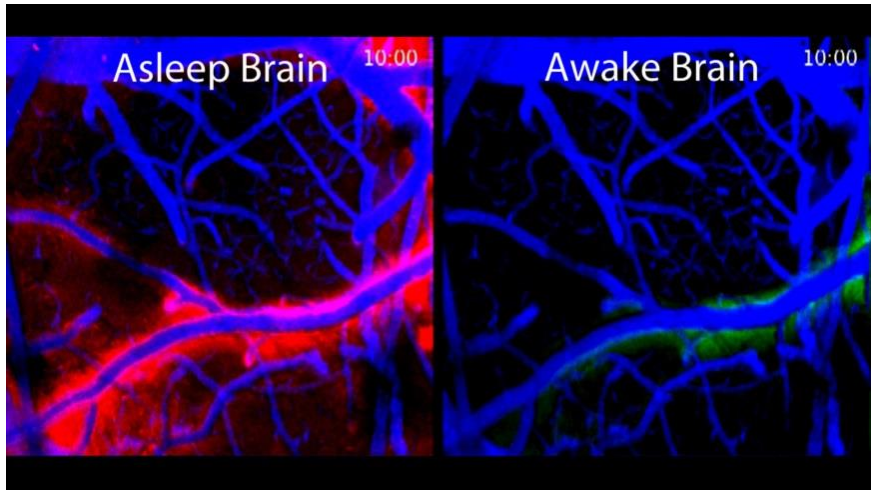
  i) increasing neuronal activity thus increasing Aβ production; and/or

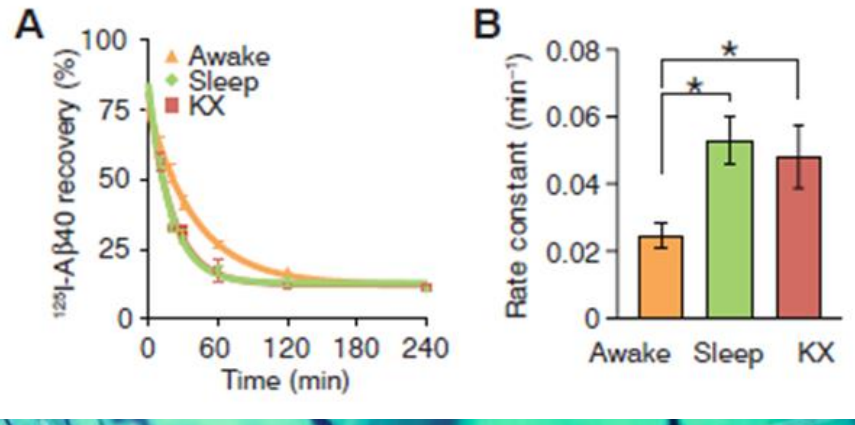
  ii) impeding clearance of metabolites from the interstitial fluid

- The glymphatic system degrades with age, and is suppressed in response to a number of disorders

Sleep Drives Metabolite Clearance from the Adult Brain (2013) Science

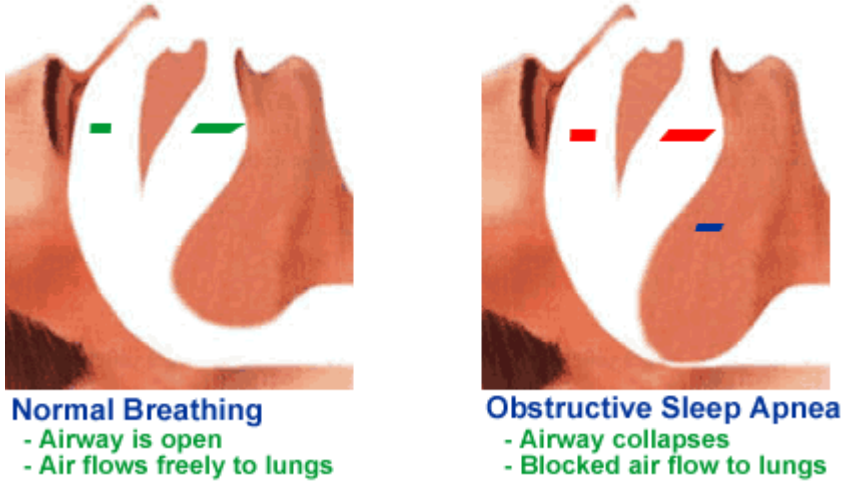
Lulu Xie,[1*] Hongyi Kang,[1*] Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

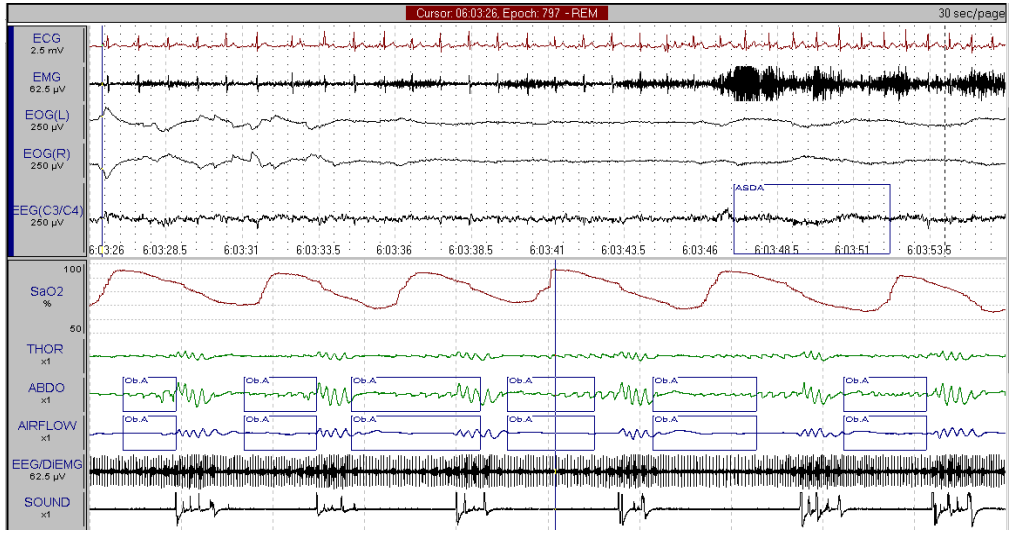




Obstructive Sleep Apnoea (OSA)

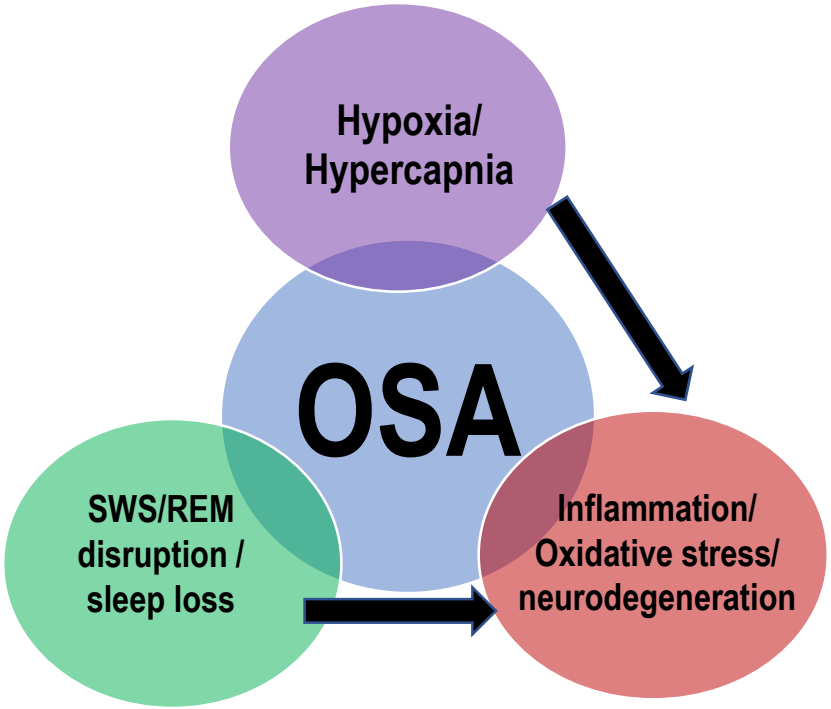
- OSA affects ~ 1 billion people worldwide (Benjafield et al., 2019)
  - **~24% adult males and 9% adult females**
- OSA is caused by airway collapse or airway obstruction
  - **Apnea (< 25% flow) & Hypopnea (< 50% flow)**
  - **Hypoxia (oxygen desaturation, increased CO_2)**
  - **Frequent Awakenings**
- Risk factors
  - **Male gender: 2.5 x more likely to have OSA**
  - **Age: ~30% in people over 65**
  - **Obesity: visceral adiposity strongest risk factor**
  - **Craniofacial features**



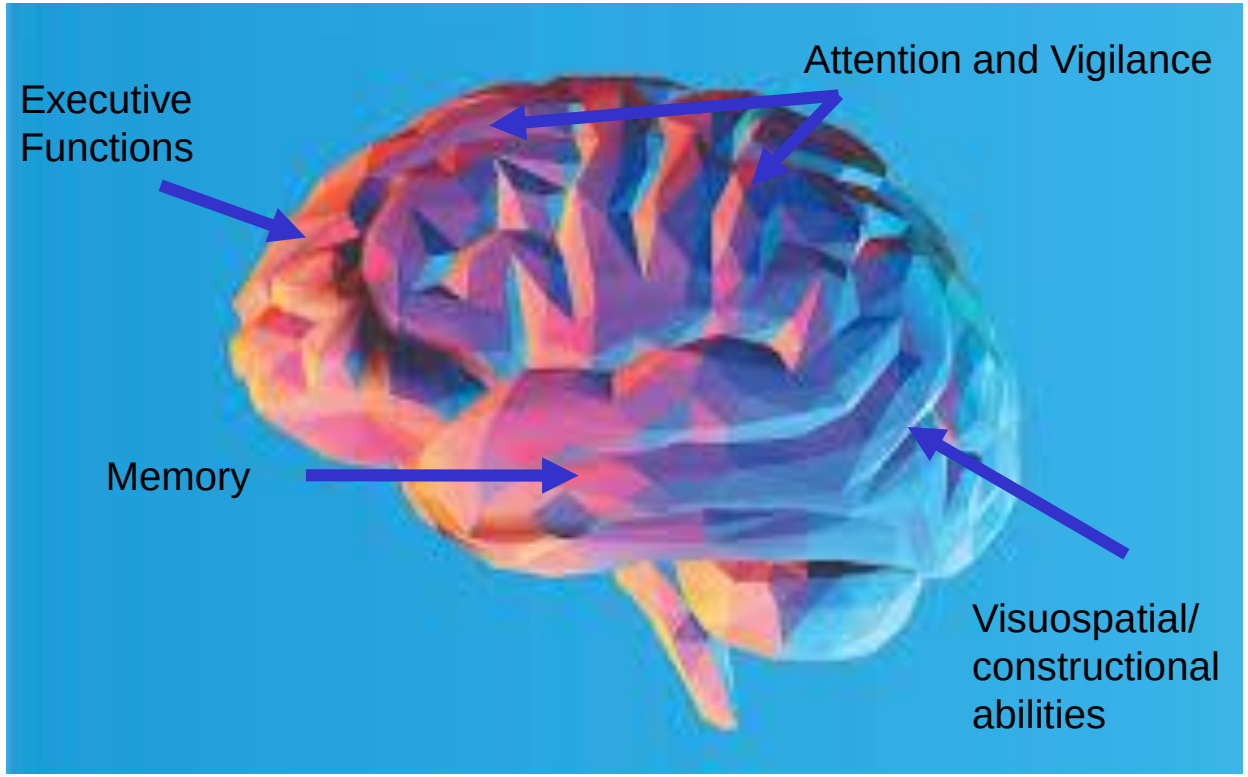


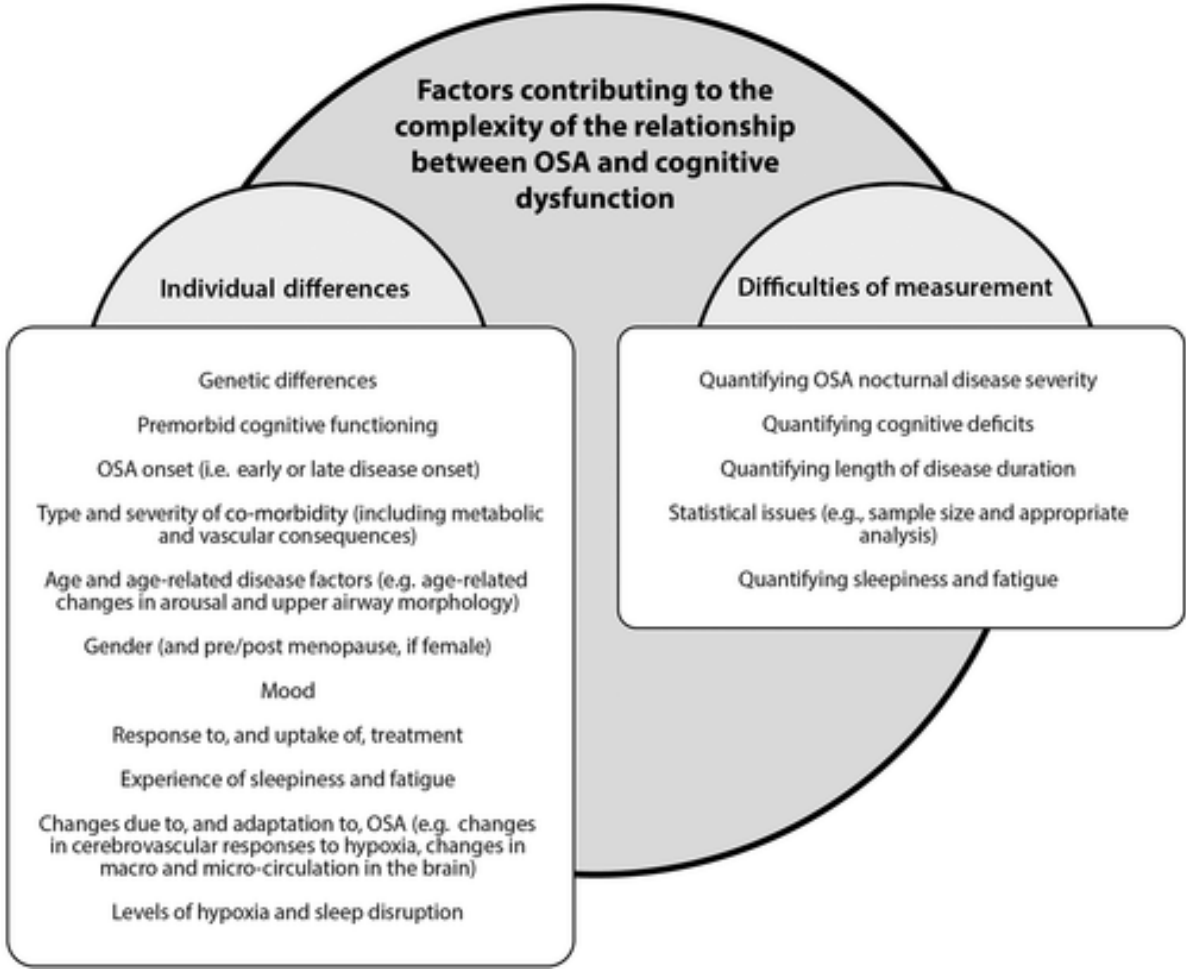
OSA and dementia risk

- OSA results in both sleep fragmentation and intermittent hypoxia – both of which can cause neuroinflammation, cell death and upregulation of Aβ.
- Patients with OSA
  - **1.7-2.3 times increased risk of all-cause dementia** **(Chang et al., 2013; Lutsey et al., 2018)**
  - **26% more likely to develop cognitive impairment** **(Leng, et al. 2017)**
- Persons with AD are 5 times more likely to present with OSA (Emamian et al., 2016)



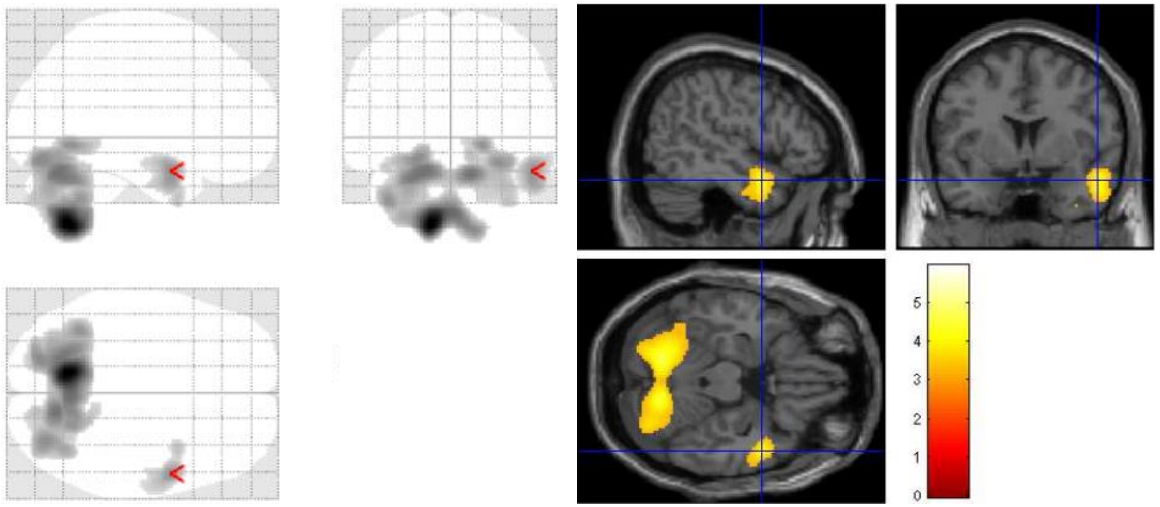
OSA and cognitive deficits





Bucks et al. 2013 *Respirology*
Cross et al. 2017 *Psychological Review*

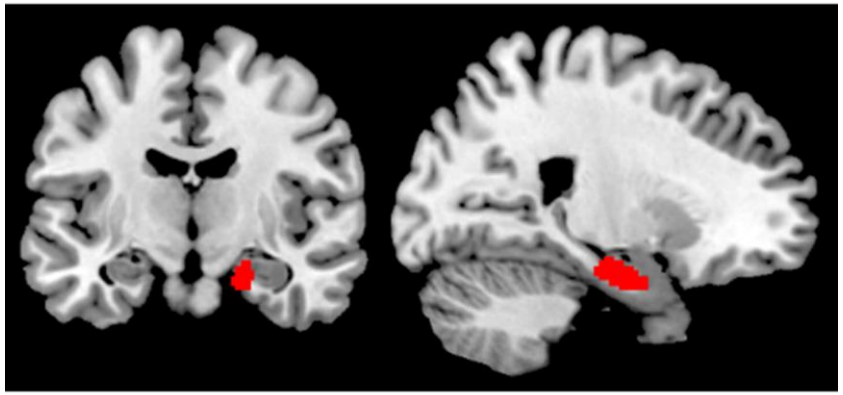
OSA and structural brain changes



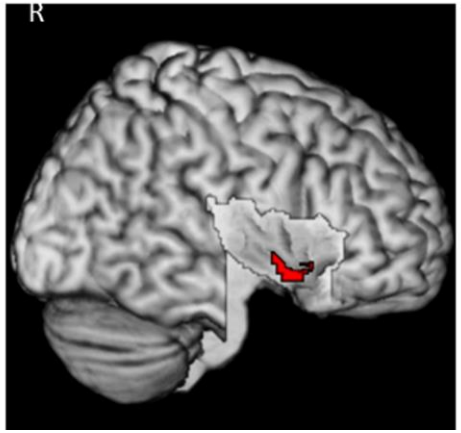
Significant grey matter reduction in right middle temporal gyrus in OSA patients compared to healthy controls (t = 4.05, p<0.05 corrected for topological false discovery rate across the entire brain)

Morrell, Jackson, et al., Thorax 2010

A. Location of significant convergence in the right amygdala/hippocampus ($p < 0.05$, cFWE corrected)

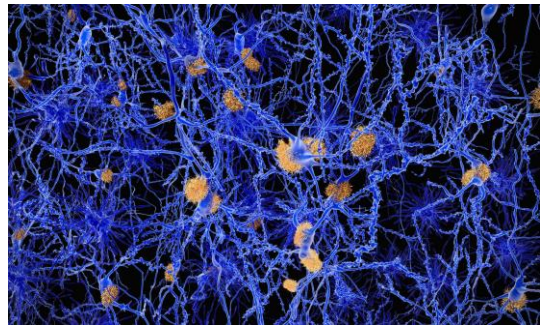


B. Location of significant convergence in the right insula ($p < 0.05$, cFWE corrected)



Tahmasian et al., Neurosci & Biobehav Rev 2018

OSA and amyloid burden



Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly

A Longitudinal Study

Ram A. Sharma[1]*, Andrew W. Varga[2]*, Omonigho M. Bubu[3], Elizabeth Pirraglia[1], Korey Kam[2], Ankit Parekh[4], Margaret Wohlleber[1], Margo D. Miller[1], Andreia Andrade[1], Clifton Lewis[1], Samuel Tweardy[1], Maja Buj[1], Po L. Yau[1], Reem Sadda[5], Lisa Mosconi[1], Yi Li[1], Tracy Butler[1], Lidia Glodzik[1], Els Fieremans[6], James S. Babb[6], Kaj Blennow[7,8], Henrik Zetterberg[7,8,9], Shou E. Lu[10], Sandra G. Badia[11,12,13], Sergio Romero[14,15], Ivana Rosenzweig[16,17], Nadia Gosselin[18,19], Girardin Jean-Louis[20], David M. Rapoport[2], Mony J. de Leon[1], Indu Ayappa[2], and Ricardo S. Osorio[1]

Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes

Claudio Liguori, MD[1]; Nicola Biagio Mercuri, MD[1,2,3]; Francesca Izzi, PhD[1]; Andrea Romigi, PhD[4]; Alberto Cordella, MD[2]; Giuseppe Sancesario, MD[3]; Fabio Placidi, PhD[1]

Serum amyloid-beta levels are increased in patients with obstructive sleep apnea syndrome

Xian-Le Bu[1,*], Yu-Hui Liu[1,*], Qing-Hua Wang[1], Shu-Sheng Jiao[1], Fan Zeng[1], Xiu-Qing Yao[1], Dong Gao[2], Ji-Chuan Chen[3] & Yan-Jiang Wang[1]

Obstructive Sleep Apnea Decreases Central Nervous System–Derived Proteins in the Cerebrospinal Fluid

Yo-El S. Ju, MD,[1] Mary Beth Finn, BS,[1,2,3] Courtney L. Sutphen, BS,[1,2,3] Elizabeth M. Herries, BA,[4] Gina M. Jerome, MS,[1,2,3] Jack H. Ladenson, PhD,[4] Daniel L. Crimmins, PhD,[4] Anne M. Fagan, PhD,[1,2,3] and David M. Holtzman, MD[1,2,3]

Journal of Alzheimer's Disease xx (2020) x–xx
DOI 10.3233/JAD-200571
IOS Press

Severe Obstructive Sleep Apnea Is Associated with Higher Brain Amyloid Burden: A Preliminary PET Imaging Study

Melinda L. Jackson[a,b,*], Marina Cavuoto[b,d], Rachel Schembri[f], Vincent Doré[c,g], Victor L. Villemagne[c,e], Maree Barnes[b,e], Fergal J. O'Donoghue[b,e], Christopher C. Rowe[c] and Stephen R. Robinson[b,d]

- N=34 OSA patients and N=12 age- and sex-matched healthy controls

OSA: OSA diagnosis (AHI>10 events/hr); treatment naïve

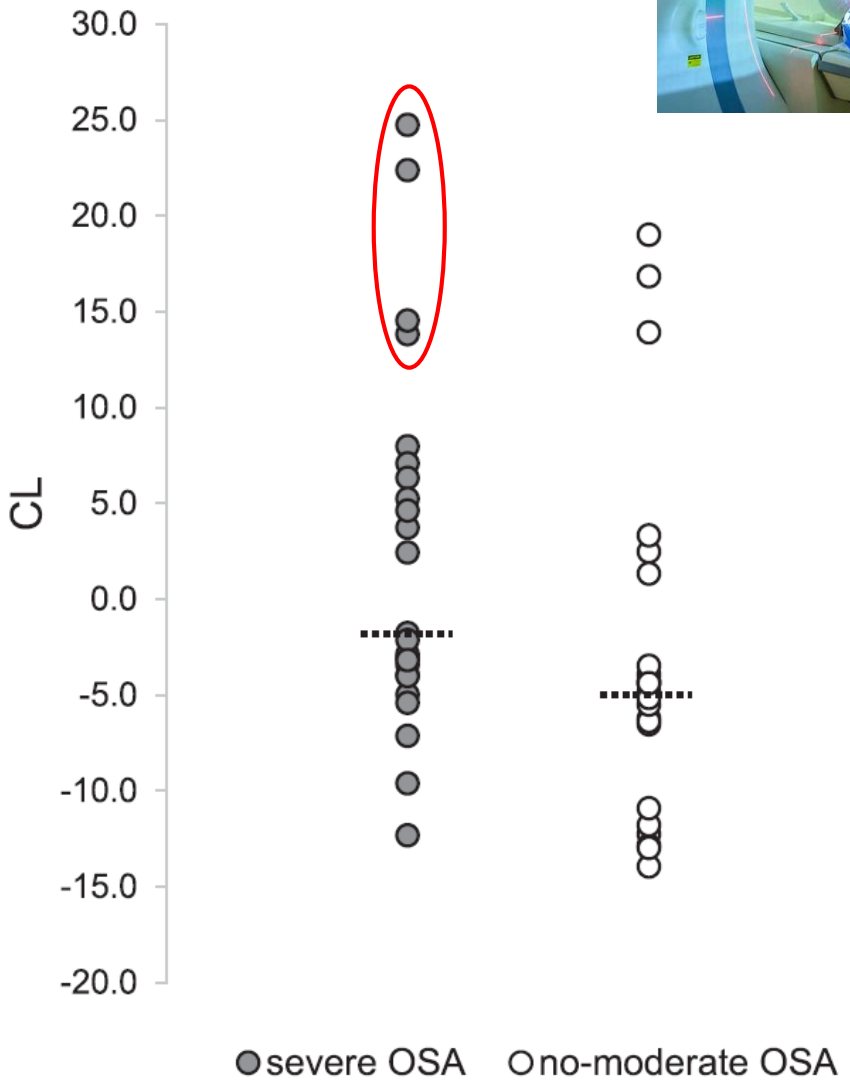
Controls: No sleep or circadian disorder, no OSA (confirmed with overnight sleep study)

	OSA Mean (SD)	Controls Mean (SD)
Age (years)	57.5 (4.1)	58.5 (4.2)
Gender (M/F)	19/15	6/6
AHI (events/hr) ***	40.4 (17.6)	2.9 (1.8)
BMI***	35.6 (8.4)	24.1 (3.1)
ESS**	9.2 (5.7)	4.6 (2.9)
Predicted FSIQ	106.8 (8.4)	109.4 (6.0)
MMSE	29.0 (1.3)	29.5 (0.5)
HADS depression***	4.9 (3.7)	1.4 (1.6)
APOE e4	27%	42%

** $p < .01$, *** $p < .001$

Global brain amyloid burden

- Significantly higher Aβ in severe OSA compared to no-mild OSA, controlling for age (p=0.002)
- Higher Aβ associated with higher AHI, lower sleep efficiency and less N3 sleep (p's=0.04)
- Trend level association between vascular risk score and Aβ (p=0.06)



Jackson et al., *J Alz Dis* 2020

Discussion

- These preliminary data suggest that individuals with untreated OSA have and higher brain Aβ burden than age-matched controls
  - **Supports previous studies demonstrating increased brain Aβ burden in OSA samples (e.g. Yun, et al., 2017, Elias et al., 2018)**
- AHI appears to be associated with greater Aβ burden, suggesting the driver of Aβ accumulation may be the severity of apnoeic events
- Hypertension was more common in OSA group (9 in OSA vs 1 in controls)
  - **Need to examine the impact of comorbidities**

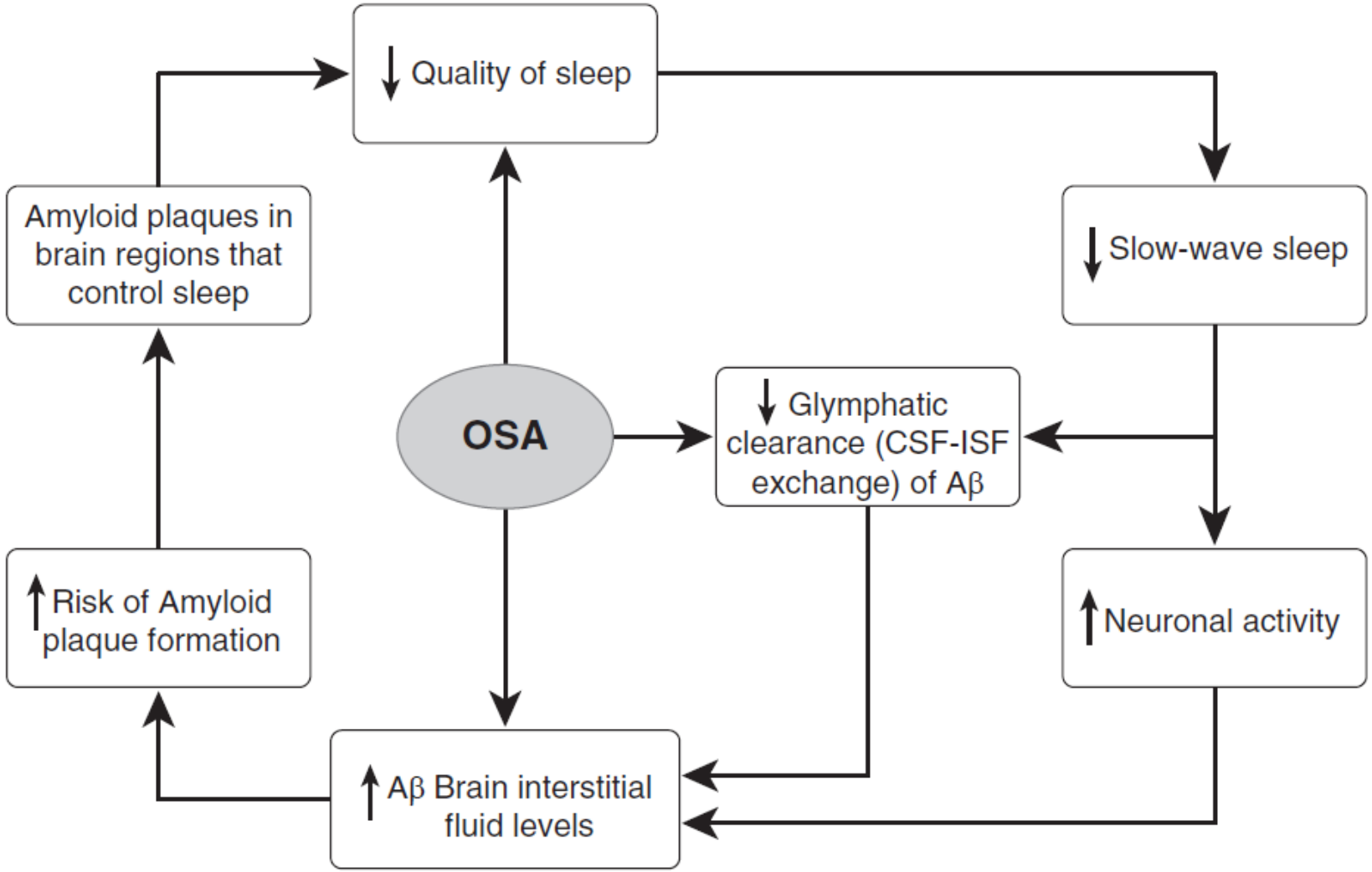


Figure 4. Obstructive sleep apnea–related arousals may worsen sleep quality and increase amyloid deposition in a feed-forward cycle. Aβ = amyloid β; CSF = cerebrospinal fluid; ISF = interstitial fluid; OSA = obstructive sleep apnea.

Sharma et al., *AJRCCM* 2017

Does treatment of OSA improve cognitive and neural impairments?

CPAP treatment in cognitively-normal OSA

- Meta analyses (e.g., Krysta et al., 2013; Pan et al., 2015)
  - **Impact of CPAP treatment for domains of processing speed, attention, vigilance, working memory, memory, verbal fluency and visuo-construction ability.**
  - **A small, significant effect of CPAP on attention (*d* = 0.19) and sleepiness (*d* = 0.30–0.53). NS for other cognitive domains.**
- More recent studies have shown some improvement in memory function with CPAP (McMillan et al., 2015; Jurádo-Gámez et al., 2016).
- Cross-over RCT, 3-months of CPAP in 88 OSA patients normalised verbal memory (Jackson et al., 2018).

CPAP treatment in MCI and AD

- 5 small RCTs of short-term CPAP in AD patients (Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006; Cooke et al., 2009).
  - Improvements in verbal episodic memory and processing speed
  - 1 years follow-up: those who continued CPAP displayed less deterioration of executive functioning and processing speed, with moderate to large effect size
- Observational study of CPAP use in AD patients over 3 years significantly slowed cognitive decline (Troussiere et al., 2014)
- Improvements in psychomotor and processing speed in MCI + OSA patients after 1 year of CPAP (Richards et al., 2019)
- CPAP treatment associated with lower odds of incident diagnoses of AD (OR=0.78) (Dunietz et al., 2021).

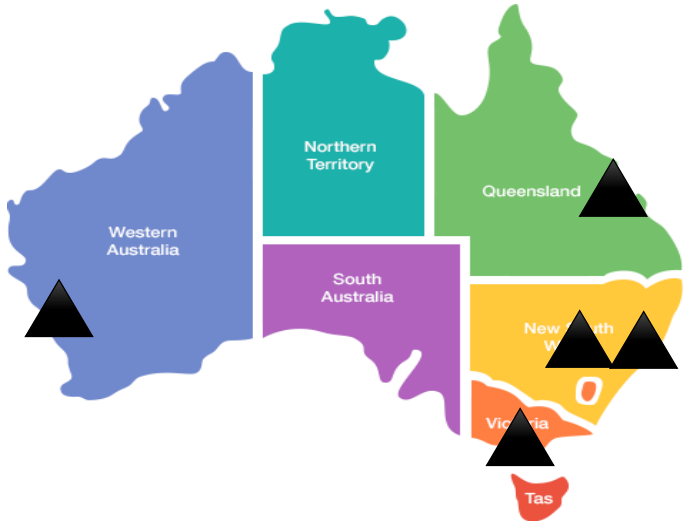
CPAP treatment on brain biomarkers

- Emerging work that CPAP has broader benefits for brain integrity
  - **Normalises brain functional connectivity** (Schultz et al., 2000)
  - **Decreases oxidative stress biomarkers** (Prilipko et al., 2014)
  - **Reversal of white matter lesions** (Castronovo et al., 2014)
  - **Normalisation of CSF-derived Aβ** (Ju et al., 2019)

- Currently lacking robust clinical trials of CPAP treatment for cognitive decline.

RESHAPED Trial: REducing Sleep Apnoea for the PrEvention of Dementia: a multi-site feasibility RCT

- To test feasibility and acceptability for a full-scale trial by:
  - Confirming that the ***prevalence*** of ODI >10 in target group.
  - Demonstrating ***acceptability*** by ≥50% of eligible participants agreeing to be randomized.
  - Alleviating ***hypoxic burden*** using our *CogSleep OSA* intervention at 6-month and 2-year follow-ups.
  - Determining ***tolerability***
  - Obtaining ***effect size*** estimates (and 95% CIs) on intended primary outcome
  - Exploring the **mechanistic factors** in relation to variation in memory and ODI over the 6-month and 2-year follow-up.

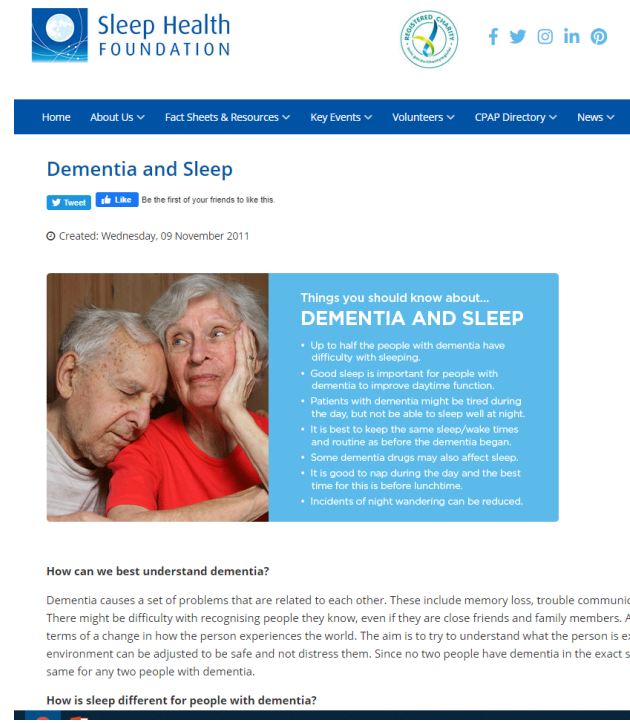


Discussion

- There is growing evidence that OSA plays a causal role in the development of AD
- Individuals with untreated OSA have poorer cognitive performance, reduced brain integrity and higher brain amyloid burden than age-matched controls
- Growing evidence that CPAP may improve brain health – larger, pragmatic trials are needed
- Consideration of confounding factors: age, cognitive reserve, length of OSA, BMI, genetic factors, CVD, depression

Clinical considerations

- Increase screening for OSA in geriatric and memory clinic settings
  - **Berlin Questionnaire, STOP-BANG, Epworth Sleepiness Scale**
- Increase awareness of OSA and other sleep issues in the community – carers and those at-risk
  - **Importance of early intervention**
  - **Sleep Health Foundation website**
- Need to assist patients when starting treatment for OSA to ensure adequate usage



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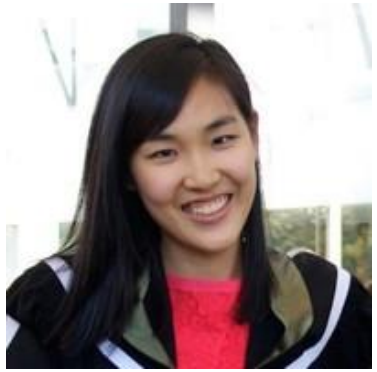
Dr. Vincent Dore


Dr. Marina Cavuoto


Dr. V Vien Lee

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

"Even my tired is tired"

Accounts of sleep disruptions from families living with dementia in New Zealand

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Research Aims

- Describe the sleep of older New Zealanders
  Analysis of national data sets & pre-existing data sets
- Gain insight into beliefs, attitudes & behaviours of older people, including people with dementia & carers
  Focus groups, open ended survey items, interviews & case studies
- Explore sleep as a predictor for admission into aged residential care
  Interviews with family carers & analysis of formal assessment data
- Represent the changing sleep experience of family carers
  Nationwide survey & interviews
- Better understand & manage sleep disordered breathing
  Focus groups with older patients diagnosed & treated, future studies regarding positional management
- Design non-medical interventions & resources
  Trial of interventions for people with dementia & carers;
  Future Ageing Well & health promotion projects

https://www.sleepwake.ac.nz/projects/sleep-in-aging-and-dementia/

Neurophysiological changes

Exposures to external time cues

Psychosocial context

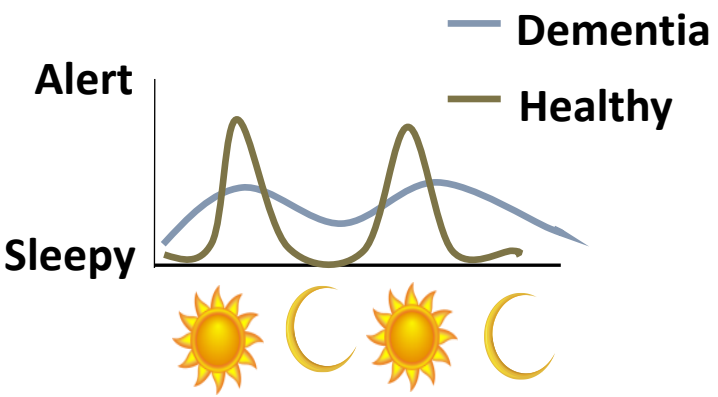
Sleep Health

Sleep hygiene

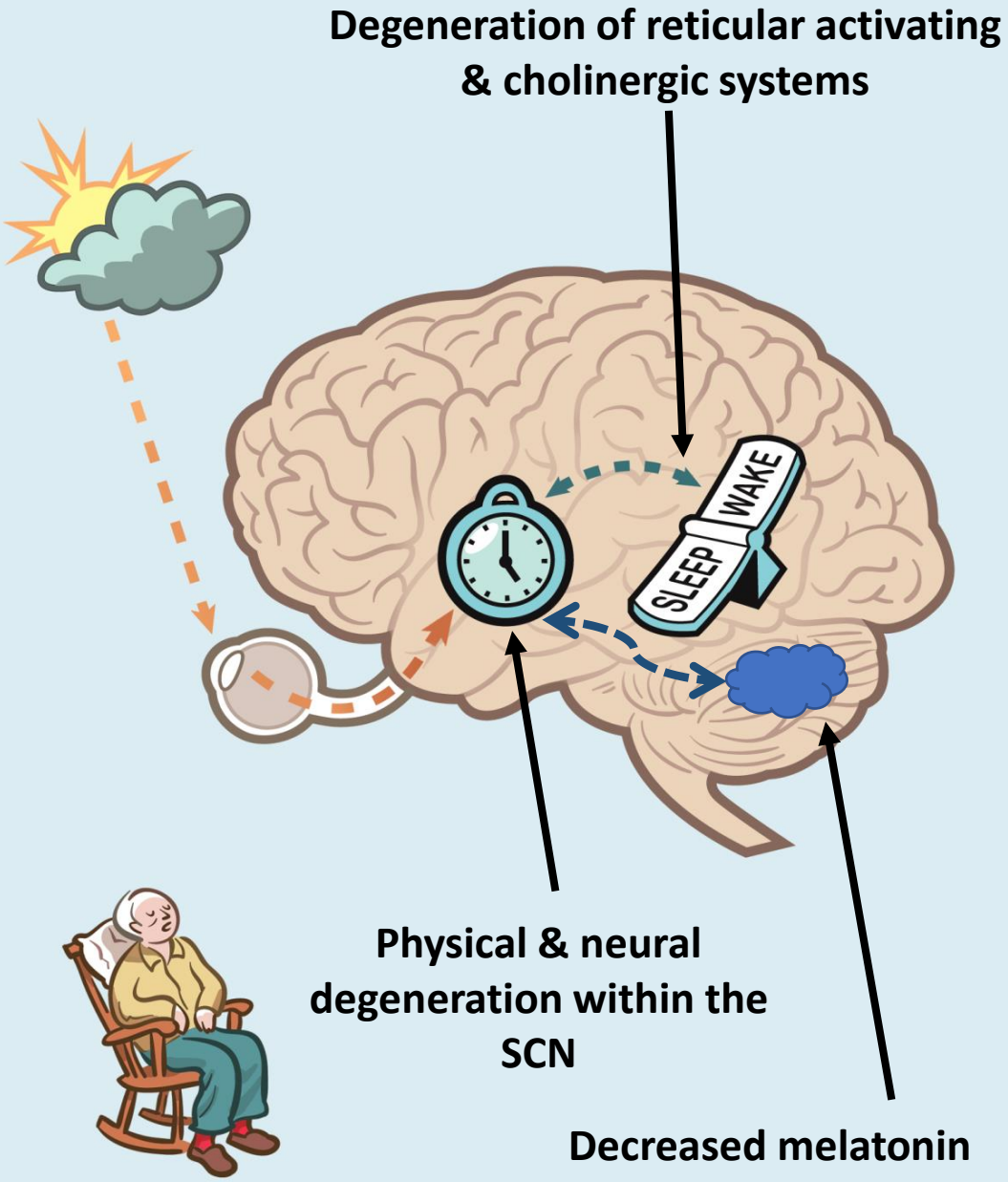
Other health conditions and their medications

Primary sleep disorders

Sleep Regulation with Dementia



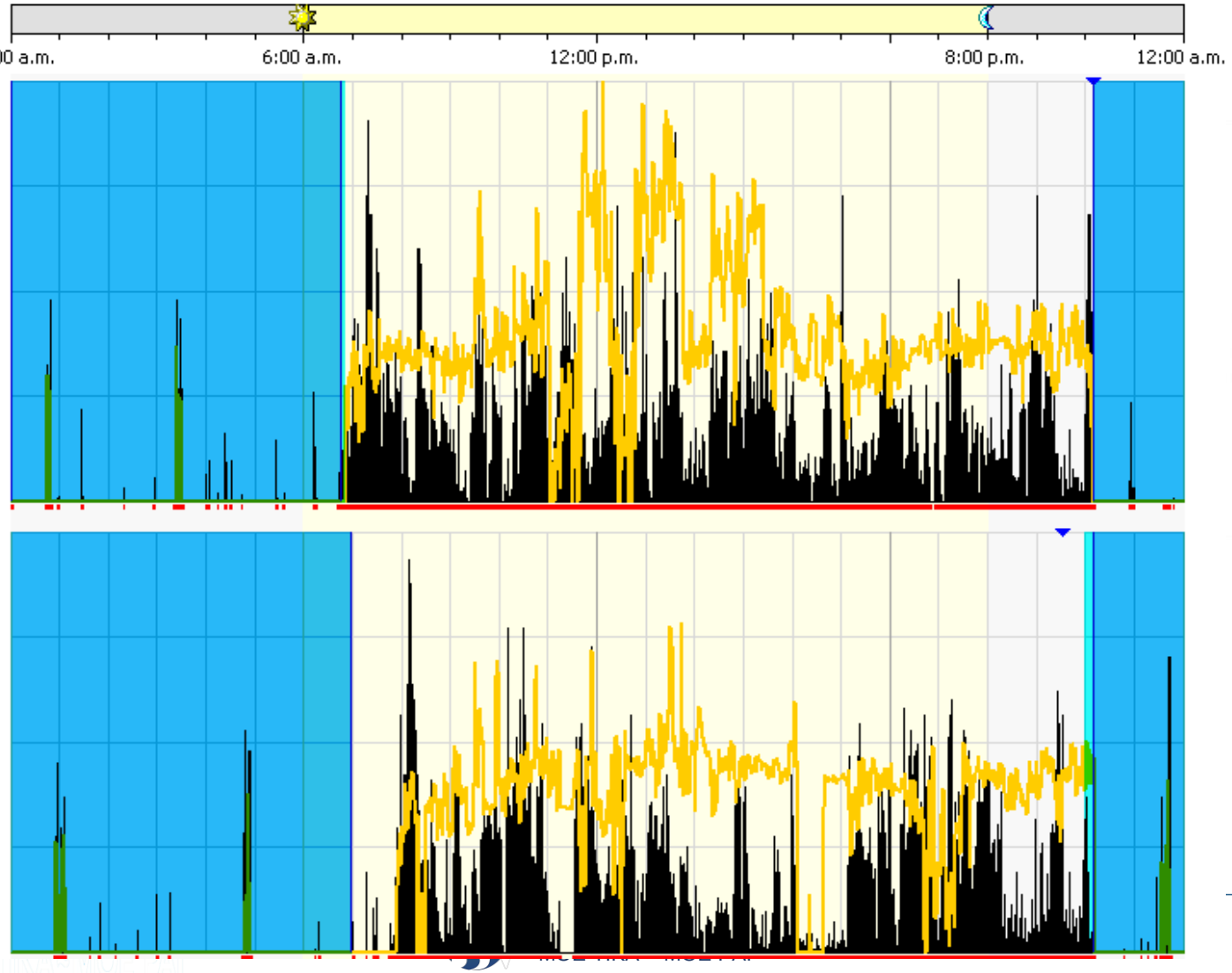
Irregular sleep / wake timing



Rose, K. M., & Lorenz, R. (2010). Duffy, J. F., Zitting, K. M., & Chinoy, E. D. (2015); Wright, K. P., & Frey, D. (2008)

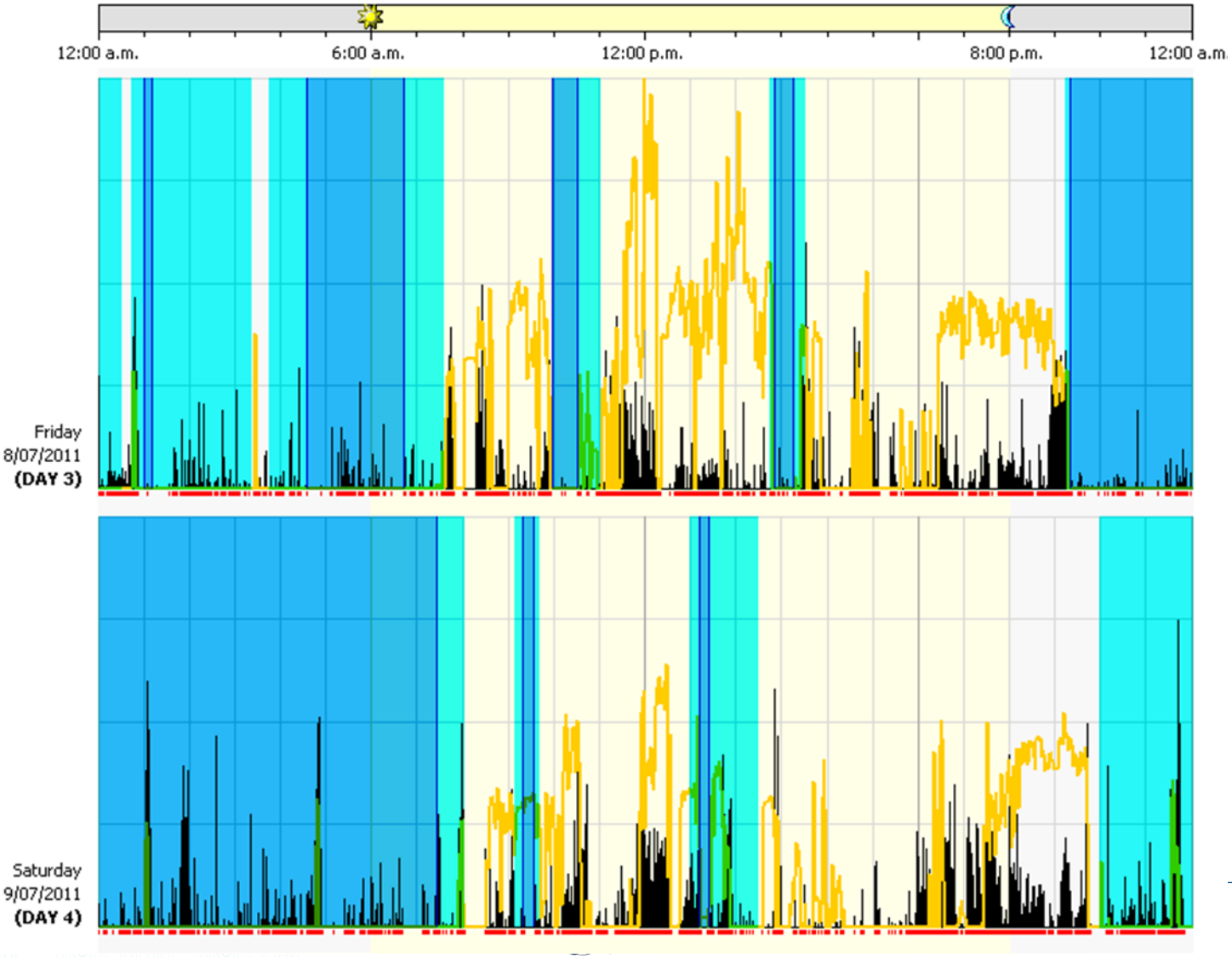
Sleep/Wake Cycle
Healthy Older Adult

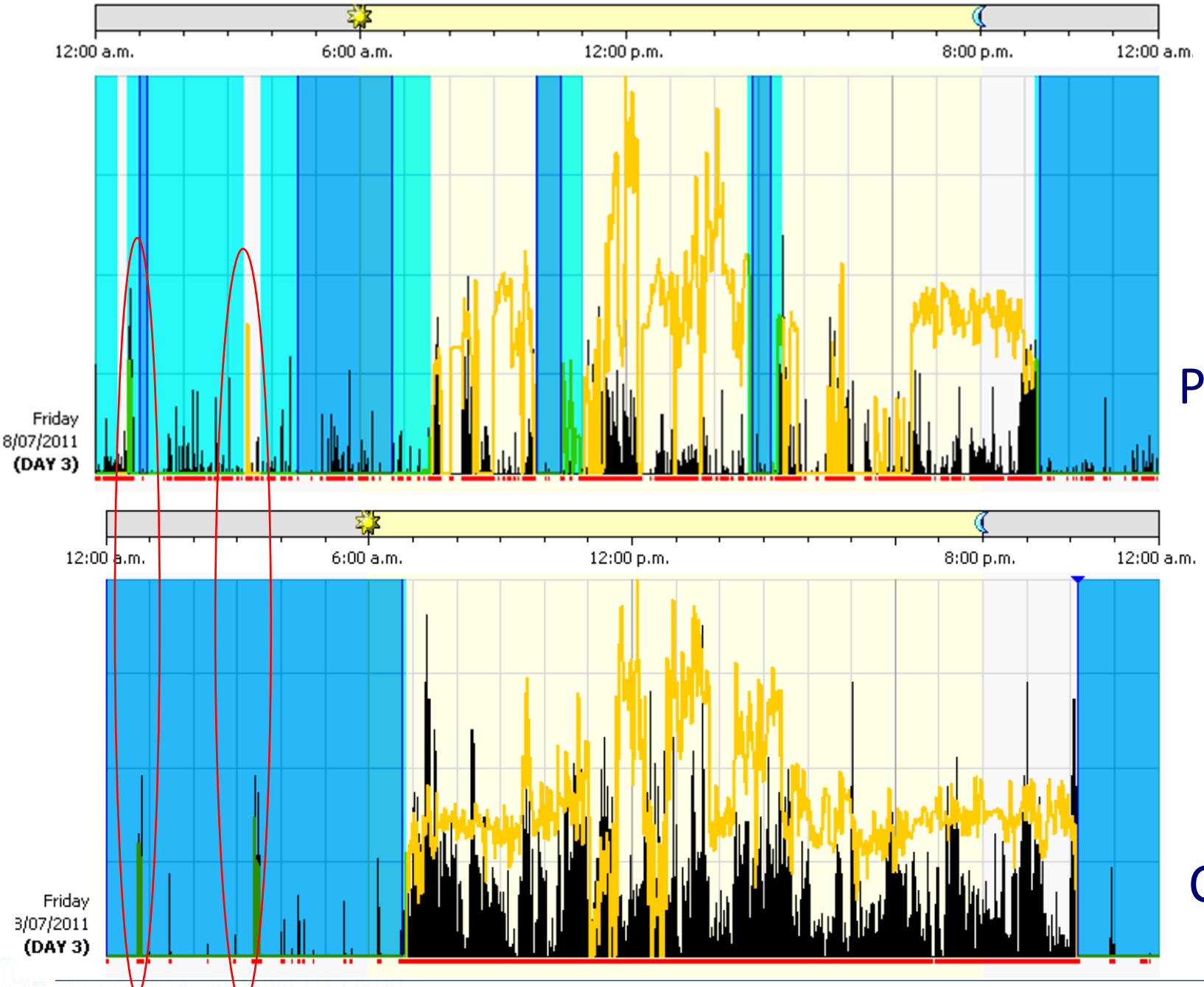
Gibson, R., Gander, P., Jones, L. & Dowell, A. (2016)



Sleep/Wake Cycle Person With Dementia

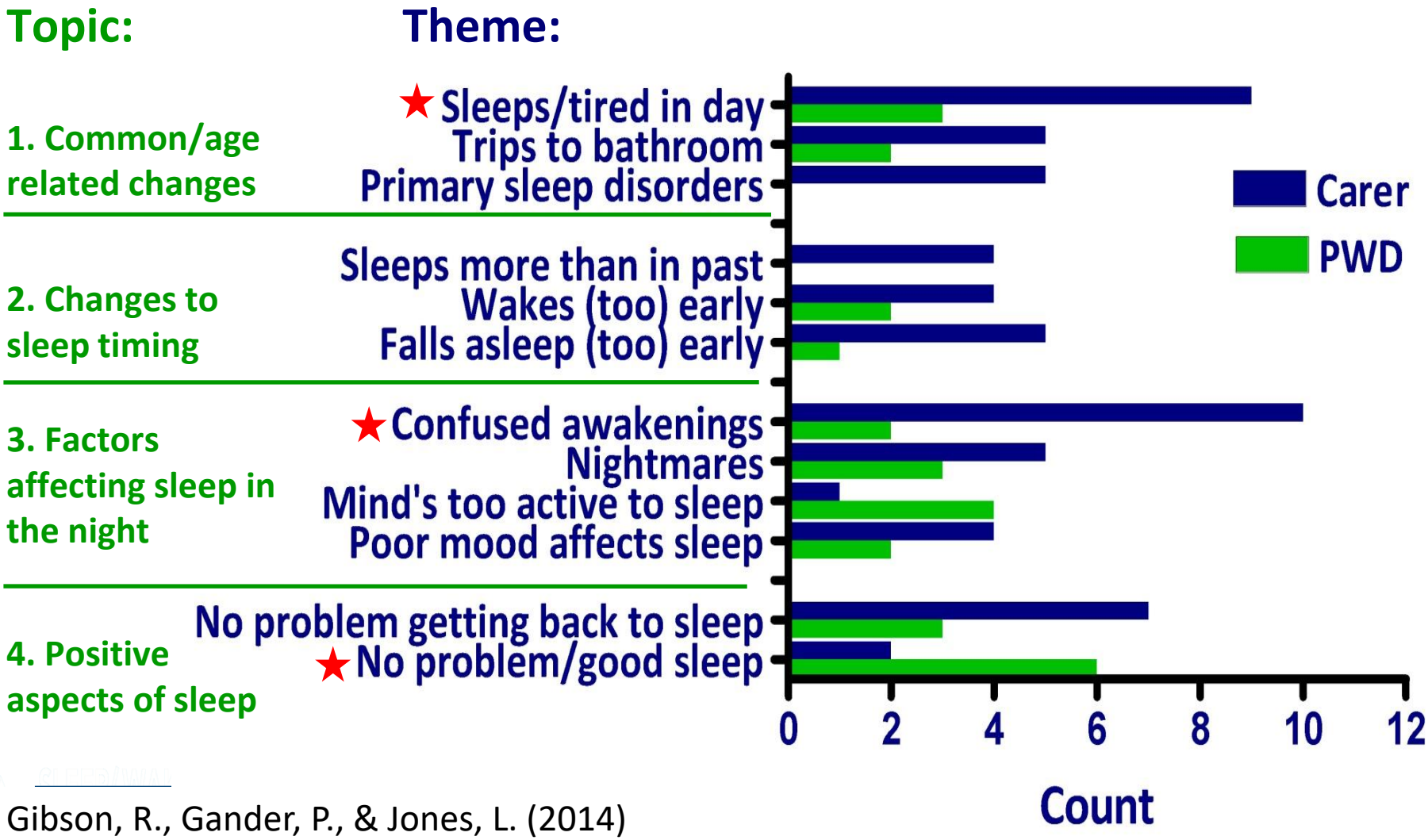
Gibson, R., Gander, P., Jones, L. & Dowell, A. (2016)




12:00 a.m.
6:00 a.m.
12:00 p.m.
8:00 p.m.
12:00 a.m.
Friday
8/07/2011
(DAY 3)
PWD
12:00 a.m.
6:00 a.m.
12:00 p.m.
8:00 p.m.
12:00 a.m.
Friday
3/07/2011
(DAY 3)
Carer

Sleep of People with Dementia (PWD)

Focus Groups



Gibson, R., Gander, P., & Jones, L. (2014)

Including the voice of care recipients

- **Daytime sleepiness:** *"I'm conscious, you know of falling asleep with visitors and things like that, but I can't stop it."* (PWD gp.3)
- **Confused awakenings:** *" I have to get up and look for the doors and make sure that everything is – I suppose I am walking in [my] sleep and go back and I sleep."* (PWD gp.1)
- **Nightmares:** *"I can't remember the nightmares, but I know I am absolutely terrified when he wakes me up"* (PWD gp.1);

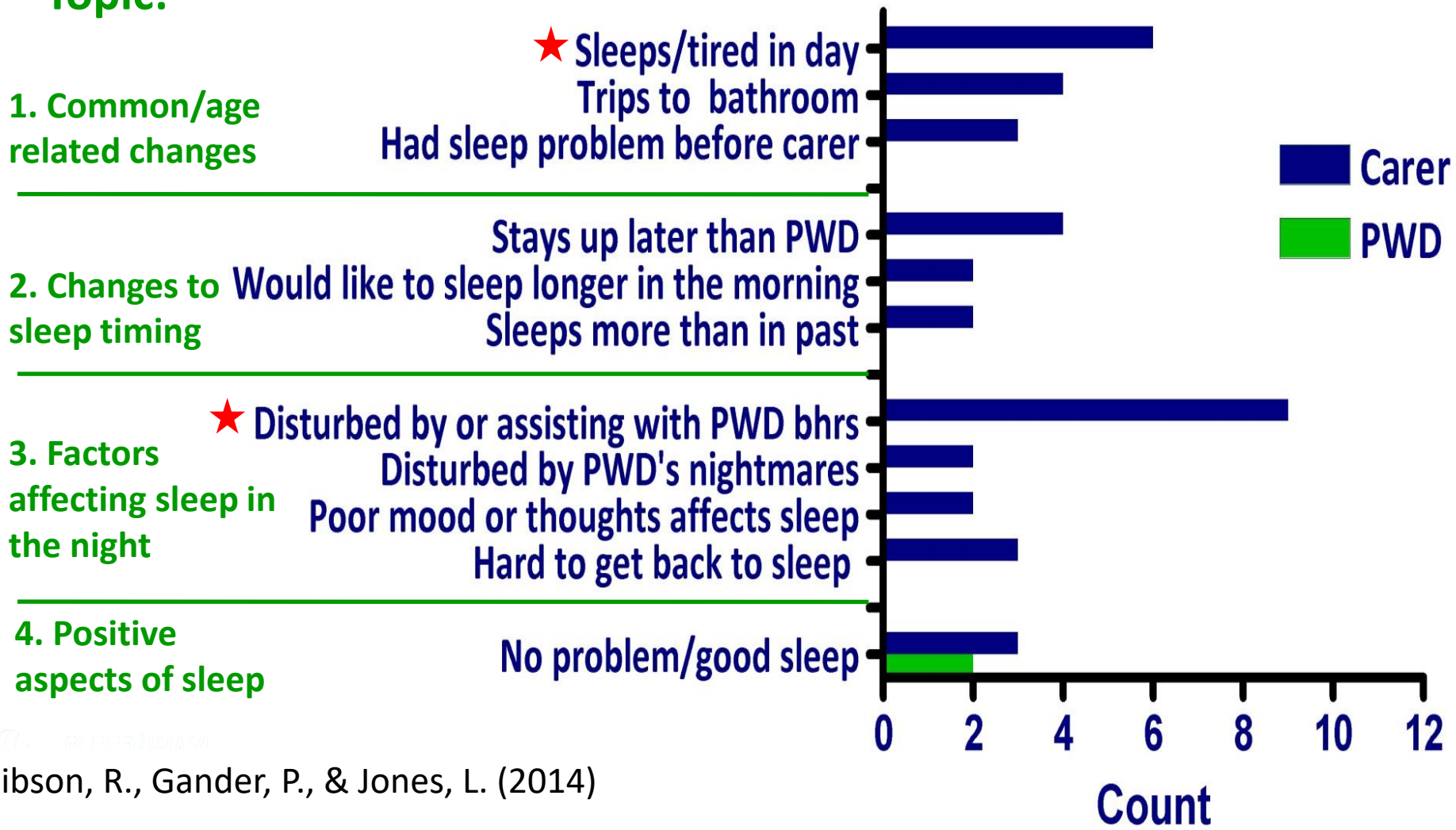
  "I can't wait to get up in the morning can I?!" (PWD gp.2)
- **Overactive mind***: "If I could switch my brain off and stop thinking I would be able to go to sleep"* (PWD gp.1)

Gibson, R., Gander, P., & Jones, L. (2014).

Sleep of Carers

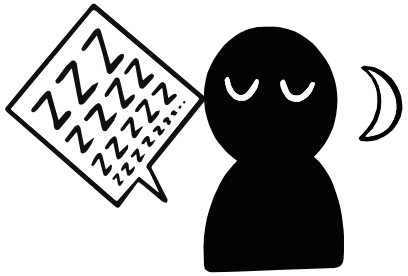
Focus group

Topic:



Gibson, R., Gander, P., & Jones, L. (2014)

Sleep of Carers



- **Daytime sleepiness:** *"Just tired really yes, just tired all day. But you still have to do things because it is your responsibility really, you are the carer. I find sometimes it is a bit hard."* (carer gp.2)
- **Restlessness:** *" ...he has been stretching out and kicking me and knocking me around, was terrible. He is terribly apologetic of course!"* (carer gp.2)
- **Frustration:** *"I find that sometimes ___ takes so long [with the light switch] that I get quite churned up and that is extremely hard to go back to sleep"* (carer gp.2)
- **Providing support:** *"When she is having had a nightmare I am usually woken up. I can hear screaming ,you know, so I wake up and I will hold her for a while and then she goes off to sleep. But sometimes it happens three or four times a night."* (carer gp.1)

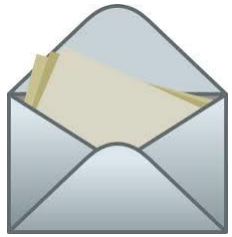
Gibson, R., Gander, P., & Jones, L. (2014)

Sleep and informal dementia care

Postal survey 526 carers, 66% female, age 23-96 yrs, (mean 74),

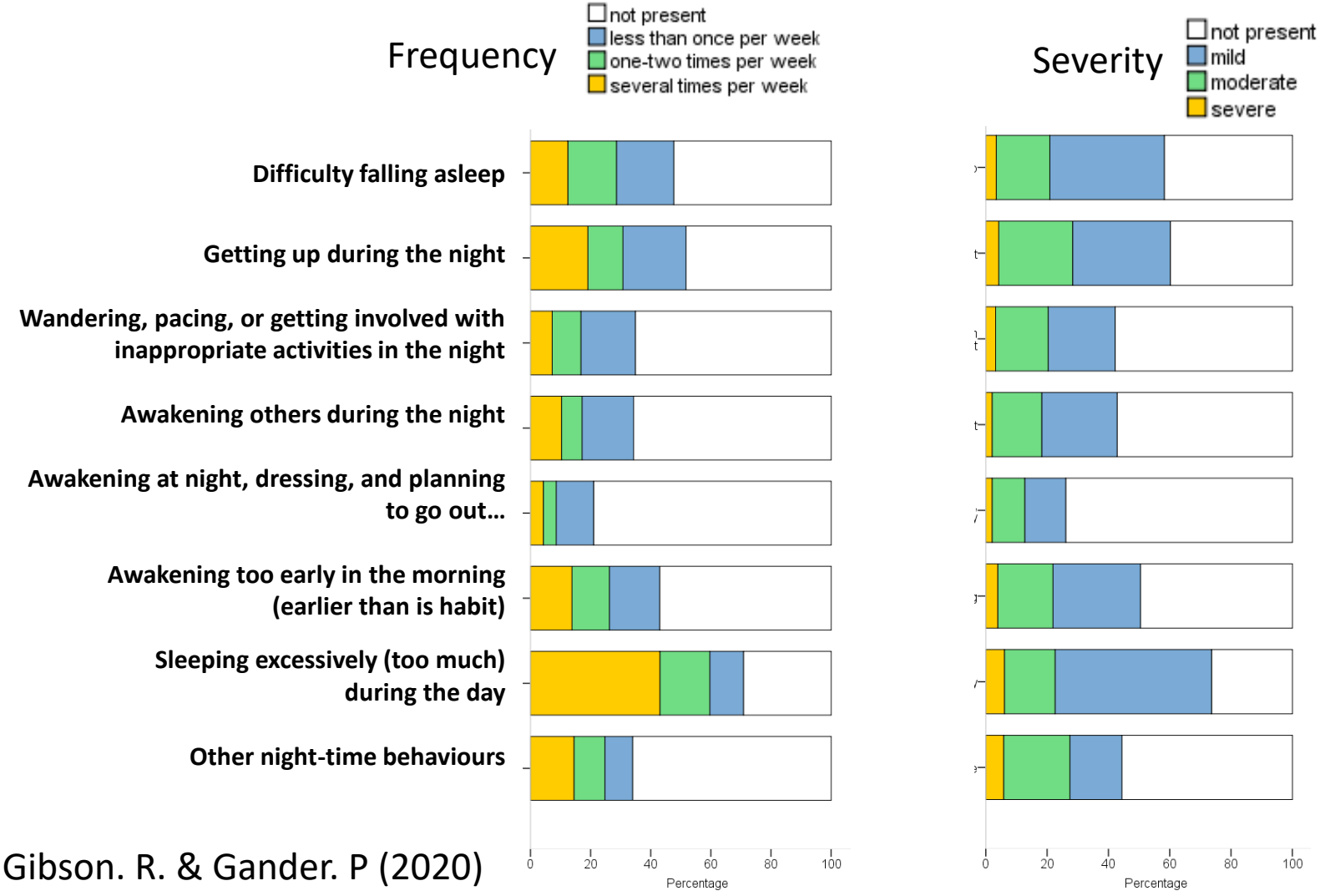
Care recipients: 87% spousal, 42% female, age 53-99 yrs (mean 78)

1. **Themselves and situation:** age gender, ethnicity, living standards (LSCAPE-6), who support (relationship, age, gender, ethnicity), years supporting, type of diagnosis, dementia-related symptoms, time of day required, respite and permanent care considerations
2. **Sleep of carer:** Insomnia Severity Index (7 items), place of sleep, diagnosis of sleep disorder, and use of sleeping medications
3. **Sleep of care recipient:** Sleep Disturbance Index
4. **Health of carer:** general health and pain (SF12), health conditions, and medications



Sleep of Care Recipient

Sleep Disorders Inventory AD (Tractenberg, 2003)



Gibson. R. & Gander. P (2020)

Sleep of Carers

N=526, mean age = 72 (SD 10)

- Insomnia Severity Index (Morin, 2011)
- 23% moderate to severe (15-28)
- 42% mild problem (8-14)

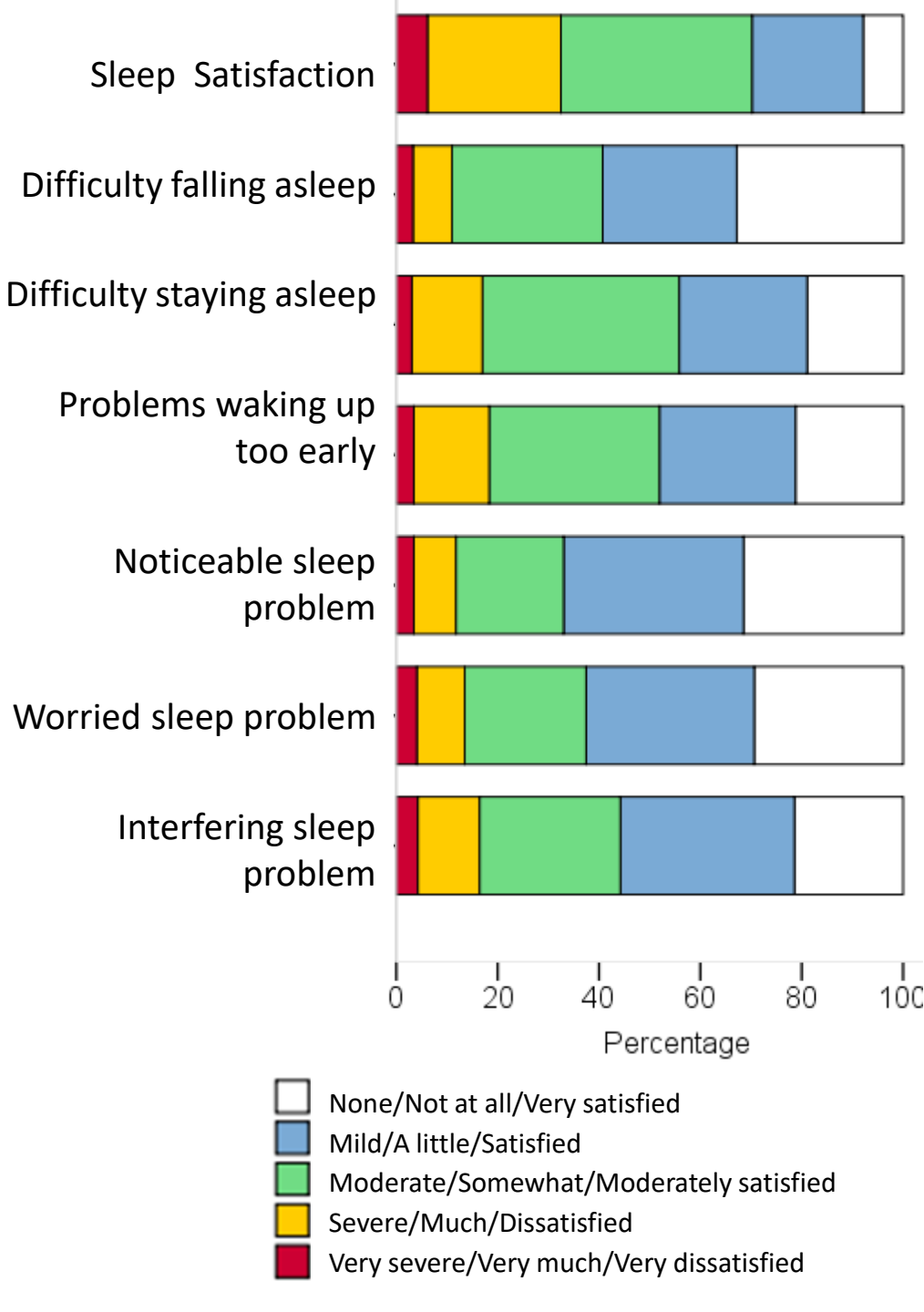
Independent predictors poor sleep::

Female, caring at night, poorer health, sleep symptoms of care recipient

Independent Outcomes:

Poorer health, use sleep medications, poorer standards of living and considering formal care

Gibson. R. & Gander. P (2020)



“I think I could have coped if I was sleeping better”

Sleep across the trajectory of family-based dementia care

Aim: To represent sleep experience of informal carers across the trajectory of dementia care and transitions into residential care

Method: Semi-structured interviews with 20 carers who had transitioned their family member with dementia into formal care (≤2yrs). 13 face-to-face, 7 telephone (rural)

Qualitative analyses: coding of transcripts, writing case studies, and workshops to construct sleep-related themes and underlying narratives

Sleep got progressively worse

In those earlier days it wasn't so bad. I wouldn't know often if he'd been in and out and sometimes I did, and sometimes I didn't and then he started, he would just. He would go to bed really early. He'd be awake early, you know at 11 o'clock. He'd go to the toilet. He couldn't go back to sleep. Or he'd get up and wander round. And then he might go back to bed. And then it just became progressively worse really.

…..And then I – as things progressed I'd find him in the shower. I'd find. He will have left the house. He'd be out in the shed looking for things that didn't exist. He would be checking the house because he was hallucinating a lot. He thought that people were in the house. And so when it got to the stage of him getting up and down a lot, that's when my sleep was really affected. (Nathalie, 64)

Didn’t realise how tired I was
Sleep should have been prioritised

“I don't think I could have gone over, gone on much longer. I think I probably would have just collapsed and died. That’s how tired I felt. …And yet while he was here, and I was looking after him I didn’t feel it.” (Pamela, 75)

“You need to sort out your cut off point….really it was to do with the sleep deprivation…. you just adjust slightly each time as well. Okay cos initially I think oh, god I've only had five hours sleep. And I'd think that was terrible. And now, or then as time got on. If I got two hours in a row, I was like yay! You know, like, so, you do of course. And I guess you do that with children too. You have periods where you know, sleep, sleep isn’t, isn’t the main thrust really

(Nathalie, 64)

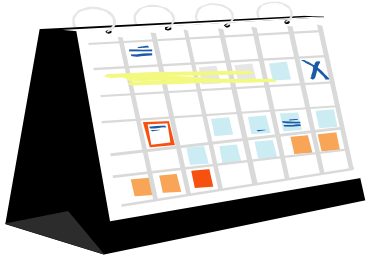
Interviews summary

- **Previous sleep** identity foundation of current narratives
- **During dementia care:** sleep became progressively worse. unpredictable nature of dementia-symptoms, routines and the 24/7 responsibilities, state of high alert
- Attempted to facilitate better sleep and wellbeing for family member, often sacrificing their own self-care. Retrospectively exhausted.
- **Transition period:** either had a period of crashing, or the busy momentum continued. Grief was common throughout.
- **Post-transition:** sleep disruptions associated with insomnia, poor sleep habits, or nightmares. Optimistic sleep would improve with grieving and many were enjoying the luxury of sleeping in their own time.

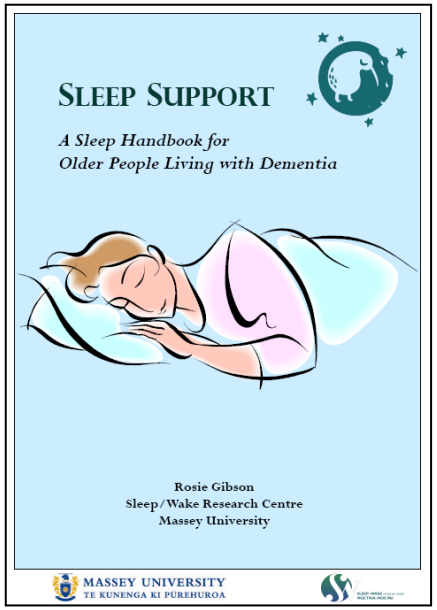
Gibson, Helm, Breheny, Gander – in production

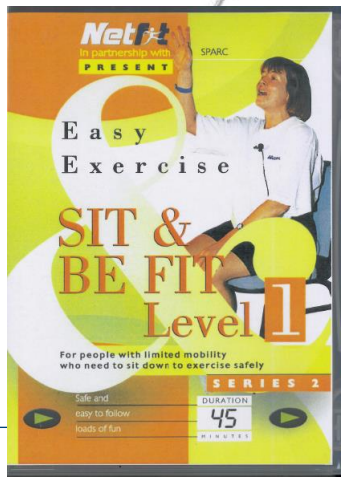
Pilot of an Intervention

Monitoring and questionnaires:

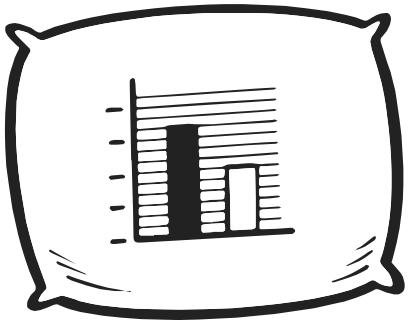


5 Week intervention





Feasibility Trial

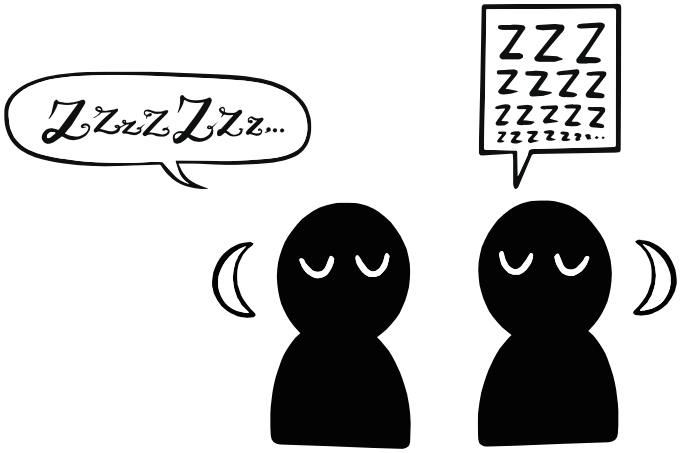


- 6 PWD had improved sleep efficiency (0.6-3.6%)
- 5 PWD had improved subjective sleep ratings (1-3 PSQI points)
- Cognition (MMSE) and Quality of life scores also improved for some but many deteriorated across trial
- 5 carers had improved subjective sleep
- 3 also had improvements to depression scores
- 6 carers indicated increased care-related stress

- Diverse population
- Case studies indicated that some benefitted

Gibson, R. H., Gander, P. H., Jones, L. M., & Dowell, A. C. (2016).

Case: Adam and Claire

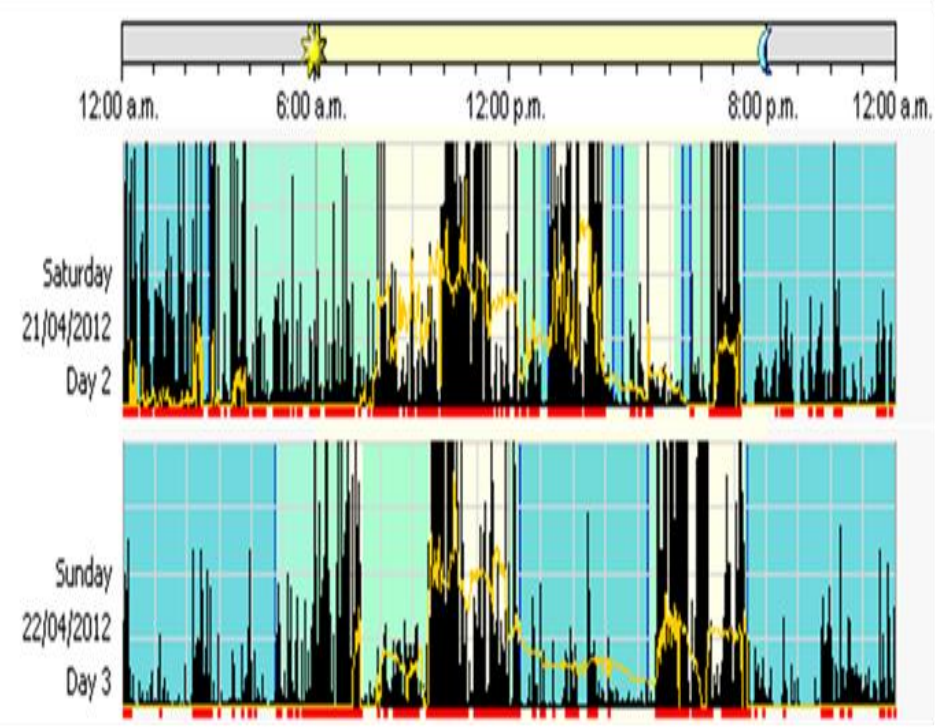


Adam: 82 year old with LBD,
plus Parkinson's and lung disease, MMSE = 5
Claire: 68 year old who worked full time plus provided support to Adam
Time 1: Waking up in night, coughing snoring, bad dreams, restless legs, up in the night, confusion disorientation, waking Claire

Gibson, R. H., Gander, P. H., Jones, L. M., & Dowell, A. C. (2016).

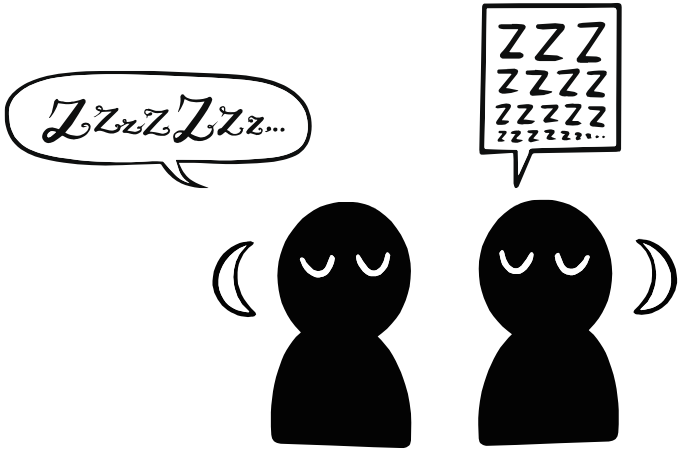
Non-pharmacological interventions trial Case study: Adam's Sleep

Time 1



Gibson, R. H., Gander, P. H., Jones, L. M., & Dowell, A. C. (2016)

Adam and Claire: Time 2



- Still rated sleep poorly, but severity and distress associated with disruptions improved
- No longer waking as early
- Less sleepy in the day
- Frequency of memory-related problems improved
- Quality of life rated more highly

Sleep, Dementia & Caregiving

Some key findings

- Sleep problems of PWD and carers are varied, diverse and complex
- It is feasible for PWD and carers to use non-pharmacological interventions at home
- Improving sleep can positively influence waking life
- Carers sleep undergoes changes across the caregiving trajectory and post caregiving responsibilities
- Dementia-related research has unique challenges

Gibson, R., Gander, P., & Jones, L. (2014)
Gibson, R., Gander, P., Jones, L., & Dowell, A. (2016)
Gibson, R. & Gander, P. (2020)

Thank you

"Overall I can only draw one conclusion, that's my conclusion of course, the whole way of living affects your sleep, affects your rest, and I realise now that there must have been times that, yeah, I was tired and didn't really function as well as I should." (Jacob, 87)

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- Dementia Wellington
- Participants
- Funders:

Managing Sleep and Wake Disturbances in Dementia

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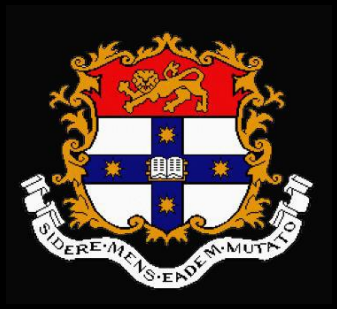


University of Sydney

Sleep

- Active process
  - Plenty going on when the lights go out
- Regulated with wakefulness
  - Multiple systems
- Non-Sleep factors
  - Sleep apnoea
  - Bladder
  - Mood
  - Medications

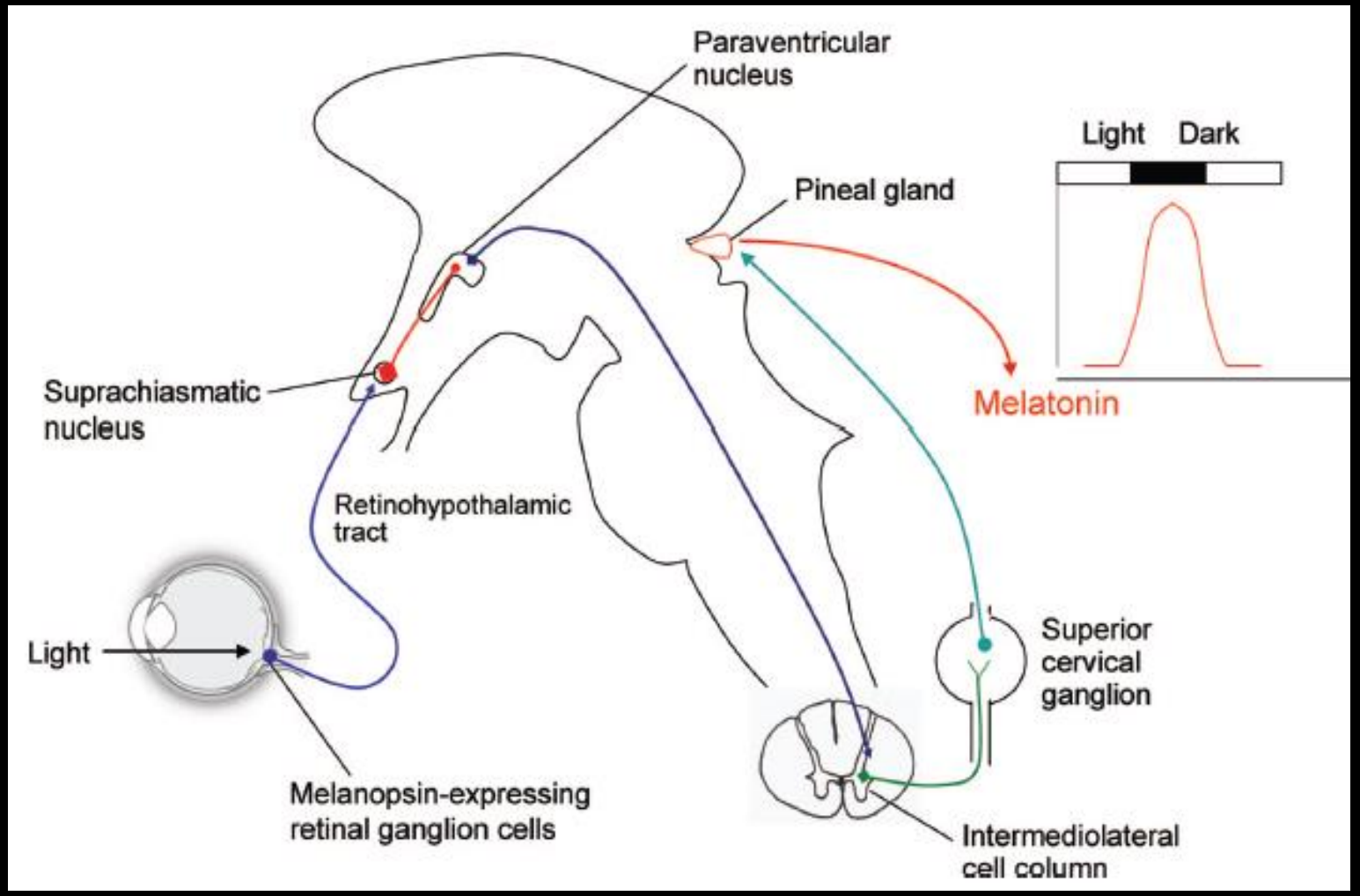
Sleep-Wake Regulation Systems

- Circadian
  - Daily cycle
  - Operating over changing Seasons
- Sleep Homeostat
  - Drive to wakefulness or sleep
  - Individual day
- Ultradian
  - Sleep stages throughout the night

Sleep-Wake Regulation

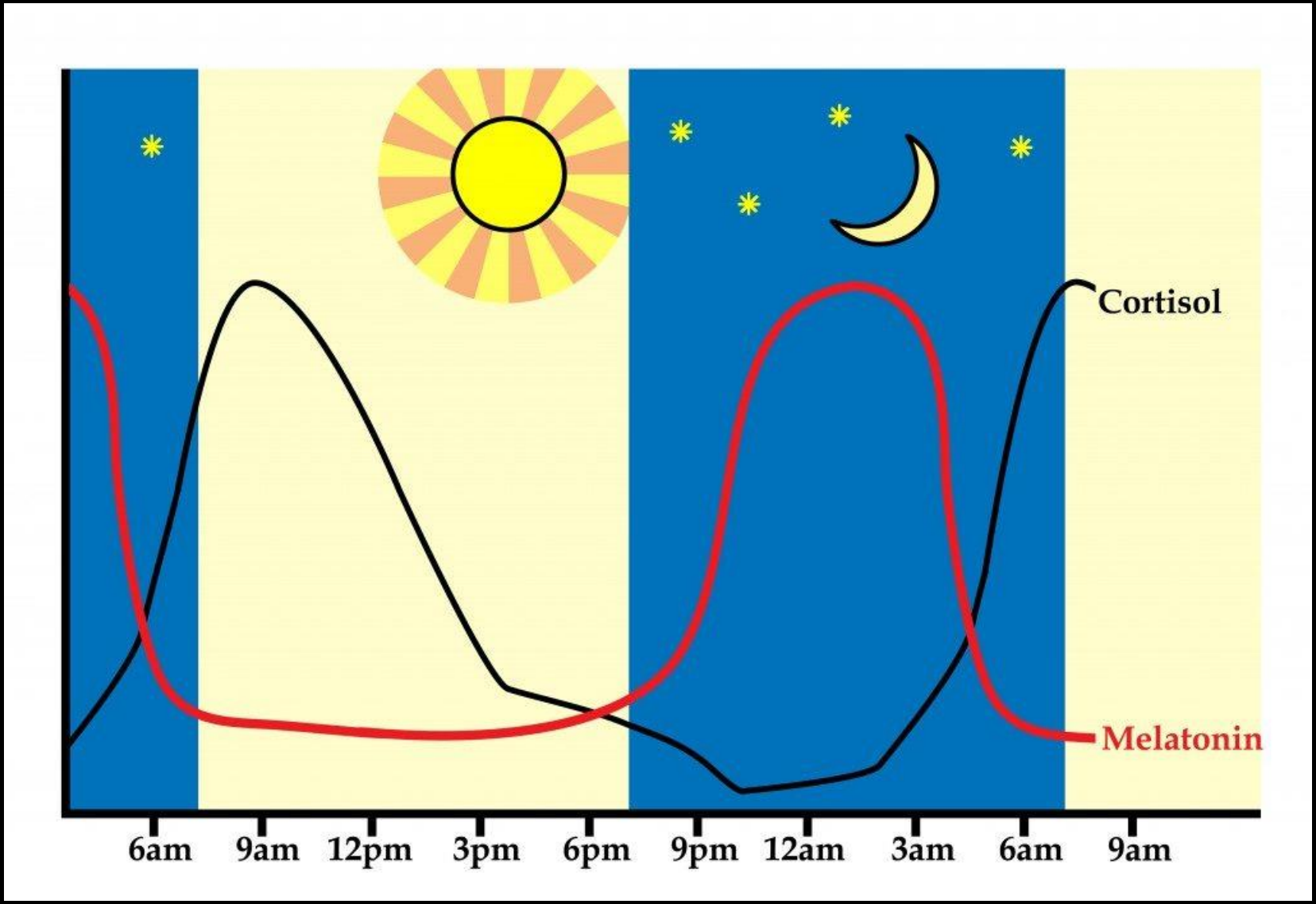
- Circadian disruption
  - Insomnia and Somnolence
  - Sundowning?
- Circadian control
  - Melatonin

Melatonin Regulation



Benarroch Neurol 2008

Melatonin-Cortisol Regulation



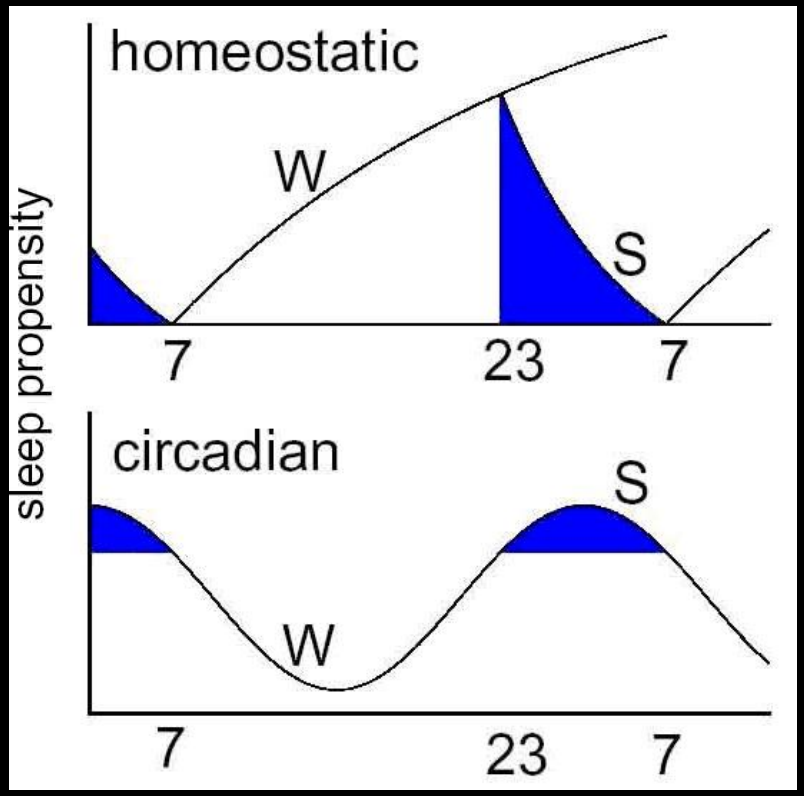
Melatonin

- Natural hormone in the brain
- Levels rise with falling light
- Involved in regulation of circadian system
  - Sleep onset/offset
  - Thermoregulation
  - Appetite
- Concentrations diminish with ageing
- Onset changes with ageing

Clock Genes

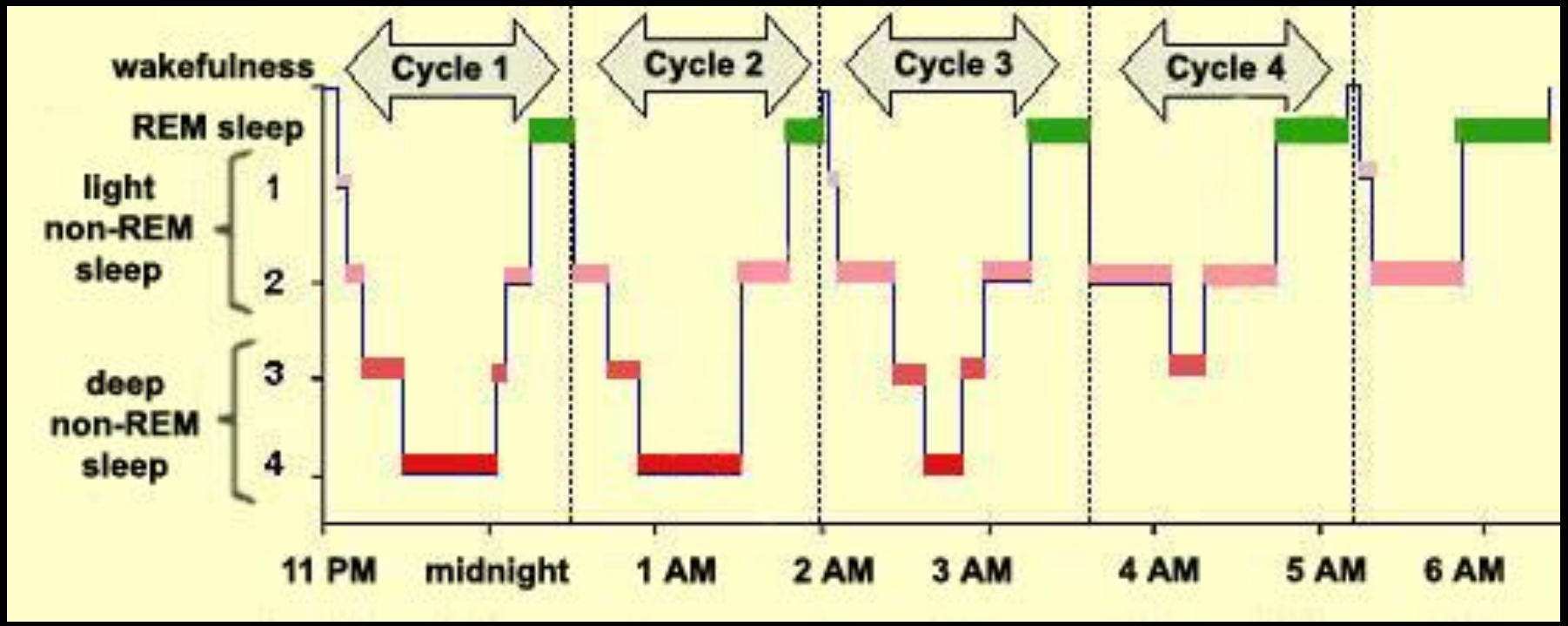
- Every cell on 24 hour cycle
  - Regulated by Clock Genes (e.g. Bmal1, Per1 & 2)
  - Cellular homeostasis to clear aggregated proteins

Sleep Homeostat



Adenosine as a by-product of ATP?
Analgoue - Caffeine

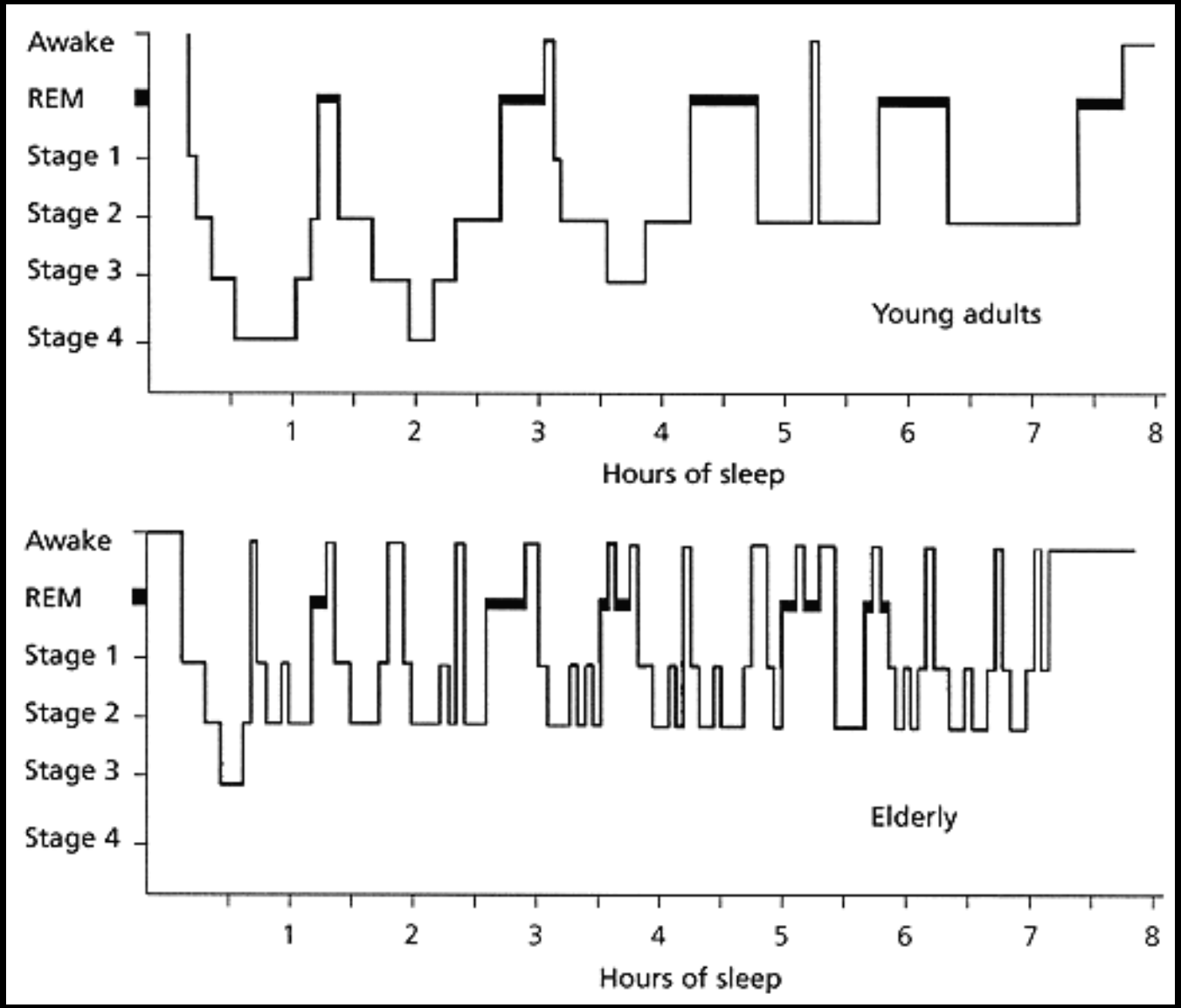
Hypnogram - Ultradian



Ascending Arousal & Sleep Promoting Systems

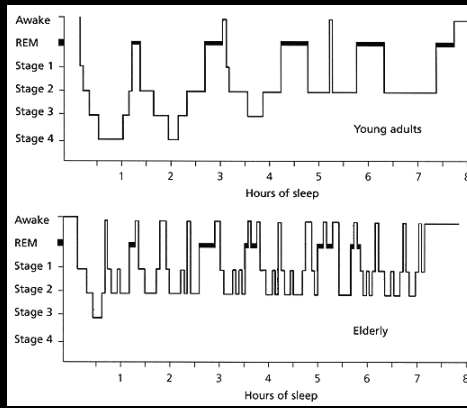
- Neural circuits
  - Reciprocal inhibitory connections
  - AAS↔VLPO (hypothalamus)
- Neurotransmitters
  - Monoaminergic, Dopaminergic, Cholinergic, GABAergic, Galaninergic, Orexinergic
- Homeostatic drivers
  - Adenosine?

Sleep in Ageing



Sleep in Ageing

- Poor consolidation of deeper NREM stages
  - Declarative memory (knowing what)
  - Remembering facts and events
- Less REM
  - Procedural memory (knowing how)
  - Learned actions



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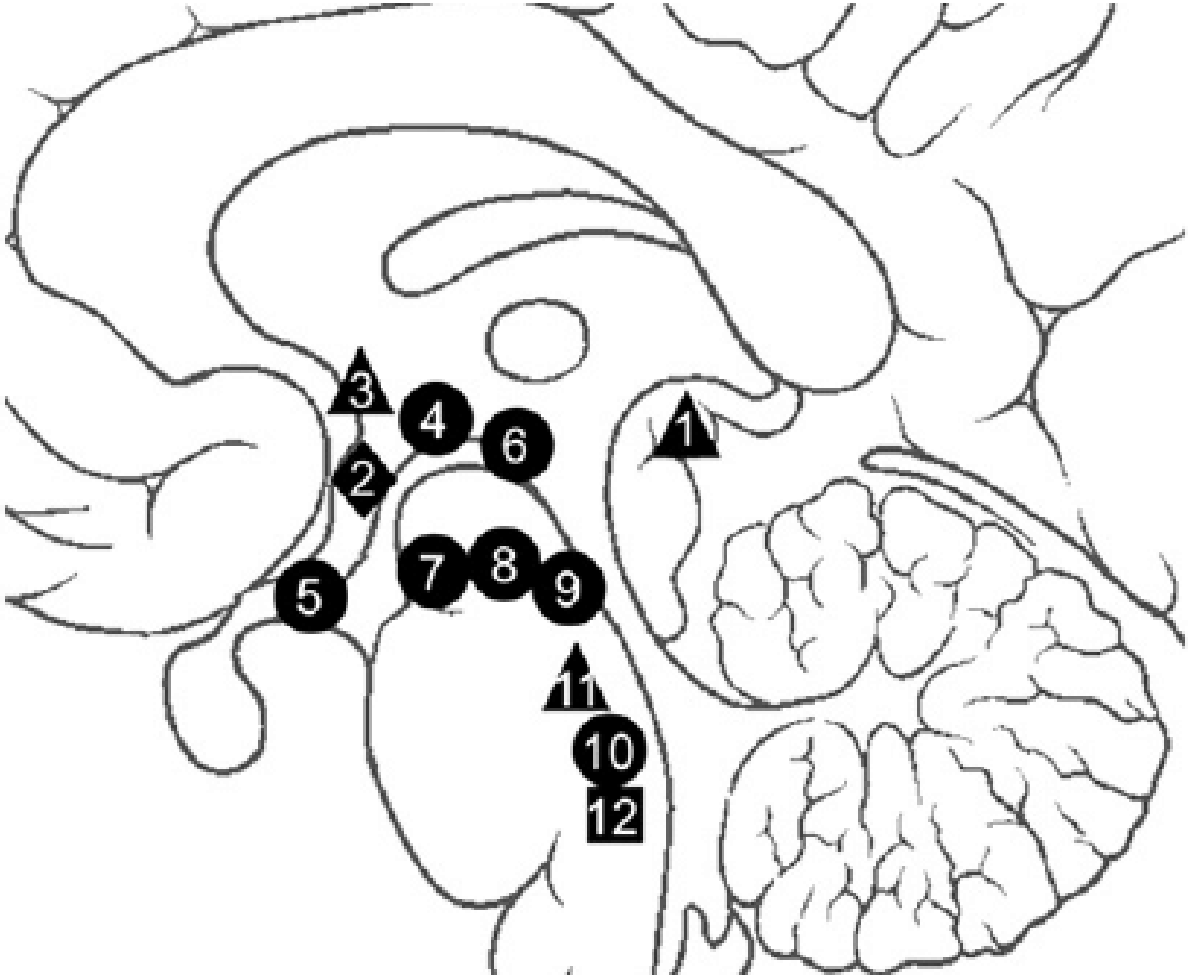
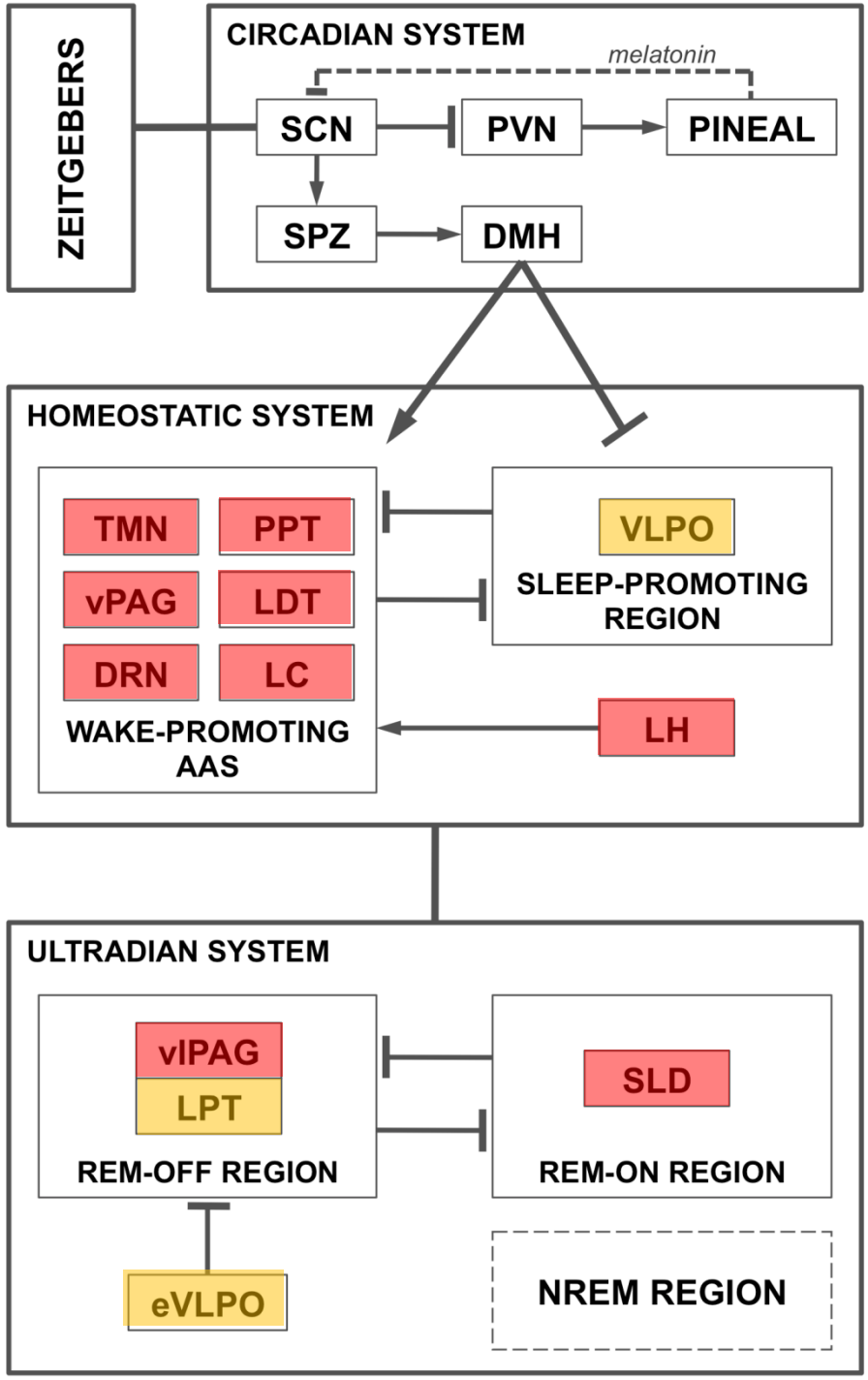
journal homepage: www.elsevier.com/locate/jns

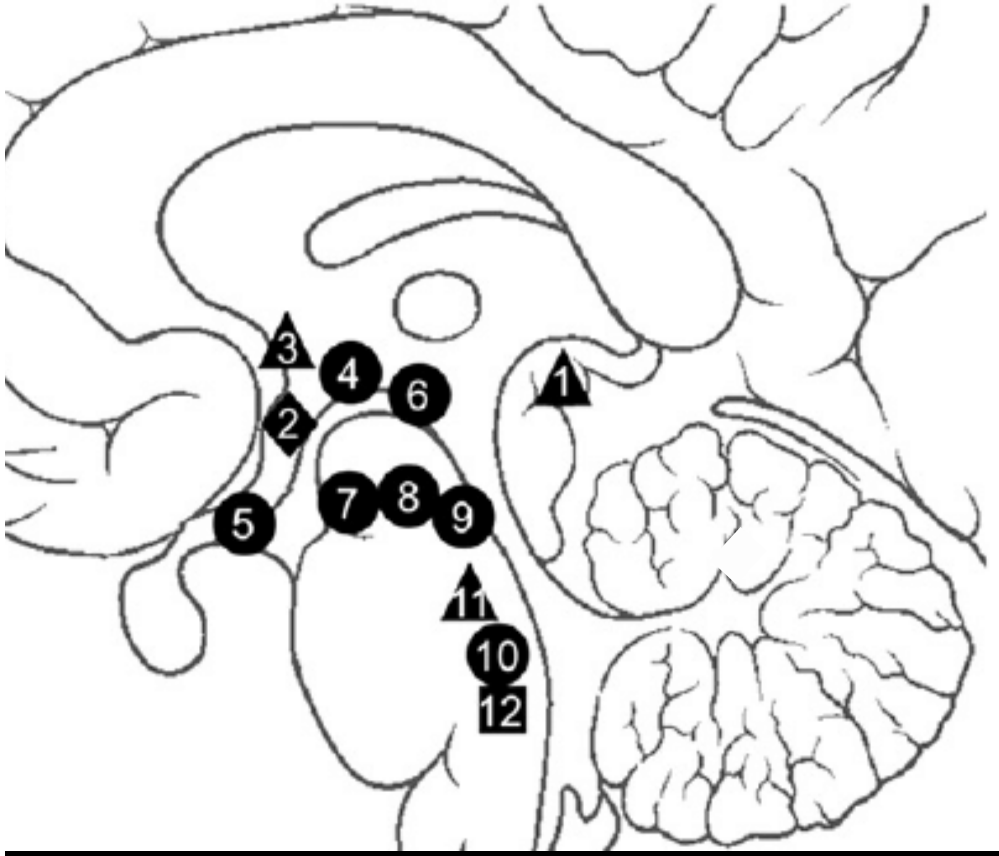
Sleep–wake disturbances in common neurodegenerative diseases: A closer look at selected aspects of the neural circuitry☆,☆☆

George Zhong [a], Sharon Linda Naismith [a], Naomi Louise Rogers [b], Simon John Geoffrey Lewis [a,*]

1. Pineal
2. SCN
3. VLPO
4. LH
5. TMN
6. vlPAG
7. DRN
8. LDT
9. PPT
10. LC
11. LPT
12. SLD







▲ Alzheimer's

■ Parkinson's

● AD/PD

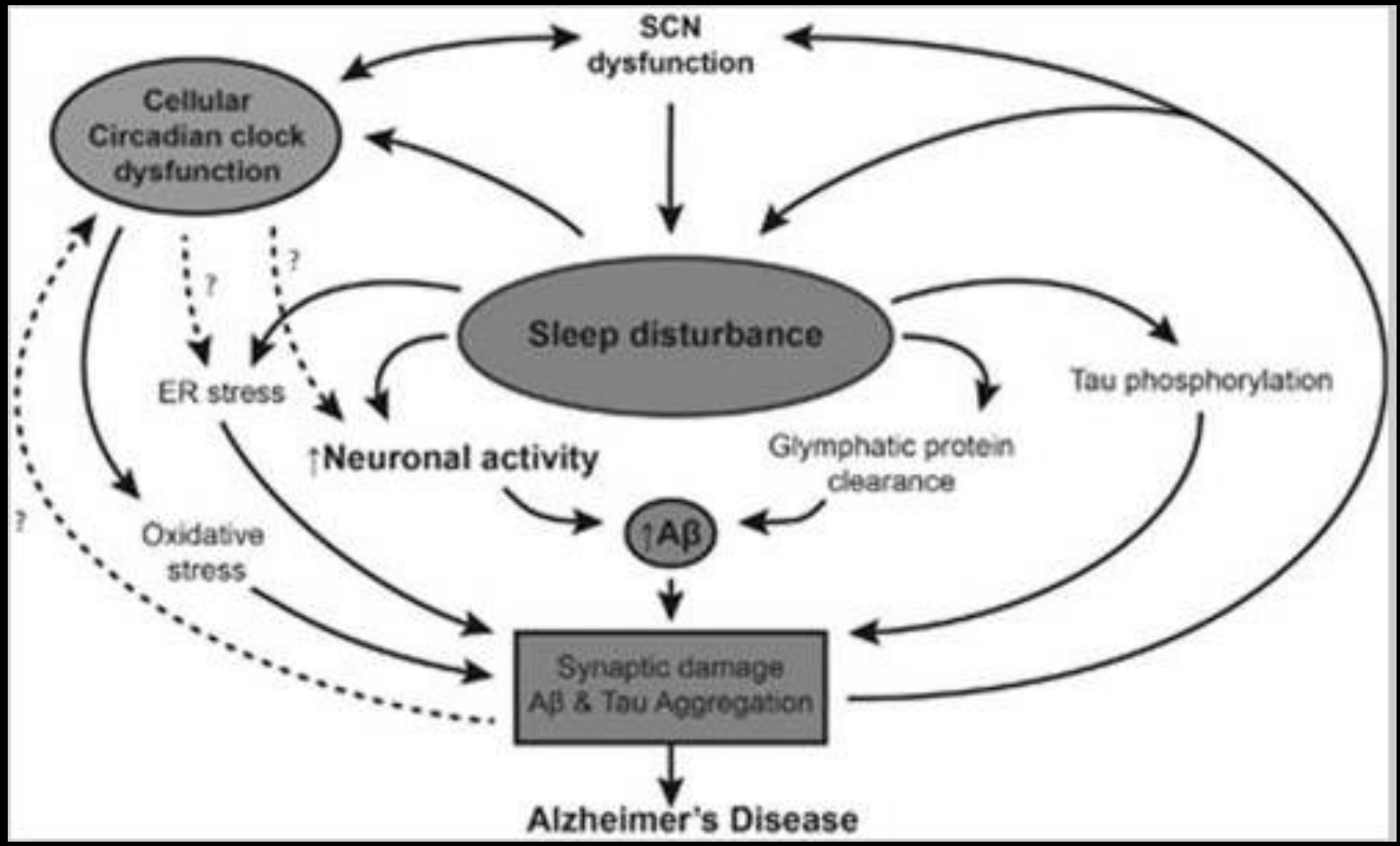
♦ Unclear

Zhong et al 2010 J Neurol Sci

Circadian disturbance in AD

- Sleep-wake disturbance common
  - >40% (insomnia, sundowning, somnolence)
- Pathology in SCN
  - Disrupted circadian rhythms
  - Also seen in MCI
- Bidirectional pathophysiology
  - Sleep–wake cycle regulates levels of beta-amyloid in the brain
  - Animal models manipulate sleep to clear beta-amyloid

Sleep disruption and pathogenesis in AD



Musiek et al Exp Mol Med 2015

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Pharmacotherapies for sleep disturbances in dementia

Jenny McCleery[1], Ann L Sharpley[2]

Citation: McCleery J, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database of Systematic Reviews* 2020, Issue 11. Art. No.: CD009178. DOI: 10.1002/14651858.CD009178.pub4.

- Hypnotics (BDZs and Z-drugs)
  - No RCTs
- Melatonin (up to 10 mg) or Receptor agonists
  - No benefit
- Trazadone and Orexin Antagonists
  - May be beneficial with no harmful effects
  - Large trials required

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- Trazadone
  - Serotonin receptor antagonist and reuptake inhibitor (SARI)
  - *Psychiatrist*
- Orexin Antagonists
  - Suvorexant
  - *Sleep Physician*

Treating sleep-wake disturbance in AD

- Sundowning
  - BPSD strategies
- Circadian manipulation
  - No evidence to support: Melatonin, Bright Light
- Exclude/Treat OSA
  - OSA may exacerbate/drive dementia[1]
- Cholinesterase inhibitors
  - May remediate sleep architecture possibly via cholinergic systems critical to REM sleep

1. Dunietz et al Sleep 2021

Treating sleep-wake disturbance in AD

- Insomnia
  - Hypnotics (BDZ and z-drugs)?
  - Sedation, confusion, falls, OSA
- Antidepressants
  - May help insomnia but may suppress REM
  - Sedation, cardiovascular
- Antipsychotics (atypical)
  - Sedating, may worsen sleep–wake disturbance
  - Increase mortality (cardio/cerebrovascular)

Sleep-wake complaints in PDD and DLB

- Insomnia (Early, Mid and Late)
- Daytime Somnolence (Medications, OSA)
- Motor (Wearing Off, Dystonia)
- Non-motor (Mood, Nocturia, OSA)
- REM Sleep Behaviour Disorder
- Restless Legs Syndrome

RESEARCH ARTICLE

The *Movement* Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi, MD,[1]* Daniel Weintraub, MD,[2] Miguel Coelho, MD,[3] Santiago Perez-Lloret, MD, PhD,[4] Susan H. Fox, MRCP (UK), PhD,[5] Regina Katzenschlager, MD,[6] Eva-Maria Hametner, MD,[1] Werner Poewe, MD,[1] Olivier Rascol, MD, PhD,[4] Christopher G. Goetz, MD,[7] and Cristina Sampaio, MD, PhD[8]*

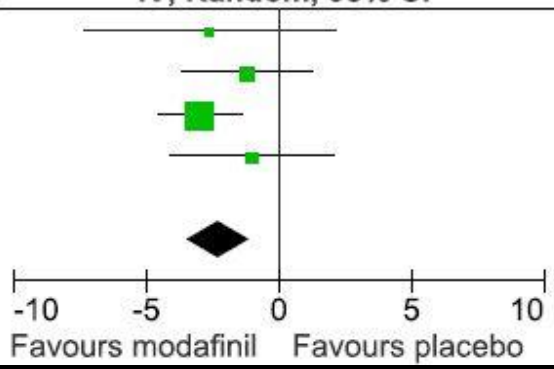
	Efficacy	Safety	Practice implications
Insomnia			
Controlled-release formulation of levodopa/carbidopa	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Pergolide	*Insufficient evidence*	*Acceptable risk with specialized monitoring*	*Not useful*
Eszopiclone	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 3–5 mg	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 50 mg	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

Modafanil

- Combined data from 4 of the studies

Study or Subgroup	Modafinil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adler 2003	14.4	5.7	10	17	5.1	10	6.3%	-2.60 [-7.34, 2.14]
Hogl 2002	9.8	2.2	12	11	3.8	12	22.8%	-1.20 [-3.68, 1.28]
Lou 2009	6	1.6	6	9	1.5	10	56.2%	-3.00 [-4.58, -1.42]
Ondo 2005	13.5	4.8	19	14.5	4.8	18	14.7%	-1.00 [-4.09, 2.09]
Total (95% CI)			**47**			**50**	**100.0%**	**-2.27 [-3.46, -1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.75 (P = 0.0002)

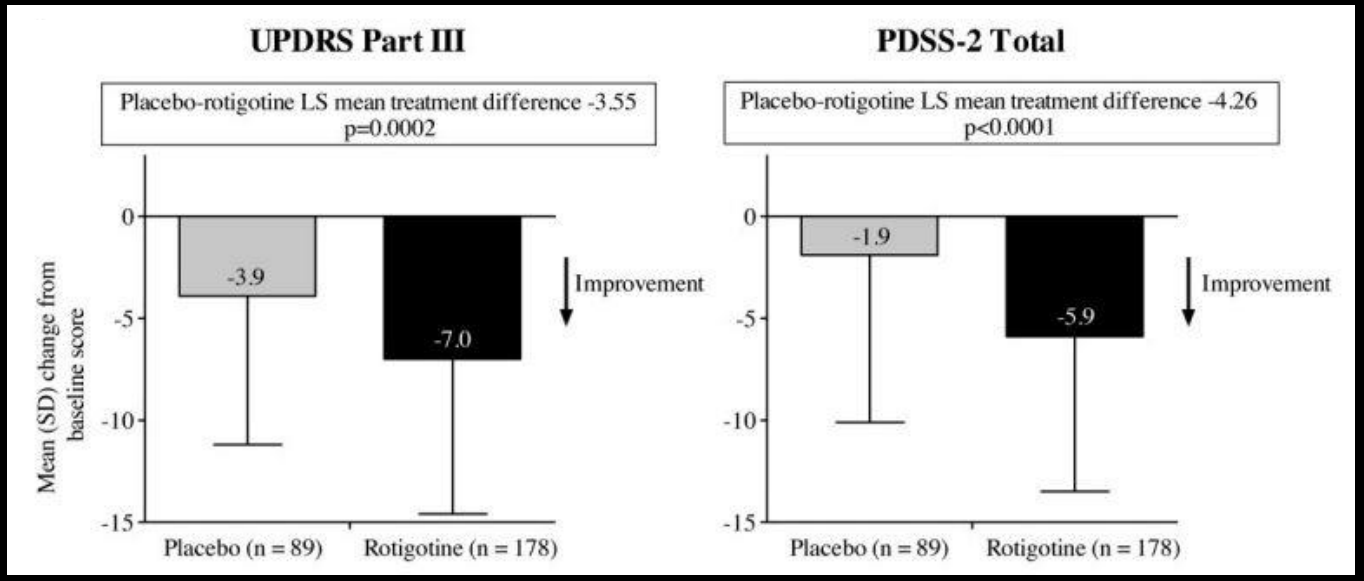


- Modest ESS improvement
- Cautious use with monitoring?

Trotti and Bliwise Neurotherapeutics 2014

Early morning motor and overnight sleep

- RECOVER study: Rotigotine v Placebo
- Co-Primary endpoints
  - Problematic early morning motor symptoms
  - PDSS-2 (self-report questionnaire)



Trenkwalder et al Mov Disord 2011

Sleeping with the Enemy!

Rapid Eye Movement Sleep Behavior Disorder (RBD)

- Loss of normal muscle atonia during REM sleep
- Dream enactment behaviour
- Congruent motor activity
  - Punching or shouting
- Injury
  - Make bed environment safe
  - Self & bed partner 33%[1]

(1) *Comella et al. (1998) Neurology*

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

Clonazepam for probable REM sleep behavior disorder in Parkinson's disease: A randomized placebo-controlled trial

Chaewon Shin[a], Hyeyoung Park[b], Woong-Woo Lee[c], Hyun-Jeong Kim[d], Han-Joon Kim[d,*], Beomseok Jeon[d]

Efficacy results (intention-to-treat population).

Outcome measure[a]	Placebo (n = 20)	Clonazepam (n = 17)	p-value[b]
Primary outcome: CGI-I score			
Week four, median (min, max)[c]	3 (1,6)	2 (1,5)	0.253
Week four, mean (SD)	2.95 (1.36)	2.47 (1.23)	

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

Melatonin for Rapid Eye Movement Sleep Behavior Disorder in Parkinson's disease: A Randomised Controlled Trial

Moran Gilat PhD, Alessandra Coeytaux Jackson MD, Nathaniel S. Marshall PhD, Deborah Hammond RN, Anna E. Mullins PhD, Julie M. Hall MSc, Bernard A.M. Fang MD, Brendon J. Yee MD, Keith K.H. Wong MD, Ron R. Grunstein MD, Simon J. G. Lewis MD https://doi.org/10.1002/mds.27886

Movement Disorders
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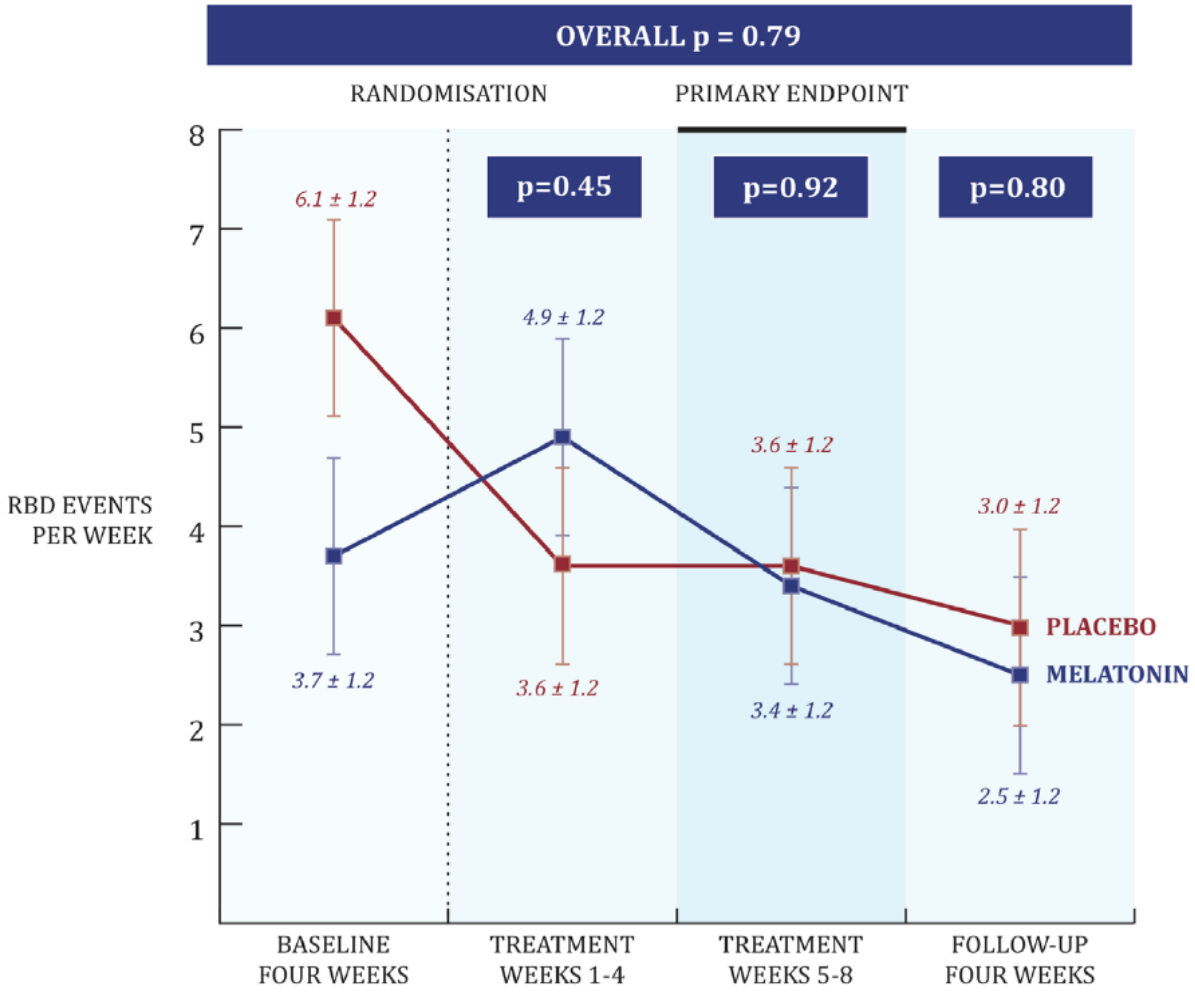
Melatonin for Rapid Eye Movement Sleep Behavior Disorder in Parkinson's disease: A Randomised Controlled Trial



Restless Legs Syndrome

- Weak association between PD and RLS
  - Case-control study including PSG
  - 400 study subjects
  - RLS: PD (3%) Controls (0.5%) in controls) *Loo & Tan J Neurol Sci 2008*
- RLS screening
  - Iron studies, neuropathy screen
  - Vascular studies (doppler)
  - Nerve conduction studies

Restless Legs Syndrome

- First line dopaminergic therapy
- Meta-anaylsis demonstrated benefits
  - Dopamine agonists
  - L-dopa
  - Gabapentin
  - Pregabalin
  - Oxycodone (only one RCT)
    Hornyak et al Sleep Med Rev 2014

Restless Legs Syndrome

- Pregabalin
  - 52 week RCT
  - Pregabalin 300mg
  - Pramipexole (0.25-0.5mg)
  - Placebo
- Pregabalin
  - Reduced symptoms compared with placebo
  - Augmentation rates were lower than with pramipexole

Allen et al NEJM 2014

Frontotemporal Dementia

- Severe sleep fragmentation
  - bvFTD>Language variants
  - May be correlated with other hypothalamic disturbance (hyperphagia)
- Insomnia
  - Circadian disruption not well characterised
- Excessive daytime sleepiness
- Supportive management

Motor Neurone Disease

- Respiratory failure
  - Major prognostic indicator
  - May have normal respiratory function
  - May have no signs of diaphragmatic denervation
- Non-invasive positive pressure ventilation (NIV)
  - Improves respiratory symptoms, quality of life, and survival
  - Should be offered to all patients at early stage

Ahmed et al Sleep Med Rev 2016

Managing Sleep Fragmentation

- Nocturia
  - Urology referral if voiding ≥2 times per night
- Depression and Anxiety
- Medication review
  - Corticosteroids, beta-blockers
- Non-pharmacological
  - Exercise, stretching
- Avoid alerting events
  - Devices (blue light)

Summary

- Common: Over 60% of patients
- Quality of Life
- Trigger for residential care
- More research needed

https://brainmasterclass.com.au

OCTOBER 9TH & 10TH 2021