



NCCRED

National Centre for Clinical
Research on Emerging Drugs

WELCOME TO THE WEBINAR



Australian Government
**Department of Health
and Aged Care**



THE UNIVERSITY OF
SYDNEY
—
Matilda Centre

Acknowledgement of Country

We would like to acknowledge and pay respects to the Traditional Custodians of Country throughout Australia and recognise their continuing land, water and culture.

We pay out respects to those who have cared and continue to care for Country.





Housekeeping

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1 You are in **listen-only** mode

2 Please type your questions using the **Q&A button** on your dashboard.

3 This **webinar is being recorded** and will be made available on *Cracks in the Ice*.

4 *Cracks in the Ice* and NCCRED both hold regular webinars/seminars. For more information visit *Cracks in the Ice* (cracksintheice.org.au) and/or NCCRED (nccred.org.au) websites



Methamphetamine and Sleep

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NDARC
National Drug &
Alcohol Research Centre
The Difference is Research



Acknowledgements

The work presented here was conducted on Gadigal land, and I would like to pay my respects to elders past and present and extend that to any Aboriginal and Torres Strait Islander peoples here today.

Sovereignty never ceded.

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NDARC
National Drug &
Alcohol Research Centre
The Difference is Research



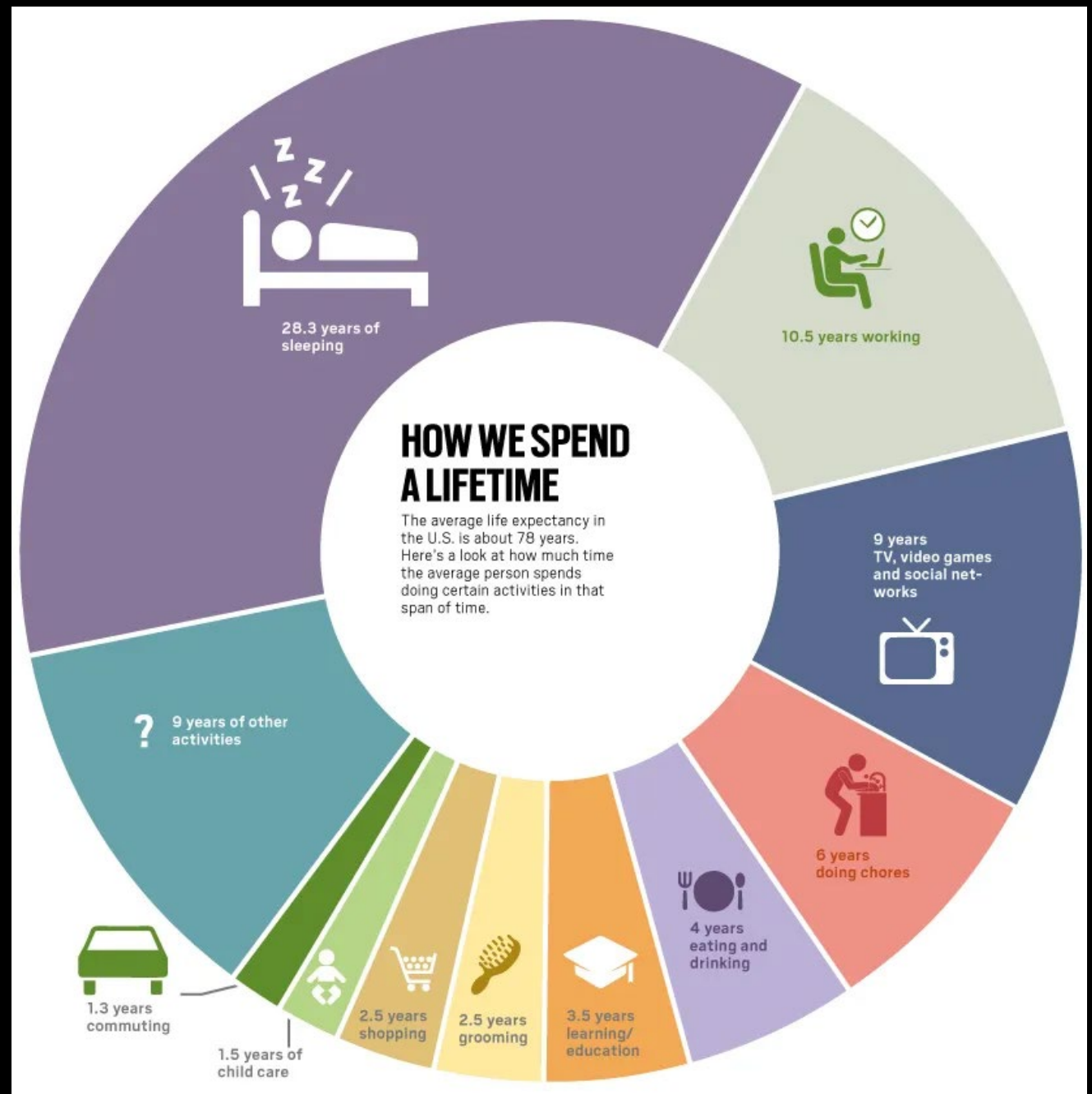
Conflicts of interest

The National Centre for Clinical Research on Emerging Drugs (NCCRED) is funded by the Australian Government Department of Health and Aged Care.

We have no conflicts of interest to declare

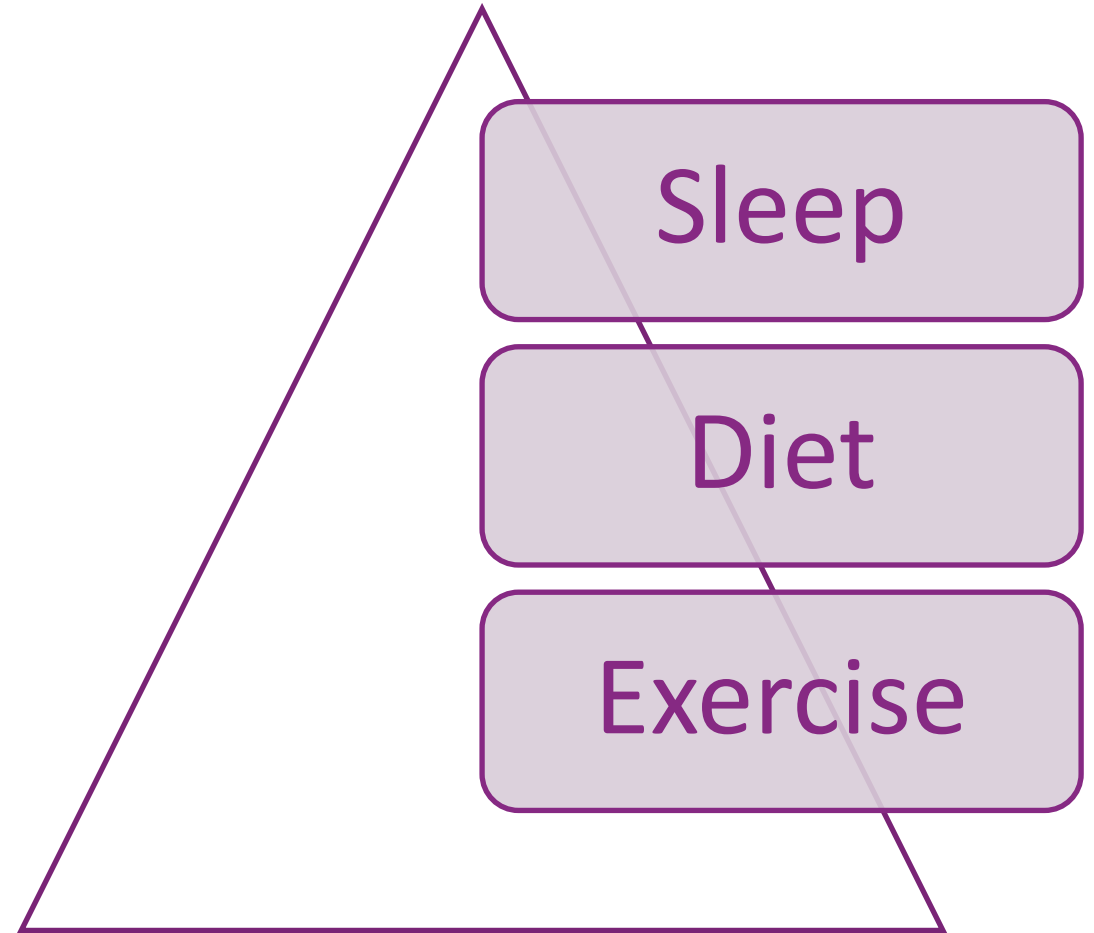
Why do we sleep?

Single most important (and continued) experience in your life



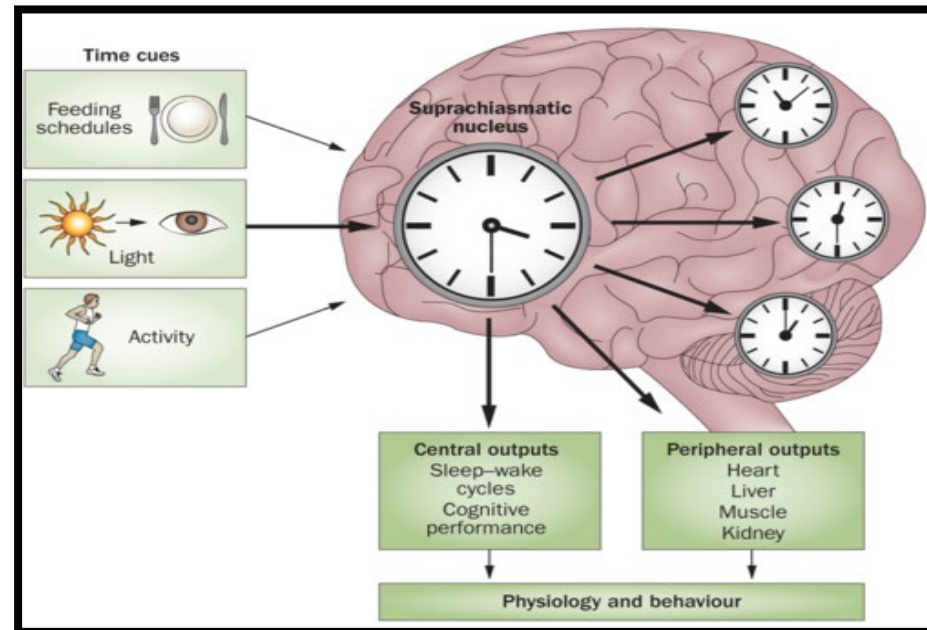
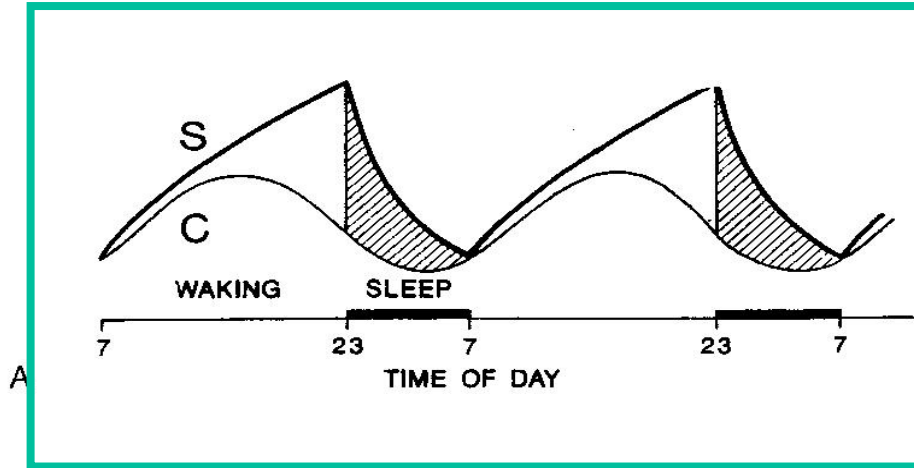
Why do we sleep?

- Sleep is an **active, complex state**
- **Rest & Recuperation**
(Tobler, 2005)
- **Memory encoding and consolidation**
(Stickgold, 2005 Nature)
- **Maintain cognition and performance**
(Jewett et al, 1999; Sleep)

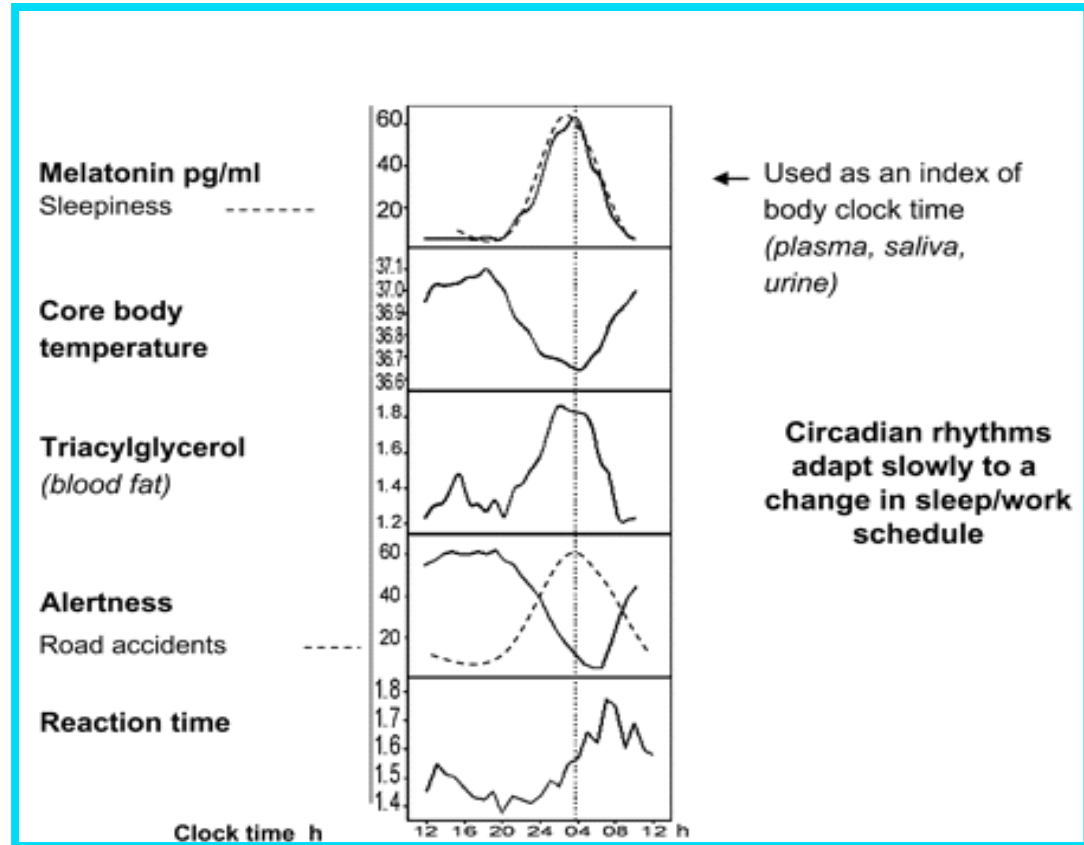


The Body Clock: Sleep timing extraordinaire





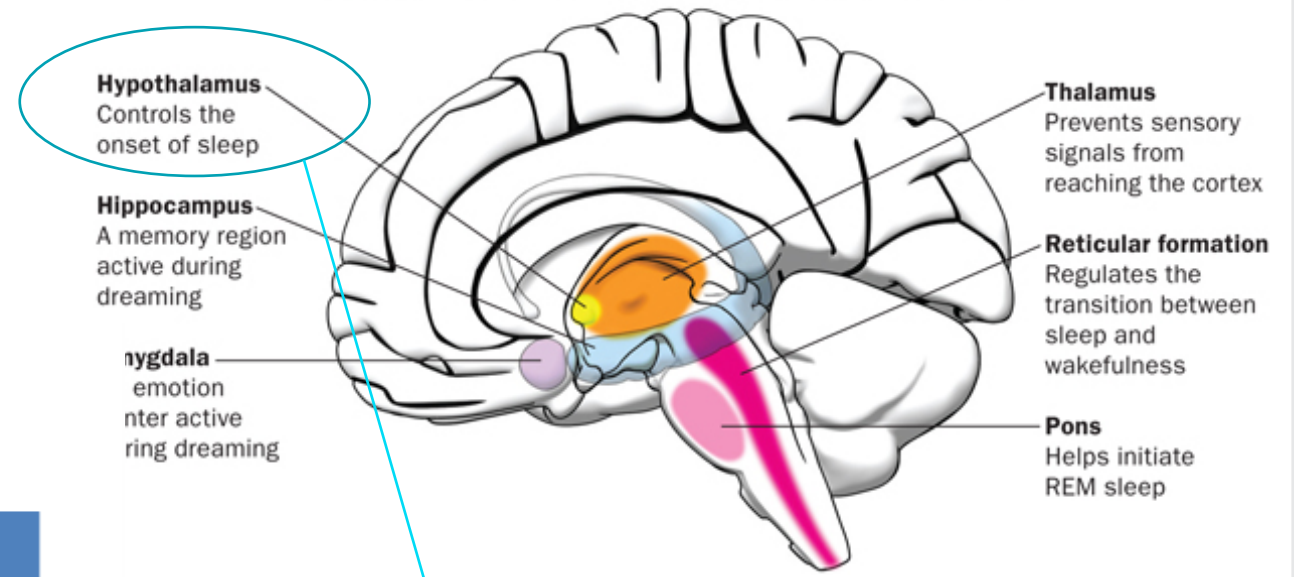
Circadian Physiology



(Arendt, 2010, Occ Med; Rajaratnam & Arendt, 2006, Lancet)

- **Hyperarousal**
- Sleepiness
- Detection of Light/dark signals

Central Brain Regions Involved in Sleep



SCN

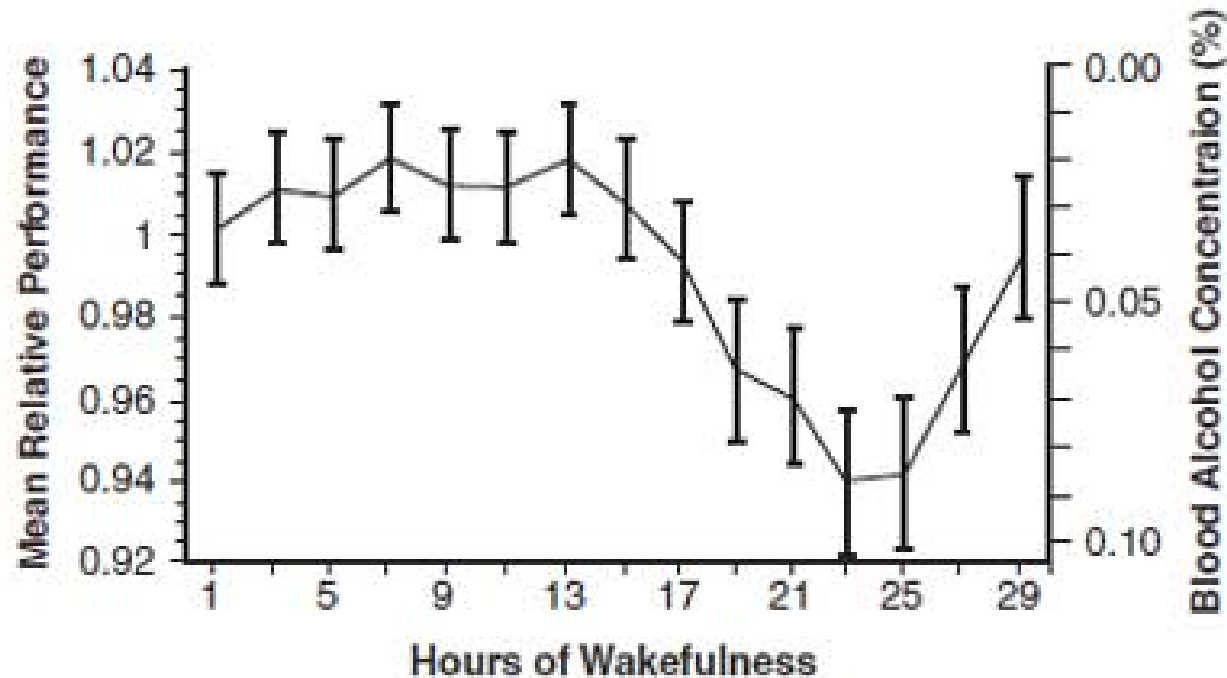
Neurotransmitters in wakefulness and sleep

Wakefulness
<ul style="list-style-type: none"> • Monoamines • Dopamine (DA) • Norepinephrine • Serotonin (5-HT) • Acetylcholine • Histamine • Orexin/hypocretin

Sleep
<ul style="list-style-type: none"> • Adenosine • GABA • Melatonin • Galanin

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Magnitude of performance impairment



17 hours awake performance degraded to equivalence of **0.05% BAC**

=2x chance of accident

24 hours awake performance degraded to equivalence of **0.10% BAC.**

=7x chance of accident

Consequences of circadian desynchrony

INDIVIDUAL

PUBLIC HEALTH



Disease

- Risk factor for type II diabetes
- Increased risk of developing and/or dying from cardiovascular disease

Depner et al. 2014 Curr Diab Rep
Morris et al. 2014, PNAS



Performance

- Medical interns more likely to make errors
- More likely to be injured

Lockley et al. 2004, N Engl J Med
Dijke et al. 1992, J Sleep Res



Public Safety

- Main predictor for road traffic accidents (>3x higher – FR)
- Impact on health & safety outcomes of fire fighters

Phillip et al. 2014. PLoS One
Barger et al. 2015 J Clin Sleep Med

Many drugs affect sleep

- **Some increase sleepiness**

- (e.g. Benzodiazepines: prescription antihistamines: OTC (+ performance))

- **Some promote vigilance**

- (e.g. Caffeine, nicotine)

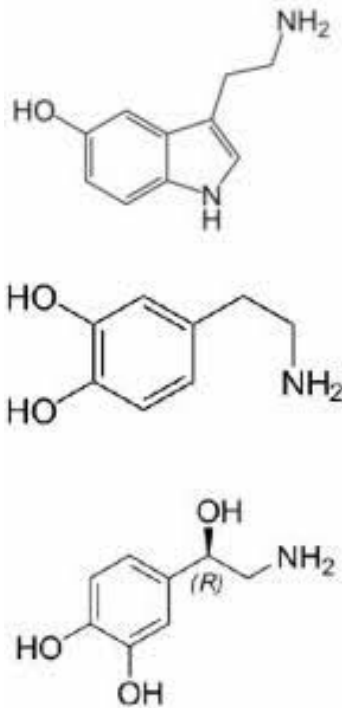
- **Some have sleepiness as a side-effect**

- (e.g. drugs to treat cardiovascular disease, SSRIs – but not performance)

- **These drugs can affect:**

- Subjective experience of sleep
- Underlying sleep architecture
- The body clock and entrainment to the external environment

Methamphetamine and sleep



- Methamphetamine affects sleep
- Wakefulness promotion likely due to interactions with monoamines and the CNS
- Causes increased production of, and longer duration of:
 - Dopamine
 - Serotonin
 - Noradrenaline
- All of which influence sleep

Immediate interactions

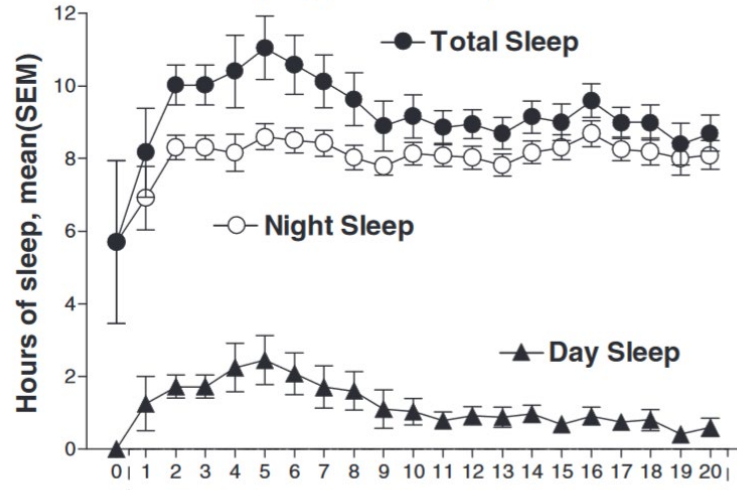
- Based on patterns of use and individual biology
- Binge-crash
 - Involves heavy use for a period of days
 - **Heavily disrupted sleep** (73% reported sleeplessness)
 - **More hallucinations** (54%)
 - No to very little sleep while using
 - **Crash and hypersomnia**
- Non-binge
 - Characterised by **more regular daily use**
 - May or may not involve other substances to aid in sleep
 - **Less disrupted sleep** (53% sleeplessness)
 - **Less hallucinations** (20%)

(Semple et al. 2003)

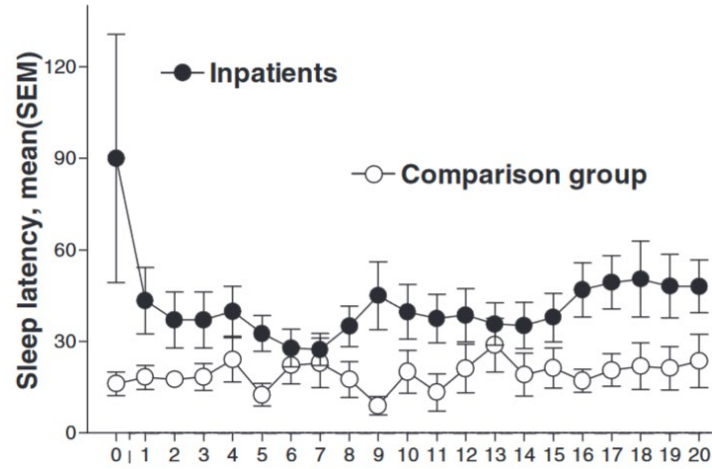
MA withdrawal and sleep

- Hypersomnia immediately post cessation (i.e. the crash) particularly prevalent
 - Usually lasting 1-3 days
 - People are particularly difficult to rouse
- During protracted withdrawal (weeks) both **hypersomnia** and **insomnia** are reported
 - Vivid and particularly unpleasant dreams

Panel 1: Sleeping patterns - Inpatients

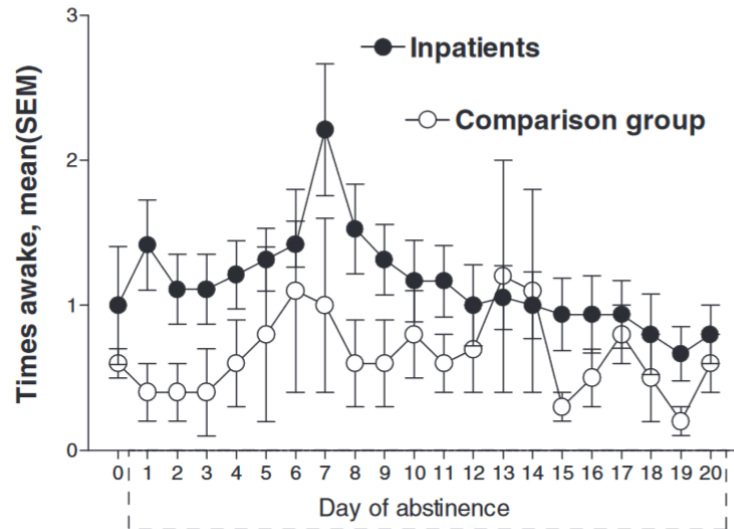


Panel 3: Sleep latency

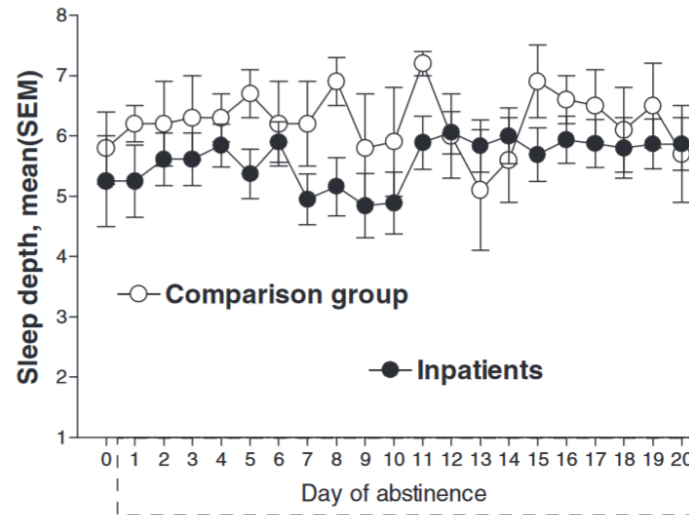


Is there data to back this up?

Panel 4: Times awake



Panel 8: Depth of sleep



McGregor et al. 2005

Paradoxical insomnia during withdrawal?



- Small study of lisdexamfetamine for the treatment of acute MA withdrawal, combined subjective and objective measures
- Participants **underestimated their nightly total sleep by 58.5 minutes** when compared to an objective measure (actigraph)
- Might indicate paradoxical insomnia, where **subjectively perceived sleep and objectively measured sleep are mismatched** (Edinger and Krystal, 2003)
- Possible **reduction in slow wave sleep** (Lecci et al., 2020), associated with:
 - **Restorative sleep, hormonal regulation and memory consolidation** (Asif et al., 2017; Gronfier and Brandenberger, 1998; Walker, 2008)

Long term effects

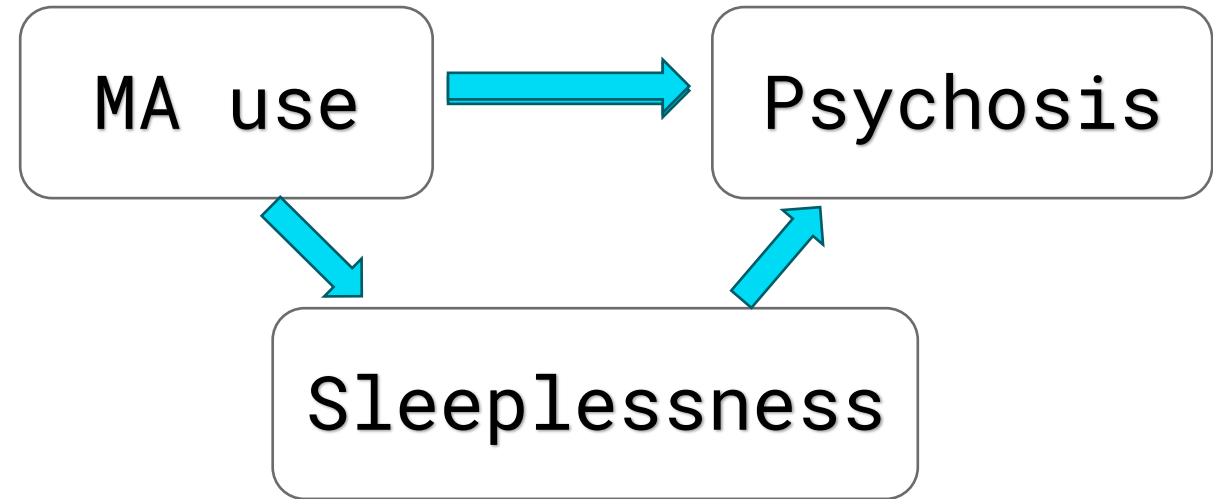
- Can cause disruption to the circadian rhythm
- Leading to lasting sleep disturbances
- Associated with use *and withdrawal*, meaning cessation may not bring immediate relief to sleep problems

Does this matter?

- For those who binge (n=41, Semple 2003), the three **main reasons for stopping use** were:
 - To get some **sleep (34.3%)**
 - Crashed from **exhaustion (23.7%)**
 - Ran out of drugs (10.5%)
- During withdrawal sleep disruption has been **described as some of the most undesirable symptoms of withdrawal** (McGregor et al., 2005; McGregor et al., 2008; Perez et al., 2008)
 - Sleep issues hypothesised **risk factor driving return to dependent use** post cessation (Brower and Perron, 2010)



Methamphetamine, sleep and psychosis – what's the link?



- **MA use and sleeplessness** are both associated with **psychosis**
- The **causal relationship** between the three is **yet to be established**
- Previous authors have hypothesised that the **efficacy of pharmacological interventions** for MA use may be mediated by that **medications ability to improve sleep**
- If this link is driven by sleeplessness, **what would happen if we could improve sleep without clients having to become abstinent?**
- We do not have enough data to answer these questions

Clinical presentations of MA use, withdrawal and sleep deprivation

Chronic MA use	MA withdrawal	Sleep deprivation
<ul style="list-style-type: none"> • Neurological • Cerebrovascular • Stroke • Hypertension • Cardiovascular complications • Hyperpyrexia • Rhabdomyolysis • Cognitive impairment • Psychosis 	<ul style="list-style-type: none"> • Craving • Increased appetite • Dysphoria • Anxiety • Slow movement • Agitation • Hyper or hyposomnia • Vivid or unpleasant dreams • Cognition 	<ul style="list-style-type: none"> • Physical exercise capacity • Vision impairments • Cognitive functioning • Metabolic changes and hunger • Hormonal changes • Immune system impairment • Neurological measures • Cardiovascular function • Mental health (incl. anxiety, depression, hallucinations) • Hypertension

Are these related? Do they compound risk? We don't know

More gaps in the knowledge

- Sleep architecture and neurological measures of sleep
- Short-term monitoring during withdrawal
- Long-term sleep monitoring in community, in people actively using
- Tools that exist to measure sleep are not fit for purpose
- Interventions for sleeplessness (behavioural, pharmacological) – would they work in a stimulant using population?

Conclusions - research

- Sleep is essential and under prioritised
- MA use and withdrawal interact with the sleep-wake cycle
- The effects on sleep are sometimes the worst experiences associated with MA use and withdrawal
- There is serious work to be done to try and fill the gaps in knowledge
- There are people starting to look into it

Clinician's perspective on sleep and methamphetamine use

1. Sleep / substance use diaries and awareness
2. Encouraging the importance of sleep and nutrition
3. Avoidance of / management of benzodiazepine and sedative dependence (including GHB)
4. General principles of sleep hygiene (see <https://sleep.hms.harvard.edu/sites/default/files/assets/Insomnia%20Pictures/Healthy%20Sleep%20Hygiene.pdf> for more)
5. CBT for sleep (e.g. This Way Up, find out more at <https://thiswayup.org.au/programs/insomnia-program/>)

Thank you!

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