# Thesis

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## Contents

# Introduction

## Problem statement

Non-restorative sleep (NRS) is a condition characterised by unrefreshing sleep upon awakening despite normal sleep parameters as measured by polysomnography (PSG) (Roth et al., 2010). It has debilitating daytime effects including persistent daytime fatigue, diminished cognitive performance, and reduced mental wellbeing (**cite?**). Despite the significant impacts of this condition, it is poorly diagnosed and not included in the Diagnostic and Statistical Manual-5 (Association, 2022a), with no established guidelines for clinical management. A potential reason for the lack of diagnostic criteria is the reliance on subjective measures for diagnosis **and the close association with insomnia?**. As this population have normal sleep as measured by PSG, an emerging explanation is that current methodologies of PSG recordings provide inadequate sleep state measurement (**cite?**).

Measuring subjective sleepiness and objective drowsiness upon awakening offer a novel and effective potential solution for diagnosis.

# Introduction to sleep disorders

## Insomnia with short sleep duration

Insomnia is the one of the most common sleep complaints in Australia, affecting approximately 33% of the population and causing a significant health burden (Sweetman et al., 2021). It is characterised by complaints of shortened overnight sleep, difficulty with sleep initiation, and frequent overnight arousals causing clinically significant distress or dysfunction in daily life (Association, 2022a).

**highly heterogeneous condition for both aetiology and symptoms (Benjamins et al., 2017)**

In contrast to many other sleep disorders that are diagnosed through PSG data, diagnosis of insomnia is recommended based on subjective reports of impairment through self-assessed questionnaires (American Academy of Sleep Medicine, 2005). This diagnostic approach is recommended due to the variability in objective PSG data among individuals with insomnia, leading to the identification of distinct phenotypes of the disorder. **fix** The more biologically severe insomnia with objective short sleep duration (ID-SSD) and insomnia with normal sleep duration but non-restorative sleep (ID-NRS) (Vgontzas et al., 2013) **where do we get NRS term from?**.

Literature has found discordant results on how insomnia affects excessive daytime sleepiness. Individuals with ID often report excessive daytime sleepiness *>10 ESS* (Hein et al., 2017), **and other things associated with subjective daytime drowsiness**. Additionally, they experience reduced sleep latency in comparison to healthy controls [Roehrs et al. (2011); haung2012], **but why can they not sleep at night?**

Although some studies have found EEG measures of sleepiness are not elevated in people with ID-SSD,

- cortical hyperarousal model
  - increased EEG band beta power

**People with NRS and Insomnia may experience subjective and objective sleepiness differently to healthy controls, which impacts their daily life and functioning. This could affect how they need to be managed clinically, and greater understanding of this problem could lead to improved outcomes.**

## Non-restorative sleep

`definition, symptomology, burden, impact`

Although both conditions are characterised by complaints of inadequate sleep, NRS is distinct from ID due to having a normal sleep duration and architecture as measured by PSG (Roth et al., 2010). Patients have a primary complaint of sleep being subjectively unrefreshing or unrestorative without the presence of another sleep disorder (Stone et al., 2008).

Daytime impairments associated with NRS include significant daytime fatigue, reduced cognitive performance, and reduced psychological well-being, leading to reduced quality of life and impaired daily function (**cite?**). Despite the debilitating effects of this condition, the condition was removed in the DSM-5, meaning the condition is not clinically managed. As there are significant differences between NRS and ID regarding sleep architecture, functional impairment, and longitudinal course [kao2021; zhang2013], it is important to clearly distinguish between the two groups.

**variation in definition of NRS leads to impairment of research and clinical management (Stone et al., 2008)**. Prevalence in range of 1.4-35% across studies and populations (Zhang et al., 2012) (this paper has good references) although variation in definitions and a lack of a validated measure poses an issue for classification.

Although this population has normal sleep duration, unrefreshing sleep may be a consequence of disruptions in physiological processes occurring during slow-wave sleep, which are critical for neural function [kao2021; Tononi & Cirelli (2006)].

As current PSG techniques cannot reliably identify NRS through PSG data, they may be insufficient for accurately recording the deficiencies occurring specific to individuals with NRS. NRS patients exhibit lower non-rapid eye movement (NREM) delta power compared to healthy controls, despite having similar objective sleep durations (Kao et al., 2021). **second sentence contradicts first**

The lack of a clear diagnostic criteria and omission in the DSM-5 means that reporting prevalence rates is difficult, and patients are unable to be reliably phenotyped or classified **improve clarity of this sentence**.

# Mechanisms of sleep

## Current understanding of sleep

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how do understanding these mechanisms inform the study's approach to
evaluating sleepiness and drowsiness in NRS
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Sleep is regulated by both a homeostatic and circadian system, wherein the homeostatic system increases the level of perceived sleepiness as waking time increases while the circadian system regulates internal synchrony with the environment (Borbély, 1982). The build-up of perceived sleepiness created by the homeostatic system is deemed sleep pressure, which has both a time and intensity domain (Borbély et al., 2016). **impaired sleep homeostasis suspected in both NRS and ID**

Sleep pressure increases proportionately to the duration and **quality** of the waking episode and dissipates during sleep in proportion to sleep duration and intensity **fix sentence**. The best established method of measuring sleep pressure is the overnight dissipation of delta power, most prominent during slow-wave sleep (SWS) (**cite?**).

Sleep architecture is identified through **changes in EEG patterns which display the shift from wakefulness to sleep**, and is categorised into N1, N2, N3 and REM sleep stages. N3 sleep is the deepest stage of sleep, characterised by slow waves of delta activity of 0.5-4 Hz and increased amplitude of 75µV, constituting between 20-25% of sleep in healthy adults (**cite?**). **sleep architecture is affected in ID through shortened sleep, however NRS has normal sleep as measured by PSG**

### SWA

Slow waves are neuronal oscillations of membrane potential between hyperpolarised and depolarised states, occurring in the 0.5-4 Hz frequency range (Achermann & Borbély, 2003; Steriade et al., 2001). Although the precise function of SWA remains unclear, it appears to be critical for cellular maintenance and repair, allowing neurons to reverse minor cellular damage before it becomes irreversible (Vyazovskiy & Harris, 2013). Slow wave activity (SWA) is a reliable measure of homeostatic sleep pressure, being greatest during the first period of N3 sleep, dissipating with sleep, and increasing with time awake (**cite?**).

Slow waves have topographic variations throughout the brain, occurring locally and asynchronously across brain regions (Siclari & Tononi, 2017). SWA is most prominent in brain regions associated with increased activity during wake, with the greatest power in frontal regions and during early sleep (Cajochen et al., 1999; Werth et al., 1996). `thalamus and claustrun play a role in synchronising localised slow waves` Following sleep deprivation, increased SWA has been observed in the frontal and lateral centro-parietal regions compared to baseline (Plante et al., 2016).

SWA is correlated with decreased levels of subjective and objective measures of sleepiness following sleep.

`How do differences in SWA reflect variations in symptoms?`

`How might topographical differences in NRS compared to ID/HC differ?`

`What are the implications of this?`

## Daytime impacts

### What is sleepiness

Insufficient sleep can lead to the intrusion of sleep-like characteristics into waking consciousness, creating the subjective experience of sleepiness and the objective measure of drowsiness. These symptoms are experienced differently between disorders being affected by the different underlying mechanisms affecting sleep. As sleepiness and drowsiness may not be directly correlated, they should be examined as separate measures.

### EEG drowsiness

Drowsiness is the experience of moving from wake to sleep as measured through brain activity, and is operationalised as the intrusion of higher amplitude, lower frequency brain activity into resting wake

(Santamaria & Chiappa, 1987). While alert wakefulness is characterised by brain activity in the beta and alpha frequencies, increased homeostatic sleep pressure is linked to an increase in theta and delta activity (Santamaria & Chiappa, 1987).

In response to increased sleep pressure, there can be increased SWA during resting wake suggesting an adaptive process of cortical downregulation in order to prevent long-term irreversible damage (Vyazovskiy & Harris, 2013). - off-periods can appear asynchronously across brain regions increasing with time awake, in behavourally awake animals presence in motor areas negatively affects motor performance (Vyazovskiy & Harris, 2013)

EEG fatigue can be measured through various algorithms including AAC, slowing ratio, and (Jap et al., 2009)

detecting fatigue from (Jap et al., 2009): algorithm (i) $\frac{\theta+\alpha}{\beta}$, algorithm (ii) $\frac{\alpha}{\beta}$, algorithm (iii) $\frac{\theta+\alpha}{\alpha+\beta}$, and algorithm (iv) $\frac{\theta}{\beta}$, were also assessed as possible indicators for fatigue detection. Results showed stable delta and theta activities over time, a slight decrease of alpha activity, and a significant decrease of beta activity ($p < 0.05$). All four algorithms showed an increase in the ratio of slow wave to fast wave EEG activities over time. Algorithm (i) $(\theta + \alpha)/\beta$ showed a larger increase.

`How is drowsiness experienced across populations?`

**Measuring drowsiness**

Drowsiness can be measured through a range of tests, measuring associated but distinct characteristics linked to a buildup of sleep pressure. The most common measures used in clinical practice and scientific research are the multiple sleep latency test which measures sleep propensity, the maintenance of wakefulness test measuring the consequences of sleepiness, and the psychomotor vigilance task which measures sustained attention and reaction time, known to diminish with increased sleepiness (Basner & Dinges, 2011; Martin et al., 2023). However, these measures do not directly measure the experience of drowsiness, instead measuring its consequence. As drowsiness may be experienced differently across populations, it is therefore important that the physiological experience of drowsiness, rather than its consequences, are measured.

The Karolinska Drowsiness Test (KDT) was developed as a specific and sensitive measure of drowsiness that can provide insight into the neurobiological markers of drowsiness across populations. The test uses EEG to measure brain activity during resting wake. The 7 minute test takes place in a quiet room, wherin participants look at a set point for 2.33 minutes with their eyes open, followed by an 2.33 m eyes closed condition, and a subsequent 2.33 eyes open condition. The test has been validated in healthy populations,

being a reliable marker of drowsiness in accordance with sleep pressure and circadian rhythm fluctuations. This recording provides measures of brain activity across frequencies and channels, providing insight into both the level of drowsiness experienced and any topographical variations in activity.

- relevance to diagnosis and treatment of sleep disorders (??)

**increased cortical arousal in ID**

- (Zhao et al., 2021) meta-analysis found throughout wakefulness and sleep, patients with ID exhibited increased beta band power, although such increases sometimes extended into neighbouring frequency bands, increased theta and gamma power during wake, increased alpha and sigma power during REM, decreased delta and increased theta, alpha, sigma power during NREM sleep.
- ID is associated with significantly increased EEG activity in high-frequency bands (beta/gamma) during g reststate wakefulness, sleep-onset, non-rapid eye movement, may reflect cortical hyperarousal (Zhao et al., 2021)
- no significant differences in waking or NREM sleep power were observed across all frequency bands in PI (Wu et al., 2013)

**Differences of brain waves of people with insomnia/NRS and healthy controls**

- Increased slowing ratio
- Higher delta and theta power
    - Associated with increased sleepiness and cognitive implications

## Self-reported sleepiness

- measured primarily through ESS, SSS, KSS (Martin et al., 2023)

Subjective sleepiness is a measure of an individual's self-assessed level of drowsiness, often assessed through self-report questionnaires such as the Karolinska Sleepiness Scale or the Epworth Sleepiness Scale (Åkerstedt & Gillberg, 1990; Johns, 1991). Sleepiness scores fluctuate throughout the day as a result of the impact of system S and C (Kaida et al., 2006) and increased subjective sleepiness scores is linked to reduced cognitive performance (Babkoff et al., 1991) and delayed reaction time (Åkerstedt et al., 2014). Persistent excessive daytime sleepiness is strongly associated with depressive symptoms and illness intrusiveness (Hossain et al., 2005).

Self-reported sleepiness strongly correlates with objective measures of drowsiness (MSLT, actigraphy, (Kaida et al., 2006)), however discrepancies have been found in individuals with insomnia **flesh out with more evidence**.

"physiological indices of sleepiness did not occur reliably until subjective perceptions fell between "sleepy" and "extremely sleepy-fighting sleep"; i.e. physiological changes due to sleepiness are not likely to occur until extreme sleepiness is encountered. " [@akerstedt2009]
- weak association ($r$=0.18) between subjective fatigue and sleepiness in individuals with sleep disorders. Analysis of variance testing showed strong association between those patients with prominent fatigue and depressive symptoms (P < 0.01) and illness intrusiveness (P < 0.001). The findings support the notion that subjective fatigue and sleepiness can be independent manifestations of sleep disorders [@hossain2005]
- excessive sleepiness is regarded as one of the cardinal manifestations of sleep disorders and often is accompanied by fatigue, many patients with fatigue complain of insomnia and do not report falling asleep or feeling sleepy at inappropriate times [@hossain2005]

**subjective-objective mismatch**

There is a subjective-objective mismatch that is observed in people with NRS (Bianchi et al., 2013), however unknown if this persists in daytime drowsiness

## approach

- why are we doing things in the way we are doing? Integrate with theory
  - Link psychological construct to approach you are using it to measure it
  - Operationalise how you are going to measure constructs
- description of overall research study
  - what type of study it is,
    - observational, age and sex matched

## Aim

This study aimed to examine if there are differences in how populations with NRS, ID, and healthy controls experience subjective sleepiness, and if these differences are associated with topographic differences in brain activity during resting wake. Using mixed linear models, we aimed to assess if there was a difference in the correlation between subjective and objective measures based on population group. Finally, to examine

if delta power is a potential mechanism for non-refreshing sleep in NRS, we investigated if clusters associated with a higher slowing ratio were associated with reduced delta power during the previous night's sleep.

By examining regional brain activity during resting wake, the study aims to examine if there are differences in how NRS, ID and HC experience and dissipate sleep pressure. Differences in delta power and SWA among groups may reveal differences in how sleep pressure is dissipated and if there are adaptive processes emerging as a result of ongoing sleep deprivation.

## Hypotheses

1. KSS scores upon awakening will be highest in the NRS group compared to ID and healthy controls, reporting higher subjective sleepiness following sleep.

2. The correlation between KSS score and global Slowing Ratio will be significantly different between groups.

3.Topographic cluster analysis of SR will reveal cluster differences between groups. We hypothesise that at least one cluster of EEG channels will demonstrate a significantly different slowing ratio power that will differentiate the NRS group from ID and healthy controls.

4. For those with NRS, channel clusters with high values of slowing ratio will also show reduced delta power in NREM3 sleep.

# Method

## Participants

MQ HREC provided ethical approval for this project (FoRA ID 17112).

12 participants from each clinical population were recruited: individuals with insomnia disorder (ID), individuals with non-restorative sleep (NRS), and healthy controls (HC). Recruitment was conducted through referrals from the Woolcock Institute and the Royal Prince Alfred sleep clinics, in addition to social media advertising. Due to the influence of age and sex on sleep architecture (Mongrain et al., 2005), participants were sex and age matched with a maximum difference of 1 year.

Participants were excluded if they had any comorbid sleep apnoea, as measured by wrist oximetry (oxygen desaturation index above 10 during any night of monitoring) (WristOX has high sensitivity of diagnosing OSAS (Nigro et al., 2009)). Participants were additionally excluded if they had clinically significant depression or anxiety scores as measured through the DASS-21, heavy alcohol use, pregnancy, circadian rhythm disruption through shift work or recent international travel, or a natural sleep time that of less than 6 hours or outside the hours of 21:30 and 8:00. As medications are known to affect sleep architecture, participants taking regular medications affecting sleep were excluded.

The inclusion criteria for the ID group was as set by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Association, 2022b) criteria, with difficulty initiating or maintaining sleep persisting for over 1 month causing clinically significant distress or impairment in daily life. They additionally were required to have a Pittsburgh Sleep Quality Index (PSIQ) score of 6 or higher, and an Insomnia Severity Index (ISI) score of 16 or higher.

Individuals in the NRS group could not have a mean Total Sleep Time (TST) below six hours as measured by sleep diary or actigraphy, or a mean refreshed score above 3. Inclusion in this group required a PSQI of 6 or more, with subcomponent scores of at least 2 on the PSQI Component 1 and 10 on PSQI Component 5.

Healthy controls needed to have a PSQI score of 4 or less and an ISI score of 6 or less.

**consent was voluntary and could be discontinued at any time** All patients were remunerated $100 upon successful completion of the study.

## Protocol

The study was approved by the Macquarie University Human Research Ethics Committee. Participants attended the sleep laboratory at the Woolcock Institute of Medical Research for initial screening by a sleep physician. Participants baseline sleep and activity patterns were measured via an Actigraphy watch (**which one**) for 7 days prior, which was validated against self-reported sleep diaries. Participants additionally completed the Restorative Sleep Questionnaire Daily Version (RSQ-D) for 7 days prior.

Upon arrival at the laboratory at 17:00, participants underwent final medical screening and a series of cognitive assessment. They were then served dinner and fitted with a high-density electroencephalography (HD-EEG) cap. Further cognitive assessments were conducted before the administration of the Karolinska Drowsiness Test (KDT) approximately 45 minutes prior to their habitual bedtime. Overnight polysomnography using HD-EEG was recorded, in addition to sleep video recording using a AXIS P3225-LV camera.

Lights were turned on at the participant's natural wake time and they were asked if they were already awake or wakened by researchers. The KDT was repeated five minutes post-habitual wake time. Following the morning KDT, participants completed further cognitive testing and an MRI scan.

## Measures

### KSS

Subjective sleepiness was assessed using the Karolinska Sleepiness Scale (KSS), a 9 point scale with verbal anchors at steps 1("extremely alert")., 3 ("alert"), 5 ("neither alert nor sleepy"), 7 ("sleepy-but no difficulty remaining awake"), and 9 (Extremely sleepy-fighting sleep) (Åkerstedt & Gillberg, 1990) **confirm if this kss or one with anchor at each step**. The KSS has been vaidated in healthy populations as being closely related to EEG and behavioural variables of sleepiness (Kaida et al., 2006).

- sensitive to manipulations known to affect sleepiness, correlate with impaired waking function and appear to be used consistently across individuals (Åkerstedt et al., 2014)

### KDT

The KDT was used to measure electrophysiological drowsiness as measured through HD-EEG recordings. Participants were instructed "Look at the dot in front of you and be as relaxed as possible while staying awake. Keep your head and body still and minimize blinking. After a few minutes, I'll ask you to close your eyes and keep them closed for a few minutes. Finally, I'll ask you to open your eyes again and keep them open for a few minutes." They commence with their eyes open, close their eyes at 2m10, open eyes again at

4m40, and the test ends at 7m10.

**HD-EEG**

High-density EEG data were collected using 256-channel caps (**which one**). Th `signals were amplified and digitised, impedences, recordings were acquired with electrodes referenced to the vertex processing of original eeg signals was performed`

The data was visually inspected for artefacts and arousals using a **semi-automatic process** and was manually verified and cleaned. `The record was visually inspected for bad channels and channels identified as poor quality (2.5% ± 1.4% of 164 chan- nels) were replaced with an interpolated EEG signal using a spher- ical spline interpolation algorithm. After artifact removal and bad channel interpolation, the EEG signals were average-referenced.` **did we do this?**

## Power spectra

- The most common quantitative method employed in sleep studies is spectral analysis, which decomposes a time series of EEG data into power (squared amplitude) in frequency bins (mV2/bin) , can be expressed as absolute or relative to the summed power in all bins, spectral analysis may represent an objective method for examining the pathophysiological mechanisms underlying insomnia (Zhao et al., 2021)
- Raw PSD has a straightforward connection to signal amplitude, with channels expressing larger signal amplitudes typically showing larger power, useful when absolute differences in signal amplitude are deemed meaningful (topographical analysis) (Cox & Fell, 2020)

To calculate power spectral density, cleaned EEG signals were analysed using a fast Fourier transform `with 50% overlapping between con- secutive 4-second windows with a Hanning filter function, resulting in a frequency resolution of 0.25 Hz`

EEG spectral power densities were quantified as: delta (1–4.5 Hz), theta (4.5–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), beta (15–25 Hz), and gamma (25–40 Hz).

## Statistical analysis

z-score normalised power spectral data were analysed for eyes open and eyes closed conditions for each participant

To control for Type I error rate in cluster analysis, statistical nonparametric mapping (SnPM) with the suprathreshold cluster test will be used. SnPM uses permutation tests (10 000 random shuffles of the data) to establish a distribution of cluster size findings that occur due to chance. This distribution can then be used to compare cluster size to the a priori set threshold of $p < .05$, determining if it is statistically significant (D'Rozario et al., 2023).

EEG processor

All analyses were performed using MATLAB version r2024a (MathWorks, Natick, MA, USA).

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