Thesis

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# Introduction

## Problem statement

Non-restorative sleep (NRS) is a condition characterised by unrefreshing sleep upon awakening despite normal sleep duration and architecture as measured by polysomnography (PSG), leading to excessive daytime fatigue and significant daytime functional impairment (Roth et al., 2010). Despite the significant impact of this condition, it is poorly diagnosed and not included in the Diagnostic and Statistical Manual-5 (Association, 2022), with no established guidelines for clinical management. This population has previously been clinically managed as a subtype of insomnia disorder (ID) despite evidence suggesting the disorder is phenotypically distinct, with different underlying aetiology. Although this population has normal sleep parameters as measured by traditional PSG methodologies, new technologies and techniques such as HD-EEG and spectral analysis enable exploration of the underlying neural mechanisms in greater resolution, which may reveal differences in sleep processes that result in non-restorative sleep.

Combined, these results suggest that EEG spectral power during sleep, in contrast to standard polysomnography, may provide a better biomarker distinguishing insomnia subtypes, relate to subjective insomnia symptoms and provide more informative with regard to personalised care in ID.

A potential reason for the lack of restorative sleep experienced by this population may be a dysfunction in slow wave activity (SWA), which is the strongest established marker of reduced sleep pressure (**tononi2008?**). Low SWA power during sleep leads to ineffective dissipation of accumulated sleep pressure, while increased SWA in wake is associated with increased feelings of sleepiness. Subjective sleepiness is **important because of why**

In order to explore if NRS is a result of dysfunctions in SWA processes during sleep and wake in comparison to healthy populations and those with ID, this study will high-density electroencephalography (HD-EEG) to examine the power and topographic variance of SWA during resting wake and sleep. Additionally, it will examine if there are group differences in the correlation between subjective sleepiness and SWA following sleep.

# Introduction to sleep disorders

## Insomnia disorder

ID is the most common sleep disorder 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, 2022). 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). However, this has led to high heterogeneity within the population, and there is a need for greater use of objective measures in diagnosis to better understand the underlying mechanisms of the disorder.

The hyperarousal model of insomnia proposes increased physiological and neurobiological arousal has a causal role in creating sleep initation and maintenance (Riemann et al., 2010). Neurobiological hyperarousal in insomnia is observed through increased fast frequency EEG activity during sleep and wake (Zhao et al., 2021). During sleep, ID patients have decreased SWA (Kao et al., 2021) and increased fast frequency band activity (Hogan et al., 2020; Merica et al., 1998) during NREM sleep in comparison to healthy controls, leading to diminished overnight dissipation of sleep pressure (Lunsford-Avery et al., 2021). Additionally, high frequency activity is associated with poorer subjective sleep quality (Perlis et al., 2001). Hyperarousal persists during wake, with ID being associated with increased alpha power during resting wake, indicating increased wakefulness (**fiege2017?**).

Hyperarousal may explain the low levels of excessive daytime sleepiness (EDS) observed in ID despite dysfunctional sleep architecture. Approximately half of the ID population experience EDS (Hein et al., 2017), and often have normal or increased sleep latency during daytime sleep tests (Huang et al., 2012; Roehrs et al., 2011) These findings support the hypothesis that hyperarousal contributes to ID pathology as a stable construct, rather than just during sleep (Dressle & Riemann, 2023).

## Non-restorative sleep

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 a comorbid sleep disorder (Stone et al., 2008). Prevalence in range of 1.4-35% across studies and populations (Zhang et al., 2012) although variation in definitions and a lack of a validated measure poses an issue for classification. 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 significant effects of the condition, the symptom of non-restorative sleep was removed from the diagnostic criteria of ID in the DSM-5, meaning this population is diagnoses as “other specified sleep-wake disorder” (Association, 2022). As NRS may be its own unique disorder with an underlying neurobiological cause, it is essential to develop diagnostic criteria and understand the associated neural mechanisms to improve outcomes for patients.

Although this population has normal sleep duration and architecture, unrefreshing sleep may be a consequence of disruptions in physiological processes occurring during slow-wave sleep, which are critical for neural function (Kao et al., 2021; Tononi & Cirelli, 2006). this population does not have cortical hyperarousal Power spectral analysis may present an improved criteria for classifying and understanding the cause of non-restorative sleep in this population. NRS patients exhibit lower SWA during NREM sleep compared to healthy controls, despite having similar objective sleep duration (Kao et al., 2021). This dysfunctional SWA during sleep may be associated with increased SWA during wake (**cite?**), however further exploration using improved technology is required.

# Mechanisms of sleep

## Neurophysiological correlates of sleep

Sleep is behaviourally defined as a reversible reduction in responsiveness to external stimuli, accompanied with measurable brain activity patterns (Cirelli & Tononi, 2008). The neurophysiological correlates of sleep and wake in humans can be measured through EEG recordings of brain activity patterns, providing a spatiotemporally integrated recording of neuronal signals across the cortical surface (Buzsáki et al., 2012). Wakefulness is characterised through low amplitude, high frequency signals in beta and alpha frequencies, accompanied by irregular muscle activity recorded electromyogram (EMG). Non-rapid eye movement (NREM) sleep is characterised by reduced muscle movement and the appearance of high-amplitude slow oscillations of delta frequency (0.5-4 Hz), deemed slow wave activity (SWA). Sleep progresses through cycles of brain activity throughout the night, with the greatest prevalence of SWA appearing in N3 sleep (Achermann & Borbély, 2003).

## Sleep homeostasis

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 homeostatic system determines the quantity and intensity of sleep, creating an accumulation of perceived sleepiness deemed “sleep pressure” (Borbély et al., 2016). Sleep pressure increases in proportion to the duration and intensity of the waking episode, evident through increased sleep duration and sleep intensity (Benington, 2000; Borbély, 1982). Sleep pressure can be measured through SWA, being greatest during the first period of N3 sleep and dissipating in response to sleep duration (**cite?**)

Sleep homeostasis dysfunction may be a causal factor in the impairments observed in ID and NRS patients (Pigeon & Perlis, 2006; **cite?**). In patients with insomnia with short sleep duration, there is a global reduction in SWA, while insomnia patients with normal sleep duration as measured by PSG can have either reduced delta power or normal delta power (Kao et al., 2021). Overnight SWA has not previously been examined in a NRS population.

## SWA

Slow waves are synchronised neuronal oscillations of membrane potential between hyperpolarised and depolarised states originating in thalamocortical loops which propagate through the brain (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). The frequency, amplitude and spatial topography of SWA is additionally influenced by sleep homeostasis, creating measurable variations in underlying neuronal activity (Krueger et al., 2019). Increased sleep pressure leads to longer periods of hyperpolarisation and greater synchrony between brain regions, which are reduced as sleep pressure dissipates (Vyazovskiy et al., 2011). Increased synchrony can be measured using HD-EEG through cluster analysis, which provides greater spatial resolution than EEG.

SWA has topographic variance across the cortex, varying in a use-dependent manner (Krueger & Obäl Jr., 1993). SWA has an antero-posterior cortical progression, with the greatest activity in the frontal regions at sleep onset (Huber et al., 2000). Increased SWA following sleep deprivation is additionally greatest in the frontal cortex (Cajochen et al., 1999; Werth et al., 1996). Repetitive task performance recruiting functional areas of the brain, such as the motor or sensory cortices, leads to increased regional SWA during subsequent sleep (Huber et al., 2004; Vyazovskiy et al., 2008). These findings suggest that SWA is a localised phenomenon, appearing in response to accumulated sleep pressure and dissipating with sleep.

# Daytime impacts

## SWA in wake

Although SWA is a characteristic of sleep, intrusions of localised SWA can also be observed during wake in a use and time-dependent manner in response to the accumulation of sleep pressure (Huber et al., 2004; Krueger et al., 2019). Rodent studies have found increased SWA in local cortical networks in response to sleep deprivation despite being physiologically awake, increasing in intensity and synchronicity with the duration of wake (Vyazovskiy & Harris, 2013). Localised increased in SWA have additionally been observed in humans in response to prolonged wakefulness, being greatest in the frontal and lateral centro-parietal regions compared to baseline (Hung et al., 2013; Plante et al., 2016). The increase of slower frequency power during wake is hypothesised to be an adaptive process of cortical downregulation, allowing cells to prevent long-term damage during periods of extended wake by engaging in the restorative processes observed in slow-wave sleep while maintaining consciousness (Vyazovskiy & Harris, 2013).

Increased SWA is correlated with subjective and objective markers of fatigue, meaning it is a variable of interest for this study. The appearance of SWA in task-related regions is associated with diminished behavioural performance (Bernardi et al., 2015). HD-EEG recordings observed a increased SWA during wake in the left frontal brain region following a language task and posterior parietal region following a visuomotor task, which was additionally associated with increased SWA during recovery sleep (Hung et al., 2013). This suggests that the localisation of sleep pressure observed in sleep is also observed during wake.

## Drowsiness

Drowsiness can be measured through a range of tests, measuring associated but distinct characteristics linked to the accumulation 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 the consequences of drowsiness may be create different experiences across populations, it is therefore important that the neural activity of drowsiness itself, 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 (Åkerstedt et al., 2014; Åkerstedt & Gillberg, 1990). The test uses EEG to measure brain activity during resting wake, which can be transformed into power spectra using a fast Fourier transform and then assessed through power spectral analysis (**cite?**). The test has been validated in healthy populations, being a reliable marker of drowsiness in accordance with sleep pressure and circadian rhythm fluctuations (Kaida et al., 2006).

## Self-reported sleepiness

Subjective measures of sleepiness are useful for recording the self-assessed impairment of poor sleep on the individual. The most prevalent method of measuring self-reported sleepiness is through questionnaires such as the the Epsworth Sleepiness Scale, Stanford sleepiness scale, and Karolinska sleepiness test (Martin et al., 2023). Sleepiness scores fluctuate throughout the day in response to circadian and sleep homeostatic systems (Kaida et al., 2006).

Excessive daytime sleepiness causes a significant burden on individuals.

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.

1. 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, 2022) 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

* PSA based on FFD most common method for processing EEG signal, transforms eeg signal from time domain (amplitude x time) to frequency domain (frequency x time), providing greater insight into brain activity over timw
* 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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