# 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, sleepiness, and diminished quality of life (Roth et al., 2010). Despite the impact of this condition, there are no established guidelines for diagnosis or clinical management, and it is not included in the Diagnostic and Statistical Manual-5-TR (American Psychiatric Association, 2022). NRS has previously been clinically managed as a subtype of insomnia disorder (ID) despite patients not exhibiting the symptoms associated with ID difficulty falling asleep, frequent arousals, and shortened sleep duration (Roth et al., 2010). ID has received significant attention and research due to its prevalence and detrimental effects, however how it impacts daytime function requires further exploration.

Both disorders have been consistently associated with significantly increased daytime fatigue, however findings on subjective and objective sleepiness are inconsistent. This may be due to the limitations of existing measures considering sleep as a global phenomenon. Sleep may be better considered in clinical populations as a local phenomenon, with different brain areas exhibiting varied patterns of sleep and wake like activity simultaneously (Stephan & Siclari, 2023). High-density electroencephalography (HD-EEG) and power spectral analysis enable exploration of cortical activity variations across brain regions and spectral frequencies, providing a more accurate measurement of neuronal activity than assessment through the time domain.

To examine if there are differences in morning sleepiness between NRS in comparison to ID and healthy controls, this study will examine resting wake HD-EEG recordings to see if there are group differences in brain activity when controlling for subjective sleepiness.

# Introduction to sleep disorders

## Insomnia disorder

ID is the most common sleep disorder in Australia with an estimated prevalence of 23.2% (Appleton et al., 2022). It is linked to detrimental outcomes to the individual including increased risk of comorbid psychiatric disorders, reduced physical health, diminished quality of life, and significant daytime fatigue (Kim et al., 2019; Kyle et al., 2010; Morin et al., 2015; Perlis et al., 2022). ID is diagnosed through subjective reports of shortened overnight sleep, difficulty with sleep initiation, or frequent overnight arousals, leading to clinically significant distress or dysfunction in daily life (American Psychiatric Association, 2022).

Diagnosis is recommended to be made though subjective self-reporting rather than PSG data or actigraphy, as this population does not consistently display disruptions to objectively measured sleep macroarchitecture (American Academy of Sleep Medicine, 2005; Drake et al., 2011; Harvey et al., 2014). This phenomenon has been labelled sleep-state misperception, where individuals underestimate their total sleep time, number of awakenings, and report more thought-like activity during sleep (Stephan et al., 2021; Thorpy, 1990; Wassing et al., 2016). Increased subjective-objective sleep discrepancy is associated with increased cortical activation and wake-like brain activity occurring during sleep (Andrillon et al., 2020; Krystal et al., 2002; Stephan et al., 2021). This neural activity cannot be analyzed using traditional PSG analysis techniques, which cannot account for sleep and wake like patterns occurring simultaneously. However, as sleep is a localized phenomenon, this misperception is now considered to be a mismeasurement (Stephan & Siclari, 2023; Vyazovskiy et al., 2011). As such, analysing sleep microarchitecture is insufficient for understanding the mechanisms underlying sleep in ID.

## Non-restorative sleep

NRS is distinct from ID due to having normal self-reported sleep duration and architecture, and individuals not meeting the DSM-5-TR diagnostic criteria for insomnia (Roth et al., 2010). The estimated prevalence ranges from 1.4-35% across studies and populations, although variation in definitions and a lack of a validated measure poses a challenge for classification (Zhang et al., 2012). Patients have a primary complaint of sleep being subjectively unrefreshing or unrestorative without regular difficulty falling asleep or frequent overnight arousals, and the absence of any comorbid sleep disorders (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 (Neu et al., 2015).

Despite the 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 diagnosed as “other specified insomnia disorder” (American Psychiatric 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 etiology to improve outcomes for patients. Analysis of brain activity during sleep and resting wake has not yet been explored within this population.

# Subjective sleepiness

**Subjective sleepiness**

Subjective sleepiness is a measure of an individual’s self-assessed level of sleep pressure, objective drowsiness, or sleep propensity, which fluctuates throughout the day in response to the influence of sleep homeostasis and circadian systems (Åkerstedt et al., 2014). Subjective sleepiness in healthy populations correlates with EEG measures of drowsiness, increases in response to sleep deprivation, and is stable within individuals (Åkerstedt et al., 2014; Kaida et al., 2006).

and is not regularly observed in ID. The prevalence of excessive daytime sleepiness (EDS) as measured by sleep propensity within ID varies between 10-41.61% and is unrelated to insomnia symptom severity (Hein et al., 2017; Fasiello et al., 2023; Seong et al., 2022). Furthermore, ID populations display similar or increased sleep latency in comparison to healthy controls (Huang et al., 2012; Shi et al., 2022). However, as a characteristic of ID is the inability to fall asleep, measuring sleepiness through sleep latency may be insufficient for measuring sleepiness.

Sleepiness is independent from fatigue. Daytime fatigue, being the subjective experience of low energy, is the most prevalent daytime complaint in ID and NRS and is associated with the most significant detrimental impact to daily functioning (Kyle et al., 2010; Raizen et al., 2023; Roth et al., 2010). Severe fatigue is associated with greater insomnia symptom severity, daytime sleepiness, depressive symptoms, and increased habitual sleep duration (Kim et al., 2019). However, fatigue is independent from sleep parameters, as it represents the deterioration in alertness, motivation, or performance that can be recovered from with rest (@cite).

In contrast, increased subjective sleepiness is a measure of sleep propensity that can only be reduced through sleep. It can be measured through

Subjective daytime sleepiness in NRS

# What is sleep?

**Why do we sleep and what happens if we don’t?**

Sleep is a necessary behavior for all humans that can be defined as a reversible reduction in responsiveness to external stimuli accompanied by brain activity patterns measurable through EEG (Cirelli & Tononi, 2008). Sleep progresses through cycles of different activity stages, with NREM sleep being characterized by slow wave activity (SWA) of synchronized neuronal oscillations of membrane potential between hyperpolarised and depolarised states (Achermann & Borbély, 2003). SWA is hypothesized to be necessary for neuronal function, with cellular maintenance and repair occurring during neuronal OFF-periods of slow wave oscillations to prevent irreversible damage (Vyazovskiy & Harris, 2013). SWA also acts as a measure of sleep pressure, with sleep deprivation leading to longer periods of hyperpolarization and greater synchrony between brain regions that dissipates with sleep duration (Vyazovskiy et al., 2011).

Sleep deprivation has significant consequences, with almost all measurable behaviours being affected by sufficient sleep deprivation (Killgore, 2010). However, sleep deprivation is associated with greater increases in subjective sleepiness than behavioural measures, with complex tasks showing the smallest effect size (Groeger et al., 2014; Lim & Dinges, 2010). A potential explanation for this is that a compensatory mechanism exists that enables organisms to continue to function under short-term sleep deprivation conditions, however the state of subjective sleepiness exists to ensure regular sleep is performed to prevent long-term damage.

**How do we compensate?**

Alert wake is characterized by a predominance of fast-frequency activity in the gamma (13-35 Hz) and beta (15-25 Hz) frequencies, with alpha (8-12) frequency appearing during relaxed wake when the eyes are closed. During conditions of sleep deprivation, increasing time awake correlates with increased theta (4-8 Hz) activity, correlating topographically with SWA during sleep (Finelli et al., 2000). This slowing is specific to wake and increases in a task-dependent manner (Huber et al., 2004; Snipes et al., 2022). Theta activity does not show the synchronization characteristic of SWA, suggesting it may be an adaptive mechanism that allows the brain to undergo the necessary restorative processes observed during sleep without global sleep onset (Vyazovskiy & Harris, 2013). This is further supported by the finding that theta activity under sleep deprivation conditions does not occur in brain areas required for task performance (Snipes et al., 2022).

# Objective sleepiness

## Neurophysiological correlates of drowsiness

However, during conditions of sleep deprivation or following insufficiently restorative sleep, brain activity measured by EEG shows characteristics that more closely resembles sleep than wake. Alert wake is characterized by low amplitude, fast frequency signals in the gamma ( and beta frequencies, with

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). Alert wake is characterised through low amplitude, high frequency signals in gamma and beta frequencies occurring asynchronously across the brain. Alpha activity can be a characteristic of either wakefulness or drowsiness. Wakefulness-alpha is decreased when the eyes are open during alert wake, but increases when the eyes are closed particularly in the occipital and parietal regions of the brain (Cantero et al., 2002). In contrast, alpha activity present while the eyes are open is associated with increased drowsiness, which reduces in power when the eyes are closed. The reduction of alpha power with increased drowsiness is replaced with a further slowing of the EEG signal and greater synchronization between neurons, leading to theta frequency activity (4-8 Hz).

Sleep is characterized by a slowing of EEG activity and the emergence of higher amplitude synchronized slow oscillations in the 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

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.

is now well established that localised sleep and wake patterns, which are not adequately captured by standard sleep recordings (PSG) and scoring methods, can coexist in both physiological and pathological conditions, and likely determine sleep-related conscious experiences [@siclari2017]

# 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). - determining if sdTheta is local sleep can only be done with intracortical data, but shape and distribution of theta waves can be indicative. - epiliepsy studies unable to find evidence of off-periods in humans during wake sleep deprivation like they did in sleep, but did find local changes in theta power linked to delays in performance (Nir et al., 2017) 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). - occurs in theta frequency - increased in theta waves observed in eeg corresponded to synchronised silence of local neuronal spoking (off-periods), the same pattern that is observed during slow wave sleep (Steriade et al., 2001), Difference is that slow waves in sleep include larger populations of neurons and longer off-periods - the same patterns underlying sleep SWA also underlie theta activity during sleep deprivation, suggesting that theta waves are smaller forms of SW. Localised increases 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). These findings suggest that intrusions of SWA in wake may be representative of accumulated sleep pressure, and therefore a measure of physiological fatigue.

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.

## Objective Drowsiness

Objective 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. 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. 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).

Spectral power is affected by increasing drowsiness, with a greater prevalence of slower frequency activity emerging with the accumulation of sleep pressure, and increased alpha activity when the eyes are open that decreased when the eyes are closed. **Alpha activity increases with drowsiness in eyes open but decreases with eyes closed!!** - alpha activity is low during wake when not fatigued and high during wake when severely fatigued - in eyes closed, alpha power is high when rested and reduces with eyes closed, as there is a gradual increase in theta power increased subjective sleepiness negatively correlated with alpha band power globally (Strijkstra et al., 2003) - drowsiness associated with increased occipital power 9.5-11 Hz (Cantero et al., 2002) - the decrease in alpha activity is most prominent in the occipital region - alpha is associated with meditative sleeps, restful wake - decrease in alpha activity with eyes closed mirrors the reduction of alpha activity observed during sleep onset Theta activity increases with accumulated sleep pressure in animals (Vyazovskiy & Tobler, 2005) and humans (**cite?**), peaking at 6.5 Hz and predominantly occuring in the frontal regions (Snipes et al., 2022). This acitivity correlates with SWA during sleep, and is hypothesised to represent intrusions of local sleep during wake (Snipes et al., 2022 (check?); Vyazovskiy et al., 2011). - it may also represent the further slowing of alpha activity that occurs when the eyes are closed, or the emergence of n1 sleep (?) check this from the snipes thesis - average correlation between theta power and KSS was .029, (z-statistic=4.11, P=0.00004). (Strijkstra et al., 2003)

## Subjective sleepiness

Subjective sleepiness is a measure of an individual’s self-assessed level of sleep pressure, objective drowsiness, or sleep propensity, which flucuates throughout the day in response to the influence of sleep homeostasis and circadian systems (Åkerstedt et al., 2014). There are two dimensions of sleepiness, sleepiness propensity being the likelihood of an individual sleeping in a given situation, and sleepiness perception being the subjective assessment of an individuals feelings of sleepiness (Johns, 2009). However, sleepiness perception is not experienced uniformly across populations, with the differential influences of factors including fatigue and arousal causing individuals to possibly mispercieve their internal state (Marques et al., 2019).

In healthy populations, subjective sleepiness scores correlate closely with objective measures of drowsiness, such as sleep latency (**cite?**), reaction time (**cite?**), and EEG spectral power (**cite?**). Subjective sleepiness is predominantly measured through self-reported questionnaires that measure either state or trait sleepiness. The most prevalent measure of trait somnolence is the Epsworth Sleepiness Scale (ESS), which measures an individual’s propensity to sleep in given scenarios robust to variations in sleep pressure and circadian variance (Johns, 1991; Martin et al., 2023). The Karolinska Sleepiness Scale (KSS) measures state sleepiness using a 1-item nine point Likert scale, and is highly correlated with EEG measures of drowsiness in response to sleep deprivation (Åkerstedt et al., 2014; Kaida et al., 2006). This correlation makes the KSS a useful measurement tool for examining the relationship between objective and subjective measures of drowsiness on clinical populations, as it measures sleepiness at a particular point in time which can then be compared to EEG activity.

The feeling of subjective sleepiness is not experienced homogeneously across populations.  
Excessive daytime sleepiness is one of the most common complaints associated with NRS, with significantly increased daytime fatigue, and self-reported cognitive and psychological impairments (Sarsour et al., 2010; Tinajero et al., 2018). Daytime sleepiness is also present in ID, with excessive daytime sleepiness (EDS) having a prevalence of 45% (Hein et al., 2017). Insomnia symptom severity is correlated to increased EDS scores across the day, particularly in the morning and evening (Balter et al., 2024). However, these symptoms are additionally associated with hyperarousal, leading to a phenomenon of co-activation of the parasympathetic and sympathetic nervous systems. This co-activation leads to high and low arousal symptoms being experienced concurrently, leading to greater variability in symptoms. Examining how the experience of subjective sleepiness varies across disorders will lead to greater understanding of the sujective experience of sleepiness across both disorders.

Although subjective sleepiness scores strongly correlate with objective measures of drowsiness in healthy populations, there is a subjective-objective mismatch observed in individuals with ID, possibly due to increased fast-frequency activity (**cite?**). ID is associated with a discrepancy between objective sleep as measured by PSG and subjective sleep as reported by a sleep diary. Patients with ID report a reduction in sleep duration of up to 4 hours greater than that measured by PSG, however this discrepancy may be attributable to mismeasurement rather than misperception (Benz et al., 2023; Stephan & Siclari, 2023). Localised spectral power cannot be recorded through traditional PSG methods, which are hypothesised to be a determinant of sleep-related consciousness (Siclari & Tononi, 2017). The relationship between EEG spectral power and subjective state drowsiness has not been explored in clinical populations, and greater understanding of this relationship is needed.

Theta power correlates with subjective sleepiness during eyes open conditions (Kaida et al., 2006; **gorgoni2014?**)

# Aim

This study aimed to explore if there are differences in how populations with NRS, ID, and healthy controls experience subjective and objective sleepiness, and if these differences are associated with topographic differences of SWA during resting wake. First, we examined if there was a difference in subjective sleepiness levels upon awakening as measured by the Karolinska Sleepiness Scale administered 5 minutes after habitual wake time. Using mixed linear models, we aimed to examine if the effect of KSS score on power spectra varied between NRS, ID, and healthy controls, evaluating if the influence of KSS score differs by group in predicting slowing ratio and alpha attenuation coefficient in eyes open and eyes closed conditions.

## 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.