# 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). On the one hand, ID has received significant attention and research due to its prevalence (~10% of adult population REFS) and detrimental health risks (increased risk of physical and mental health disorders, accidents, and decreased quality of life REFS), and the negative impacts on daytime function. On the other hand, NRS has not been studied well due to X, Y, and Z.

Both NRS and ID 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 i.e., the idea that the entire brain is asleep or awake all at once. Sleep may be better considered 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. **clarify why power spectral analysis is a better measure than something like an MSLT - gives better insight into the neurophysiology than just something that gives a time measure - why wouldn’t it apply for what we are specifically trying to do here**

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 for individuals, 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 impaired overnight sleep, difficulty with sleep initiation, or frequent overnight arousals, leading to clinically significant distress or dysfunction in daily life (American Psychiatric Association, 2022).

Clinical diagnosis is undertaken using subjective self-reporting rather than PSG data or actigraphy, as people with ID do not consistently display disruptions in objectively measured sleep macroarchitecture (American Academy of Sleep Medicine, 2005; Drake et al., 2011; Harvey et al., 2014). Whilst some patients with ID have objectively short sleep (e.g., < 6 hours), others report sleep complaints and associated daytime consequences despite normal sleep duration (7-8 hours). This phenomenon has been labelled sleep-state misperception, where individuals underestimate their total sleep time, number of awakenings, and report more thought-like (rather than dream-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 macroarchitecture is insufficient for understanding the mechanisms underlying sleep in ID.

## Non-restorative sleep

NRS is distinct from ID due to individual’s self-reported normal sleep duration and no report of problems falling asleep, staying asleep, or early morning awakenigns These patients therefore do not meet the DSM-5-TR diagnostic criteria for ID (Roth et al., 2010), and are often dismissed from adequate clinical management. 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). Individuals 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.

# What is sleep and sleepiness?

**Why we sleep**

Sleep is a necessary behaviour for all humans that can be defined as a reversible reduction in responsiveness to external stimuli accompanied by a measurable change in brain activity patterns that can be observed through EEG (Cirelli & Tononi, 2008). Sleep is critical for cellular maintenance and synaptic homeostasis, allowing neurons to downscale the increase in synaptic strength that occurs during wake (Tononi & Cirelli, 2014; Vyazovskiy & Harris, 2013). Sleep is regulated by two systems, with the circadian system regulating sleep and wake in response to the external environment and homeostatic system increases in response to wake and decreases during sleep (Borbély, 1982).

Prolonged wake leads to an accumulation of homeostatic sleep pressure, triggering feelings of subjective sleepiness. Subjective sleepiness is hypothesized to act as a protective mechanism ensuring organisms sleep regularly, despite being able to endure short periods of sleep deprivation without detrimental impacts to behaviour (McMahon et al., 2021). Reversely, sleep, and especially deep sleep, dissipataes homeostatis sleep pressure, and is thought to be reflected by subjective feelings of being refreshed in the morning (or something along those lines). Subjective sleepiness **correlates with increased sleep pressure…xxxx**

**Brain activity during sleep**

Brain activity in humans can be measured through EEG recordings of brain activity, which provides a spatiotemporally integrated recording of neuronal signals across the cortical surface (Buzsáki et al., 2012). Generally, while alert wake is characterized by low amplitude, high frequency signals, sleep is characterized by high amplitude, low frequency signals. Sleep progresses through a series of discrete stages which cycle throughout the night, with the greatest reduction in sleep pressure occurring during NREM stage 3 sleep (N3, **cite**). N3 is characterized by an increased prevalence of slow wave activity (SWA), which are synchronized oscillations of membrane potential between hyperpolarised and depolarised states that propagate throughout the brain in an antero-posterior cortical progression (Achermann & Borbély, 2003; Steriade et al., 2001). The frequency, amplitude, and topography of SWA is influenced by sleep homeostasis, with increased sleep pressure leading to longer periods of hyperpolarization and greater synchrony between brain regions, which are reduced as sleep pressure dissipates (Vyazovskiy et al., 2011).

# 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 can be measured as either trait or state sleepiness, with trait sleepiness being an individual’s propensity to fall asleep in a given situation, and state sleepiness being a measure of sleepiness at a point in time (Johns, 1991; Åkerstedt et al., 2014). Both measures are distinct from fatigue, which is a subjective experience of low energy which can be recovered from with rest, while sleepiness can only be reduced with sleep (@cite). State sleepiness is most commonly measured using the Karolinska Sleepiness Scale (KSS), a one item nine-point Likert scale that is highly correlated with EEG measures of drowsiness in healthy populations (REFS).

Excessive daytime sleepiness is one of the most common complaints associated with NRS but is inconsistently observed in ID (Hein et al., 2017; Sarsour et al., 2010). Although daytime fatigue is the most prevalent and detrimental complaint observed in ID, the inability to sleep that is characteristic of ID means that subjective sleepiness may not be a sensitive measure of daytime sleepiness in this population (Kyle et al., 2010; Raizen et al., 2023). This is further complicated by influence of sleep-state misperception, which may mean validated measures of sleepiness are less reliable. Therefore, there is a critical need for improved measurement tools that can capture the experiences of ID and NRS.

# Objective Drowsiness

Objective drowsiness refers to the quantifiable measures of sleep drive that can be measured through behavioural or physiological measures. Neurophysiologically, the level of alertness versus drowsiness can be measured using EEG data with alert wake brain activity characterized by low-amplitude, high-frequency signals in the gamma (13-35 Hz) and beta (15-25 Hz) frequencies (refs). In addition, alpha (8-12 Hz) frequency appears during relaxed wake when an individual’s eyes are closed (refs). With increased drowsiness, e.g., after experimental manipulation by sleep deprivation, brain activity shifts to lower frequency, higher amplitude activity, with increased theta (4-8 Hz) power. This slowing closely resembles characteristics of sleep and is proposed to represent a form of localized sleep, allowing neurons to perform necessary restorative processes without the loss of consciousness associated with global sleep (Vyazovskiy & Harris, 2013).

Objective drowsiness is commonly measured indirectly through tests measuring the consequences linked to increased sleep pressure. The most common measures used in clinical practice and scientific research are the Multiple Sleep Latency Test which measures sleep propensity (how long it takes to fall asleep), the Maintenance of Wakefulness Test measuring the consequences of sleepiness (how long can one stay awake), and the psychomotor vigilance task which measures sustained attention (reaction time); all tests known to be sensitive to with increased sleepiness (Basner & Dinges, 2011; Martin et al., 2023). However, these measures do not directly measure drowsiness, instead measure its consequences. These tests are of further limitation in ID populations, where a characteristic of the disorder is an inability to sleep. Therefore, it is essential to use tools that can adequately measure the neural correlates of drowsiness occurring intermittently without the need for sleep onset.

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 used to estimate the amplitude and frequency composition of oscillatory brain activitya using a fast Fourier transform. 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).

Common analysis methods for EEG measures of drowsiness are the alpha attenuation coefficient (AAC) and slowing ratio (SR). The AAC was developed to quantify the changes in alpha frequency activity that occur with increasing sleep pressure and is an objective indicator of sleepiness (Putilov & Donskaya, 2014; Stampi et al., 1995). Alpha waves are most prominent during relaxed wake when the eyes are closed, however with increasing sleepiness alpha waves appear when the eyes are open, and attenuate when the eyes are closed. The AAC measures this difference as a ratio to maximize discrimination of sleepiness levels and minimize the effects of individual variance in alpha activity (Stampi et al., 1995). The decrease in alpha activity is most prominent in the occipital region, and closely mirrors the reduction in alpha activity observed during sleep onset.

Slowing of EEG activity is an indicator of sleep onset and can be measured through the SR which compares the power of slow to fast frequencies. The SR provides spectral analysis across frequencies, providing a more comprehensive measure of brain activity than AAC alone.

# Aim

This study aimed to explore if there are differences in how people with NRS, ID, and healthy controls experience subjective and objective sleepiness, and if differences are associated with topographic differences of spectral power during resting wake. First, we examined if there were differences in subjective sleepiness levels upon awakening as measured by the KSS administered after habitual wake time. We also aimed to examine if KSS scores and power spectra covaried in NRS, ID, and healthy controls, evaluating if the influence of KSS score differed 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 and lowest in the ID group.
2. SR and AAC power upon awakening will be greatest in the NRS group and lowest in the ID group when not controlling for subjective sleepiness.
3. The influence of subjective sleepiness on brain spectral power will be moderated by group. We hypothesize that topographical analysis will reveal clusters of electrodes where the relationship between subjective sleepiness and spectral power differs by group.
4. Exploratory analysis to test for associations between KSS and PSD in classical frequency bands