Thesis

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I, Anastasia Stuart confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abbreviations

AAC	**A**lpha **A**ctivity **C**oherence
DASS-21	**D**epression **A**nxiety **S**tress **S**cales - 21 **I**tems
HC	**H**ealthy **C**ontrols
HD-EEG	**H**igh-**D**ensity **E**lectro**E**ncephalo**G**raphy
ID-NRS	**I**nsomnia **D**isorder with **N**on-**R**estorative **S**leep
ID-SSD	**I**nsomnia **D**isorder with **S**hort **S**leep **D**uration
ISI	**I**nsomnia **S**everity **I**ndex
KDT	**K**arolinska **D**rowsiness **T**est
KSS	**K**arolinska **S**leepiness **S**cale
NREM	**N**on-**R**apid **E**ye **M**ovement
PSG	**P**olysomnographic
PSQI	**P**ittsburgh **S**leep **Q**uality **I**ndex
REM	**R**apid **E**ye **M**ovement
RSQ-D	**R**estorative **S**leep **Q**uestionnaire **D**aily **V**ersion
SnPM	**S**tatistical **n**onParametric **M**apping
SR	**S**lowing **R**atio

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 (Association, 2022). NRS has previously been clinically managed as a subtype of insomnia disorder (ID) despite evidence suggesting it is phenotypically distinct with a different underlying aetiology (**cite?**).

Both disorders are associated with increased daytime fatigue and sleepiness, however there may be different causal mechanisms leading to these symptoms. A major distinction between ID and NRS is sleep architecture, with a marker of ID being percieved shortened overnight sleep duration or frequent overnight arousals, which are not present in NRS. The dysfunctional sleep architecture experienced by ID populations is hypothesised to be a causal factor for increased fatigue (**cite?**), however this population does not experience increased sleep propensity in comparison to healthy controls (**fasiello2023?**). Although NRS is associated with normal sleep architecture as measured by traditional polysomnographic (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. A potential mechanism for NRS may be reduced slow wave activity (SWA) during sleep leading to a dysfunction of sleep homeostatic processes (Kao et al., 2021).

fix thesis statement

(Colombo et al., 2016)

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 with an estimated prevalence of 23.2% (Appleton et al., 2022). It is characterised by complaints of shortened overnight sleep, difficulty with sleep initiation, or frequent overnight arousals causing clinically significant distress or dysfunction in daily life (Association, 2022). ID is associated with diminished quality of life (Kyle et al., 2010), increased risk of comorbid psychiatric disorders (Perlis et al., 2022) and increased daytime fatigue (Kim et al., 2019). Diagnosis is recommended to be made though subjective self-reporting rather than PSG data or actigraphy (Sleep Medicine, 2005), as this population has a large individual variance in sleep macrostructure due to the influence of genetics, stress reactivity, and personality (Drake et al., 2011; Harvey et al., 2014). These symptoms lead to a significant health impact, however the pathophysiology and etiology of ID remains unclear (Morin et al., 2015).

A proposed perpetuating factor in ID is 24-hour hyperarousal, being an increase of physiological, cognitive and cortical activity that contributes to the subjective and objective symptoms of the disorder (Dressle & Riemann, 2023; Riemann et al., 2010). Cortical hyperarousal is present in ID as observed through a 24-hour increase in fast frequency brain activity, which can prevent sleep onset despite significant fatigue due to the dominance of activity in cortico-limbic networks relative to sleep-promoting networks (Riemann et al., 2015). During sleep, ID is associated with increased absolute and relative beta power and relative theta, alpha, and sigma power, in addition to decreased delta power (Zhao et al., 2021). This increase is also observed during resting wake, with an increase in absolute and overall theta power, relative beta power and absolute gamma power (Zhao et al., 2021). Increased theta power in wake is associated with feelings of sleepiness, while beta and gamma power are indicators of cognitive arousal. These competing forces combine to create the 'tired but wired' feelings present in those with ID, where patients feel significant fatigue but are unable to sleep.

Daytime fatigue, being the subjective experience of low energy (Raizen et al., 2023), is the most prevalent daytime complaint in this population and is associated with the most significant detrimental impact to daily functioning (Kyle 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). Despite the prevalence of fatigue within the population, this population does not consistently exhibit increased measures of sleepiness. 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; Seong

et al., 2022; **fasiello2023?**). Additionally, despite increased fatigue, 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.

A further complexity in assessing sleepiness in this population is the subjective-objective mismatch between percieved and measured sleep, as measured through comparing self-report sleep diaries to objectively measured sleep. Individuals experiencing a misperception between their subjective and ojective sleep were intitially hypothesised to have an inability to accurately percieve their sleep or wake state leading to a skewed perception of their wake after sleep onset (Dorsey & Bootzin, 1997). However, with the introduction of more refined measurement techniques including HD-EEG and power spectral analysis, research has found that an increase of 'wake-like' brain activity in the alpha, sigma, beta and gamma bands during sleep is associated with increased percieved wakefulness (Andrillon et al., 2020; Lecci et al., 2020; Stephan et al., 2021). These findings have led the suggestion that sleep-state misperception may be due to the inability of current recording and analysis techniques to accurately identify wake-like intrusions into sleep, and the misperception experienced by ID populations possibly being better conceptualised as a mismeasurement instead (Stephan & Siclari, 2023). Therefore, measuring EEG spectral power during sleep, in contrast to standard polysomnography or questionnaires, may be a more appropriate measurement technique for analysing sleep in people with ID.

Non-restorative sleep

`potentially work on this some more`

NRS is distinct from ID due to having a normal sleep duration and architecture as measured by PSG and individuals not meeting the DSM-5-TR diagnostic criteria for insomni (Roth et al., 2010). 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). The estimated prevalence ranges from 1.4-35% across studies and populations (Zhang et al., 2012), although variation in definitions and a lack of a validated measure poses a challenge. 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?**). (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" (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.

Although this population has normal sleep duration and architecture, unrefreshing sleep may be a consequence of reduced SWA during sleep, which are critical for neural function and dissipation of accumulated sleep pressure (Kao et al., 2021; Tononi & Cirelli, 2006). 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 a necessary behaviour for all humans that can be 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 in 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.

`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 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. 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 close!!** - 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 - averave 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.

Method

Procedure

Participants were recruited through referrals from the Woolcock Institute of Medical Research and the Royal Prince Alfred sleep clinics, in addition to social media advertising. The Woolcock Institute is a specialist sleep and respiratory disorders clinic that conducts research in addition to clinical services for individuals experiencing a sleep disorder. Volunteers completed an online questionnaire to assess eligibility for inclusion in a clinical group (ID, NRS, healthy controls) which was then confirmed through telephone screening by a researcher and an in-person clinincal screening by a sleep physician.

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 (Menczel Schrire et al., 2023). Participants additionally completed the Restorative Sleep Questionnaire Daily Version (RSQ-D) to assess baseline sleep quality (**drake2014?**).

Upon arrival at the laboratory at 17:00, participants underwent a final medical screening and a series of cognitive assessments that formed part of a larger study. They were then served dinner and fitted with a high-density electroencephalography (HD-EEG) cap. Participants went to bed at their habitual bedtime, as established by self-report and actigraphy data (**schrire2022?**).

Overnight PSG data were collected using standard American Academy of Sleep Medicine (AASM) clinical practice guidelines, measuring EEG activity, in addition to electrocardiogram (ECG), electrooculogram (EOG), electromyogram (EMG), respiratory effort, nasal airflow, thermistor, snore sensor, body position, and oxygen saturation (**berry2017?**). Any overnight disturbances were recorded by research staff.

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 Karolinska Sleepiness Scale (KSS) and Karolinska Drowsiness Test (KDT) was administered five minutes post habitual wake time. Following the morning KDT, participants completed further cognitive testing and an MRI scan.

Participants were reimbursed for travel costs to and from the laboratory up to the value of $250, and remunerated $100 upon successful completion of the study.

Participants

The study was approved by the Macquarie University Human Research Ethics Committee (FoRA ID 17112) and all participants provided written informed consent. Participation was voluntary and could be discontinued at any time.

The present study was derived from data captured from a larger neuroimaging research study on phenotyping of patients with NRS. Due to the complexity of the study and large amount of outcome variables an ad-hoc power analysis was not completed. A sample size of 12 participants from each clinical population, with a total sample of 36 participants, was proposed due to funding constraints. Due to the time limitations of an honours thesis, the final sample obtained was 33 participants (13 NRS; 11 ID; 9 Controls).

Due to the influence of age and sex on sleep architecture, participants were sex and age matched with a maximum difference $\pm$ 2 years (Mongrain et al., 2005).

Participants were excluded if they had any comorbid sleep apnoea, as measured by WristOX pulse oximiter which has a high sensitivity of diagnosing obstructive sleep apnoea syndrome (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 DSM-5-TR criteria, with difficulty initiating or maintaining sleep persisting for over 1 month causing clinically significant distress or impairment in daily life, as diagnosed by a sleep physician (Association, 2022). They additionally were required to have a Pittsburgh Sleep Quality Index (PSQI) 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.

Measures

Screening questionnaire

- sex, age, alcohol consumption, pregnancy and MRI, shift work, stop-bang, ISI dass-21, PSQI, ISI

Demographic questions were administered online to assess eligibility (appendix A).

ISI

Insomnia symptoms were assessed using the Insomnia Severity Index (ISI), a seven item self-report measure of subjective insomnia symptoms (Bastien et al., 2001). Items (e.g. "Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s)") are rated on a 5-point Likert scale ranging from 0 ("none") to 4 ("very severe"). The scale ranges from 0 to 28, with scores of 10 or greater found to have 86.1% sensitivity and 87.7% specificity for detecting ID cases in a community sample and ISI scores 15 interpreted as moderate-severe insomnia (Morin et al., 2011). The ISI demonstrated good internal consistency within the sample with a Cronbach's alpha of .89.

PSQI

Self-assessed sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire assessing sleep quality and disturbance over the past month (**bussye1989?**). The PSQI measures a broader construct than insomnia severity as it measures a broader range of sleep-related disturbances beyond sleep initiation and maintenance. The convergent validity between the PSQI and ISI within our sample was r = .79. The measure produces a global score (PSQI) comprised of seven component scores, relating to subjective sleep quality (PSQI-1), sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances (PSQI-5), use of sleep medication, and daytime dysfunction. Items are rated on a four point Likert scale with greater scores indicating greater impairment. Global PSQI scores range from 0 to 21, with scores 5 recommended as the cut-off point for poor quality sleep in clinical populations (**bussye1989?**). NRS participants were required to have a PSQI-1 ("During the past month, how would you rate your sleep quality overall") subjective sleep quality score 2 ("fairly bad" or "very bad") and PSQI-5 ("During the past month, how often have you had trouble sleeping because you…") sleep disturbance component scores 10. The PSQI demonstrated acceptable internal consistency (=.72) within the sample, which is consistent with previously reported values in clinical and non-clinical populations (Mollayeva et al., 2016).

DASS-21 (can I scrap this for space?)

To control for clinically significant comorbid depression or anxiety, the short form Depression Anxiety and Stress Scale (DASS-21) was administered during the recruitment stage (**lovibond1995?**). The 21-item self-report scale is comprised of three 7-item subscales measuring depression, anxiety, and stress symptoms over the prevous week on a 4-point likert scale from 0 ("did not apply to me at all") to 3 ("applied to me very much, or most of the time"). Scale scores range from 0 to 21, with higher scores indicating incresed depression, anxiety, or stress symptoms. T The scale had acceptable internal consistency for the depression (=.74) and anxiety (=.79) subscales, but unacceptable internal consistency for the stress (= .21) subscale. As only the depression and anxiety scores were used to screen for comorbidity, the scale demonstrated acceptable reliability for the dimensions of interest.

Flinders Fatigue Scale

Daytime fatigue impairments was measured using the Flinders Fatigue Scale (FFS), a 7-item measure of fatigue characteristics (e.g. "was fatigue a problem for you") over the previous two weeks (**gradisar2007?**). The scale produces a score ranging from 0 to 31, with greater scores indicating greater fatigue. The scale explicitly defines fatigue as being distinct from sleepiness, stating "We are interested in the extent that you have felt **fatigued** (tired, weary, exhausted) over the last **two weeks**. We **do not** mean feelings of **sleepiness** (the likelihood of falling asleep)." The FFS had good internal consistency (=.86) within the sample and was not correlated with ESS scores (r = .20)

Epworth Sleepiness Scale

Situational sleep propensity was measured using the Epworth Sleepiness Scale (ESS), an 8-item measure assessing the likelihood of dozing in specific situations (e.g. "sitting and reeading") (Johns, 1991). Items are rated on a 4-point Likert scale, ranging from 0 ("would **never** doze") to 3 ("**high** chance of dozing"). Scores range from 0 to 24 with greater ESS scores indicating greater sleep propensity. The ESS had good internal consistency (=.85) within the sample.

Karolinska Sleepiness Scale

Subjective sleepiness was assessed 5 minutes after natural wake time using the Karolinska Sleepiness Scale (KSS), a 9-point scale with verbal anchors at every second step ranging from 1 ("Extremely alert") to 9, "Extremely sleepy - fighting sleep" (Åkerstedt & Gillberg, 1990). The scale measures an individual's percieved sleepiness at a given point, with the instructions "please measure your sleepiness over the past 5

minutes." *CHECK*

Karolinska Drowsiness Test

The Karolinska Drowsiness Test (KDT) was administered immediately following the KSS and 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." The test is 7 minutes long with 3 phases (eyes open/eyes closed/eyes open) each lasting 120 seconds. The eyes open conditions were concatenated during data analysis.

PSG sleep scoring and sleep macroarchitecture

Overnight polysomnography sleep data were recorded and were scored in 30 second epochs according to American Academy of Sleep Medicine Manual (AASM) criteria by an experienced rater (**berry2017?**). PSG data included 256-channel EEG, electrocardiogram (ECG), nasal airflow pressure (nasal cannula), thoracic and abdominal respiratory effort, finger pulse oximetry (SpO2%), body position, and leg EMG measurements. Sleep recordings were evaluated for the following parameters of sleep continuity: time in bed (TIB, measured as total time spent in bed independent from sleep state); total sleep time (TST, defined as time between first sleep onset and final awakening, excluding periods awake); sleep onset latency (SOL, measured as time from lights out until first epoch of sleep); snooze time (measured from time of final awakening to time out of bed); REM latency (minutes from sleep onset to first epoch of REM sleep); wake after sleep onset (WASO, time spent awake between sleep onset and final awakening); sleep efficiency (ratio of TST to time in bed $\times$ 100 %); and total minutes/percentage in N1, N2, N3 and REM sleep (as scored using the AASM criteria).

HD-EEG

High-density EEG data were collected using 256-channel electrode caps (HydroCel Geodesic Sensor Net 130 LTM, MagstimEGI, Eugene, OR, USA) with signals amplified (NetAmps 400, MagstimEGI, Eugene, OR, USA) and **which** digitised with electodes referenced to the vertex (CZ) (**cite?**). During acquisition, data were low-pass filtered at **70** Hz, high-pass filtered at **0.3** Hz, and notch filtered at **50** Hz (**cite?**). Electrode impedences were below **what** kΩ.

Slowing ratio

The EEG slowing ratio (SR) is a biomarker of sleepiness reflecting the general slowing of brain activity that appears with increasing sleepiness, with a dominance of slow frequency activity being indicative of decreased arousal (D'Rozario et al., 2013). SR has been shown to be a valid measure of reduced alertness and increased drowsiness in clinical populations (D'Rozario et al., 2013; Sivam et al., 2020) When the eyes are open, alpha, delta, and theta frequency activity is a marker of drowsiness, and the slowing ratio was calculated as [(+ +)/ (+)] power. As alpha activity reduced when the eyes are closed with increasing drowsiness, the slowing ratio was calculated as [(+)/ (+ +)] power in the eyes closed condition. The slowing ratio was calculated for both absolute power and normalised power for each channel in both the eyes open and eyes closed conditions.

Alpha attenuation coefficient

The Alpha Attenuation Coefficient (AAC) measures alpha frequency power differences between eyes open and eyes closed conditions (Stampi et al., 1995). The AAC is calculated by the ratio of alpha power in the eyes closed condition to alpha power in the eyes open condition. A lower AAC score reflects decreased cortical activity and increased sleepiness. The AAC was calculated for both absolute and normalised power for each channel.

Data processing

EEG Processing

All preprocessing was completed using the EEG Processor application for MATLAB ((**wassing2024?**)). Data were visually inspected for artefacts and arousals which were removed across all channels. Poor quality channels were replaced with an interpolated EEG signal from neighbouring channels using linear mixing, weighted by the squared non-linear distance *on average how many per participant, +-SD).*

To enhance the local signal detection of each electrode and minimise the influence of the vertex (CZ) electrode, data were re-referenced to a common average signal created through finding the mean global signal across all electrodes.

Independent Components Analysis

Following a visual inspection, independent components analysis (ICA) was used to identify and seperate components that are statistically independent from each other. This was done using a semi-automated

process using the MATLAB program *ICLabel*, which automatically removed components with a weighting of .8 or greater for non-brain activity (Pion-Tonachini et al., 2019). Visual inspection was conducted to verify artefact removal and remove any components that did not reach the weighting threshold, but were visually deemed non-brain activity. Remaining components were back-projected to the EEG data signal via regression, resulting in a cleaned time series signal.

Power Spectra

EEG power spectra was obtained for each channel using a fast Fourier transform (FFT) to deconstruct the EEG signal from the time domain to the frequency domain, allowing it to be analysed in power (squared amplitude) in frequency bins (mV2/bin). The power spectra was calculated for 50% overlapping 6-second epochs and obtained for the eyes closed condition and a concatenated recording of the eyes open condition. `with a Hanning window, resulting in a frequency step of 0.122 Hz` **boundary clip?** EEG spectral power densities were quantified as: low delta (0.5-1 Hz), 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). Power spectral densities represent the distribution of power in a signal across frequencies, allowing analysis of the frequency components that are most significant in each epoch's signal. This allows the measurement of neuronal activity on vigilance states.

To account for differences in absolute spectral power across participants, data was expressed as an absolute and normalised value for the defined frequency ranges for each participant (D'Rozario et al., 2023).

Statistical analysis

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

One-way analysis of variance (ANOVA) was calculated for group differences in categorical variables in demographic variables, survey response meaures, sleep macro-architecture, and KSS scores to assess for significant differences ($p < .05$) between groups. Post-hoc pairwise comparisons were conducted using Tukey's HSD. The normality of the distribution and outliers was conducted using Q-Q Plots, Shapiro-Wilk normality tests, and visual inspections of histograms.

Topographical high-density EEG analysis was conducted on 178 scalp channels after removal of neck, face, and forehead channels.

To account for non-normality, SR and AAC values were log transformed prior to analysis.

For hypothesis 2, EEG power (absolute and normalised values for defined frequency ranges), SR, and

AAC were compared for each condition (eyes open/eyes closed) between groups (ID, NRS, Control) using a one-way ANOVA ($p < .05$). For hypothesis 3, KSS score was added as a covariate.

Electrodes showing regional differences in EEG activity were analyses using a permutation analysis to control for the potential of Type I errors. This involved using 10 000 random shuffles of the data to build a reference distribution of cluster sizes that occur due to chance, which can then be used to compare the found cluster size against ($p < .05$). Blocks were permuted as whole-blocks and within-blocks.

Results

Participants

964 participants completed the online expression of interest questionnaire, 352 (36.51%) were deemed eligible for screening, and 33 participants were eligible for inclusion in the study. Leading reasons for exclusion included not responding to follow up calls (45.74%), having no age or sex match (15.34%), or taking regular medication that interfered with sleep (12.50%).

The final sample consisted of 33 participants, with 13 NRS, 11 ID, and 9 healthy controls. Participant demographic and survey response details are provided in Table 1. Sleep macroarchitecture tables are recorded in Table 2.

Groups did not differ significantly on age, DASS-21 scores, or daytime sleep propensity (ESS scores).

Depression (DASSD), anxiety (DASSA), and stress (DASSS) scores did not show significant group differences (all $p > .05$).

The ID and NRS groups had significantly lower sleep quality (PSQI), increased insomnia symptom severity (ISI),

higher PSQI and ISI scores compared to the control and NRS groups, reflective of increased symptoms.

ID and NRS groups reported significantly increased daytime fatigue in comparison to control

significantly different on Flinders fatigue scale scores, PSQI scores, and ISI scores.

A post-hoc power analysis using G*power (Faul et al., 2007) determined that using the found effect size for KSS AM score of 0.36 ($f = 0.355$) and a set alpha of 0.05, the study achieved a power of approximately 0.39. A post-hoc sensitivity analysis found the study was sensitive to detecting a larch effect size of 0.57 using an alpha level of 0.05 and a desired power of 0.8. This suggests that while the study was underpowered to detect small to medium effect sizes, it was adequately powered to detect large effects. As the KSS is sensitive for detecting - clinical significance would be a large effect size

964 participants completed the online expression of interest questionnaire, 352 found as eligible for participation, and 33 participants were included in the study.

The decision to proceed with the sample size despite the low power was justified by the exploratory nature of the study and the strength of the age and sex matching of participants, allowing for control of confounding variables and increased likelihood of detecting true differences between groups.

. Of these, 8 were unable to be contacted via email and 161 did not respond to a follow up email. 180 participants proceeded to pre-screening. 145 completers were excluded from participation during the pre-screening and screening visits, with 44 (30%) being excluded for medication use and 54 (15%) being excluded due to having to age or sex match.

33 participants were included, with the sample consisting of 13 individuals with Non-Restorative Sleep (NRS), 11 participants with Insomnia Disorder (ID), and 9 healthy controls (HC). Table 1 summarises the participant demographics and self-report questionnaires.

```
## Warning: package 'knitr' was built under R version 4.3.3
```

Descriptive statistics of correct recall by dosage.

group

Mean

Median

SD

Min

Max

CTL

4.222222

4

1.092906

2

6

ID

5.090909

5

2.165851

2

9

NRS

5.769231

6

1.921538

1

8

Comparing KSS scores between groups

A repeated measures ANOVA was conducted to evaluate the effect of group on AM KSS scores. For the KSS_AM1 scores, the mean score for the control group was 4.22 (SD = 1.09), for the ID group was 5.09 (SD = 2.17), and for the NRS group was 5.77 (SD = 1.92). The median scores were 4, 5, and 6, respectively. The minimum and maximum scores were 2 and 6 for CTL, 2 and 9 for GID, and 1 and 8 for NRS. The analysis revealed no significant effect of group, F(2,30)=1.897,p=.168

A post-hoc power analysis conducted in G*power Version 3.1.9.6 reported inadequate power for the given effect size, f=0.356. With a set alpha of 0.05, the power was found to be 0.396.

`huge variance in KSS_AM1 for GID, NRS higher but affected by outliers`

The ANOVA (formula: KSS_AM1 ~ group) suggests that:

- The main effect of group is statistically not significant and medium (F(2, 30) = 1.90, p = 0.168; Eta2 = 0.11, 95% CI [0.00, 1.00])

Effect sizes were labelled following Field's (2013) recommendations.

Correlation between KSS and slowing ratio scores between groups

Correlation between KSS and AAC between groups

Topography of channel-by-channel comparisons between ID and NRS groups

References

Achermann, P., & Borbély, A. A. (2003). Mathematical models of sleep regulation. *Frontiers in Bioscience-Landmark*, *8*(6, 6), 683–693. https://doi.org/10.2741/1064

Åkerstedt, T., Anund, A., Axelsson, J., & Kecklund, G. (2014). Subjective sleepiness is a sensitive indicator of insufficient sleep and impaired waking function. *Journal of Sleep Research*, *23*(3), 242–254. https://doi.org/10.1111/jsr.12158

Åkerstedt, T., & Gillberg, M. (1990). Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience*, *52*(1-2), 29–37. https://doi.org/10.3109/00207459008994241

Andrillon, T., Solelhac, G., Bouchequet, P., Romano, F., Le Brun, M.-P., Brigham, M., Chennaoui, M., & Léger, D. (2020). Revisiting the value of polysomnographic data in insomnia: More than meets the eye. *Sleep Medicine*, *66*, 184–200. https://doi.org/10.1016/j.sleep.2019.12.002

Appleton, S. L., Reynolds, A. C., Gill, T. K., Melaku, Y. A., & Adams, R. J. (2022). Insomnia Prevalence Varies with Symptom Criteria Used with Implications for Epidemiological Studies: Role of Anthropometrics, Sleep Habit, and Comorbidities. *Nature and Science of Sleep*, *14*, 775–790. https://doi.org/10.2147/NSS.S359437

Association, A. P. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text revision). American Psychiatric Association.

Balter, L. J. T., Van Someren, E. J. W., & Axelsson, J. (2024). Insomnia symptom severity and dynamics of arousal-related symptoms across the day. *Journal of Sleep Research*, e14276. https://doi.org/10.1111/jsr.14276

Basner, M., & Dinges, D. F. (2011). Maximizing Sensitivity of the Psychomotor Vigilance Test (PVT) to Sleep Loss. *Sleep*, *34*(5), 581–591. https://doi.org/10.1093/sleep/34.5.581

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307. https://doi.org/10.1016/s1389-9457(00)00065-4

Benington, J. H. (2000). Sleep homeostasis and the function of sleep. *Sleep*, *23*(7), 959–966.

Benz, F., Riemann, D., Domschke, K., Spiegelhalder, K., Johann, A. F., Marshall, N. S., & Feige, B. (2023). How many hours do you sleep? A comparison of subjective and objective sleep duration measures in a sample of insomnia patients and good sleepers. *Journal of Sleep Research*, *32*(2), e13802. https://doi.org/10.1111/jsr.13802

Bernardi, G., Siclari, F., Yu, X., Zennig, C., Bellesi, M., Ricciardi, E., Cirelli, C., Ghilardi, M. F., Pietrini, P., & Tononi, G. (2015). Neural and Behavioral Correlates of Extended Training during Sleep Deprivation in Humans: Evidence for Local, Task-Specific Effects. *Journal of Neuroscience*, *35*(11), 4487–4500. https://doi.org/10.1523/JNEUROSCI.4567-14.2015

Borbély, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology*, *1*(3), 195–204.

Borbély, A. A., Daan, S., Wirz-Justice, A., & Deboer, T. (2016). The two-process model of sleep regulation: A reappraisal. *Journal of Sleep Research*, *25*(2), 131–143. https://doi.org/10.1111/jsr.12371

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience*, *13*(6), 407–420. https://doi.org/10.1038/nrn3241

Cajochen, C., Foy, R., & Dijk, D.-J. (1999). Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Research Online : SRO*, *2*, 65–69.

Cantero, J. L., Atienza, M., & Salas, R. M. (2002). Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: Different electroencephalographic phenomena within the alpha band. *Neurophysiologie Clinique/Clinical Neurophysiology*, *32*(1), 54–71. https://doi.org/10.1016/S0987-7053(01)00289-1

Cirelli, C., & Tononi, G. (2008). Is sleep essential? *PLOS Biology*, *6*(8), e216. https://doi.org/10.1371/journal.pbio.0060216

Colombo, M. A., Ramautar, J. R., Wei, Y., Gomez-Herrero, G., Stoffers, D., Wassing, R., Benjamins, J. S., Tagliazucchi, E., van der Werf, Y. D., Cajochen, C., & Van Someren, E. J. W. (2016). Wake high-density electroencephalographic spatiospectral signatures of insomnia. *Sleep*, *39*(5), 1015–1027. https://doi.org/10.5665/sleep.5744

D'Rozario, A. L., Kao, C.-H., Phillips, C. L., Mullins, A. E., Memarian, N., Yee, B. J., Duffy, S. L., Cho, G., Wong, K. K. H., Kremerskothen, K., Chapman, J., Haroutonian, C., Bartlett, D. J., Naismith, S. L., & Grunstein, R. R. (2023). Region-specific changes in brain activity and memory after continuous positive airway pressure therapy in obstructive sleep apnea: A pilot high-density electroencephalography study. *SLEEP*, *46*(12), zsad255. https://doi.org/10.1093/sleep/zsad255

D'Rozario, A. L., Kim, J. Won., Wong, K. K. H., Bartlett, D. J., Marshall, N. S., Dijk, D.-J., Robinson, P. A., & Grunstein, R. R. (2013). A new EEG biomarker of neurobehavioural impairment and sleepiness in sleep apnea patients and controls during extended wakefulness. *Clinical Neurophysiology*, *124*(8), 1605–1614. https://doi.org/10.1016/j.clinph.2013.02.022

Dorsey, C. M., & Bootzin, R. R. (1997). Subjective and psychophysiologic insomnia: An examination of sleep tendency and personality. *Biological Psychiatry*, *41*(2), 209–216. https://doi.org/10.1016/0006-3223(95)00659-1

Drake, C. L., Friedman, N. P., Wright, K. P., Jr, & Roth, T. (2011). Sleep Reactivity and Insomnia: Genetic and Environmental Influences. *Sleep*, *34*(9), 1179–1188. https://doi.org/10.5665/SLEEP.1234

Dressle, R. J., & Riemann, D. (2023). Hyperarousal in insomnia disorder: Current evidence and potential mechanisms. *Journal of Sleep Research*, *32*(6), e13928. https://doi.org/10.1111/jsr.13928

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146

Harvey, C.-J., Gehrman, P., & Espie, C. A. (2014). Who is predisposed to insomnia: A review of familial aggregation, stress-reactivity, personality and coping style. *Sleep Medicine Reviews*, *18*(3), 237–247. https://doi.org/10.1016/j.smrv.2013.11.004

Hein, M., Lanquart, J.-P., Loas, G., Hubain, P., & Linkowski, P. (2017). Prevalence and risk factors of excessive daytime sleepiness in insomnia sufferers: A study with 1311 individuals. *Journal of Psychosomatic Research*, *103*, 63–69. https://doi.org/10.1016/j.jpsychores.2017.10.004

Huang, L., Zhou, J., Li, Z., Lei, F., & Tang, X. (2012). Sleep perception and the multiple sleep latency test in patients with primary insomnia. *Journal of Sleep Research*, *21*(6), 684–692. https://doi.org/10.1111/j.1365-2869.2012.01028.x

Huber, R., Deboer, T., & Tobler, I. (2000). Topography of EEG Dynamics After Sleep Deprivation in Mice. *Journal of Neurophysiology*, *84*(4), 1888–1893. https://doi.org/10.1152/jn.2000.84.4.1888

Huber, R., Felice Ghilardi, M., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, *430*(6995), 78–81. https://doi.org/10.1038/nature02663

Hung, C.-S., Sarasso, S., Ferrarelli, F., Riedner, B., Ghilardi, M. F., Cirelli, C., & Tononi, G. (2013). Local Experience-Dependent Changes in the Wake EEG after Prolonged Wakefulness. *Sleep*, *36*(1), 59–72. https://doi.org/10.5665/sleep.2302

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

Johns, M. W. (2009). What is excessive daytime sleepiness !!@cite fix this citation!! In *Sleep deprivation: Causes, effects and treatment* (pp. 59–94). Nova Science Publishers Inc.

Kaida, K., Takahashi, M., Akerstedt, T., Nakata, A., Otsuka, Y., Haratani, T., & Fukasawa, K. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *117*(7), 1574–1581. https://doi.org/10.1016/j.clinph.2006.03.011

Kao, C.-H., D'Rozario, A. L., Lovato, N., Wassing, R., Bartlett, D., Memarian, N., Espinel, P., Kim, J.-W., Grunstein, R. R., & Gordon, C. J. (2021). Insomnia subtypes characterised by objective sleep duration and NREM spectral power and the effect of acute sleep restriction: An exploratory analysis. *Scientific Reports*, *11*(1), 24331. https://doi.org/10.1038/s41598-021-03564-6

Kim, S. J., Kim, S., Jeon, S., Leary, E. B., Barwick, F., & Mignot, E. (2019). Factors associated with fatigue in patients with insomnia. *Journal of Psychiatric Research*, *117*, 24–30. https://doi.org/10.1016/j.jpsychires.2019.06.021

Krueger, J. M., Nguyen, J. T., Dykstra-Aiello, C. J., & Taishi, P. (2019). Local sleep. *Sleep Medicine Reviews*, *43*, 14–21. https://doi.org/10.1016/j.smrv.2018.10.001

Krueger, J. M., & Obäl Jr., F. (1993). A neuronal group theory of sleep function. *Journal of Sleep Research*, *2*(2), 63–69. https://doi.org/10.1111/j.1365-2869.1993.tb00064.x

Kyle, S. D., Morgan, K., & Espie, C. A. (2010). Insomnia and health-related quality of life. *Sleep Medicine Reviews*, *14*(1), 69–82. https://doi.org/10.1016/j.smrv.2009.07.004

Lecci, S., Cataldi, J., Betta, M., Bernardi, G., Heinzer, R., & Siclari, F. (2020). Electroencephalographic changes associated with subjective under- and overestimation of sleep duration. *Sleep*, *43*(11), zsaa094. https://doi.org/10.1093/sleep/zsaa094

Marques, D. R., Gomes, A. A., & de Azevedo, M. H. P. (2019). DSPS-4: A Brief Measure of Perceived Daytime Sleepiness. *Current Psychology*, *38*(2), 579–588. https://doi.org/10.1007/s12144-017-9638-0

Martin, V. P., Lopez, R., Dauvilliers, Y., Rouas, J.-L., Philip, P., & Micoulaud-Franchi, J.-A. (2023). Sleepiness in adults: An umbrella review of a complex construct. *Sleep Medicine Reviews*, *67*, 101718. https://doi.org/10.1016/j.smrv.2022.101718

Menczel Schrire, Z., Gordon, C. J., Palmer, J. R., Murray, J., Hickie, I., Rogers, N. L., Lewis, S. J., Terpening, Z., Pye, J. E., Naismith, S. L., & Hoyos, C. M. (2023). Actigraphic and melatonin alignment in older adults with varying dementia risk. *Chronobiology International*, *40*(2), 91–102. https://doi.org/10.1080/07420528.2022.2144744

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C. M., & Colantonio, A. (2016). The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *25*, 52–73. https://doi.org/10.1016/j.smrv.2015.01.009

Mongrain, V., Carrier, J., & Dumont, M. (2005). Chronotype and sex effects on sleep architecture and quantitative sleep EEG in healthy young adults. *Sleep*, *28*(7), 819–827. https://doi.org/10.1093/sleep/28.7.819

Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*, *34*(5), 601–608. https://doi.org/10.1093/sleep/34.5.601

Morin, C. M., Drake, C. L., Harvey, A. G., Krystal, A. D., Manber, R., Riemann, D., & Spiegelhalder, K. (2015). Insomnia disorder. *Nature Reviews Disease Primers*, *1*(1), 1–18. https://doi.org/10.1038/nrdp.2015.26

Neu, D., Mairesse, O., Verbanck, P., & Le Bon, O. (2015). Slow wave sleep in the chronically fatigued: Power spectra distribution patterns in chronic fatigue syndrome and primary insomnia. *Clinical Neurophysiology*, *126*(10), 1926–1933. https://doi.org/10.1016/j.clinph.2014.12.016

Nigro, C. A., Aimaretti, S., Gonzalez, S., & Rhodius, E. (2009). Validation of the WristOx 3100™ oximeter for the diagnosis of sleep apnea/hypopnea syndrome. *Sleep and Breathing*, *13*(2), 127–136. https://doi.org/10.1007/s11325-008-0217-3

Nir, Y., Andrillon, T., Marmelshtein, A., Suthana, N., Cirelli, C., Tononi, G., & Fried, I. (2017). Selective neuronal lapses precede human cognitive lapses following sleep deprivation. *Nature Medicine*, *23*(12), 1474–1480. https://doi.org/10.1038/nm.4433

Perlis, M. L., Posner, D., Riemann, D., Bastien, C. H., Teel, J., & Thase, M. (2022). Insomnia. *The Lancet*, *400*(10357), 1047–1060. https://doi.org/10.1016/S0140-6736(22)00879-0

Pigeon, W. R., & Perlis, M. L. (2006). Sleep homeostasis in primary insomnia. *Sleep Medicine Reviews*, *10*(4), 247–254. https://doi.org/10.1016/j.smrv.2005.09.002

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*, *198*, 181–197. https://doi.org/10.1016/j.neuroimage.2019.05.026

Plante, D. T., Goldstein, M. R., Cook, J. D., Smith, R., Riedner, B. A., Rumble, M. E., Jelenchick, L., Roth, A., Tononi, G.,

Benca, R. M., & Peterson, M. J. (2016). Effects of partial sleep deprivation on slow waves during non-rapid eye movement sleep: A high density EEG investigation. *Clinical Neurophysiology*, *127*(2), 1436–1444. https://doi.org/10.1016/j.clinph.2015.10.040

Raizen, D. M., Mullington, J., Anaclet, C., Clarke, G., Critchley, H., Dantzer, R., Davis, R., Drew, K. L., Fessel, J., Fuller, P. M., Gibson, E. M., Harrington, M., Ian Lipkin, W., Klerman, E. B., Klimas, N., Komaroff, A. L., Koroshetz, W., Krupp, L., Kuppuswamy, A., … Craig Heller, H. (2023). Beyond the symptom: The biology of fatigue. *Sleep*, *46*(9), zsad069. https://doi.org/10.1093/sleep/zsad069

Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M. L., & Spiegelhalder, K. (2015). The neurobiology, investigation, and treatment of chronic insomnia. *The Lancet Neurology*, *14*(5), 547–558. https://doi.org/10.1016/S1474-4422(15)00021-6

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, *14*(1), 19–31. https://doi.org/10.1016/j.smrv.2009.04.002

Roth, T., Zammit, G., Lankford, A., Mayleben, D., Stern, T., Pitman, V., Clark, D., & Werth, J. L. (2010). Nonrestorative sleep as a distinct component of insomnia. *Sleep*, *33*(4), 449–458. https://doi.org/10.1093/sleep/33.4.449

Sarsour, K., Van Brunt, D. L., Johnston, J. A., Foley, K. A., Morin, C. M., & Walsh, J. K. (2010). Associations of nonrestorative sleep with insomnia, depression, and daytime function. *Sleep Medicine*, *11*(10), 965–972. https://doi.org/10.1016/j.sleep.2010.08.007

Seong, M. J., Kim, J. R., Choi, S. J., & Joo, E. Y. (2022). Exploration of Insomnia With Excessive Daytime Sleepiness From Clinical and Polysomnographic Perspectives. *Journal of Sleep Medicine*, *19*(2), 65–74. https://doi.org/10.13078/jsm.220014

Shi, Y., Ren, R., Lei, F., Zhang, Y., Vitiello, M. V., & Tang, X. (2022). Elevated beta activity in the nighttime sleep and multiple sleep latency electroencephalograms of chronic insomnia patients. *Frontiers in Neuroscience*, *16*, 1045934. https://doi.org/10.3389/fnins.2022.1045934

Siclari, F., & Tononi, G. (2017). Local aspects of sleep and wakefulness. *Current Opinion in Neurobiology*, *44*, 222–227. https://doi.org/10.1016/j.conb.2017.05.008

Sivam, S., Poon, J., Wong, K. K. H., Yee, B. J., Piper, A. J., D'Rozario, A. L., Wang, D., & Grunstein, R. R. (2020). Slow-frequency electroencephalography activity during wake and sleep in obesity hypoventilation syndrome. *Sleep*, *43*(2), zsz214. https://doi.org/10.1093/sleep/zsz214

Sleep Medicine, A. A. of. (2005). International classification of sleep disorders. *Diagnostic and Coding Manual*, 148–152. https://cir.nii.ac.jp/crid/1572824499146899712

Snipes, S., Krugliakova, E., Meier, E., & Huber, R. (2022). The Theta Paradox: 4-8 Hz EEG Oscillations Reflect Both Sleep Pressure and Cognitive Control. *The Journal of Neuroscience*, *42*(45), 8569–8586. https://doi.org/10.1523/JNEUROSCI.1063-22.2022

Stampi, C., Stone, P., & Michimori, A. (1995). A new quantitative method for assessing sleepiness: The alpha attenuation test. *Work & Stress*, *9*(2-3), 368–376. https://doi.org/10.1080/02678379508256574

Stephan, A. M., Lecci, S., Cataldi, J., & Siclari, F. (2021). Conscious experiences and high-density EEG patterns predicting subjective sleep depth. *Current Biology*, *31*(24), 5487–5500.e3. https://doi.org/10.1016/j.cub.2021.10.012

Stephan, A. M., & Siclari, F. (2023). Reconsidering sleep perception in insomnia: From misperception to mismeasurement. *Journal of Sleep Research*, *32*(6), e14028. https://doi.org/10.1111/jsr.14028

Steriade, M., Timofeev, I., & Grenier, F. (2001). Natural waking and sleep states: A view from inside neocortical neurons. *Journal of Neurophysiology*, *85*(5), 1969–1985. https://doi.org/10.1152/jn.2001.85.5.1969

Stone, K. C., Taylor, D. J., McCrae, C. S., Kalsekar, A., & Lichstein, K. L. (2008). Nonrestorative sleep. *Sleep Medicine*

Reviews, *12*(4), 275–288. https://doi.org/10.1016/j.smrv.2007.12.002

Strijkstra, A. M., Beersma, D. G. M., Drayer, B., Halbesma, N., & Daan, S. (2003). Subjective sleepiness correlates negatively with global alpha (8–12 Hz) and positively with central frontal theta (4–8 Hz) frequencies in the human resting awake electroencephalogram. *Neuroscience Letters*, *340*(1), 17–20. https://doi.org/10.1016/S0304-3940(03)00033-8

Tinajero, R., Williams, P. G., Cribbet, M. R., Rau, H. K., Bride, D. L., & Suchy, Y. (2018). Nonrestorative sleep in healthy, young adults without insomnia: Associations with executive functioning, fatigue, and pre-sleep arousal. *Sleep Health*, *4*(3), 284–291. https://doi.org/10.1016/j.sleh.2018.02.006

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, *10*(1), 49–62. https://doi.org/10.1016/j.smrv.2005.05.002

Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nature Neuroscience*, *11*(2), 200–208. https://doi.org/10.1038/nn2035

Vyazovskiy, V. V., & Harris, K. D. (2013). Sleep and the single neuron: The role of global slow oscillations in individual cell rest. *Nature Reviews Neuroscience*, *14*(6), 443–451. https://doi.org/10.1038/nrn3494

Vyazovskiy, V. V., Olcese, U., Hanlon, E. C., Nir, Y., Cirelli, C., & Tononi, G. (2011). Local sleep in awake rats. *Nature*, *472*(7344), 443–447. https://doi.org/10.1038/nature10009

Vyazovskiy, V. V., & Tobler, I. (2005). Theta activity in the waking EEG is a marker of sleep propensity in the rat. *Brain Research*, *1050*(1), 64–71. https://doi.org/10.1016/j.brainres.2005.05.022

Werth, E., Achermann, P., & Borbély, A. A. (1996). Brain topography of the human sleep EEG: Antero-posterior shifts of spectral power. *NeuroReport*, *8*(1), 123. https://journals.lww.com/neuroreport/abstract/1996/12200/brain_topography_of_the_human_sleep_eeg_.25.aspx

Zhang, J., Lam, S.-P., Li, S. X., Li, A. M., & Wing, Y.-K. (2012). The longitudinal course and impact of non-restorative sleep: A five-year community-based follow-up study. *Sleep Medicine*, *13*(6), 570–576. https://doi.org/10.1016/j.sleep.2011.12.012

Zhao, W., Van Someren, E. J. W., Li, C., Chen, X., Gui, W., Tian, Y., Liu, Y., & Lei, X. (2021). EEG spectral analysis in insomnia disorder: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *59*, 101457. https://doi.org/10.1016/j.smrv.2021.101457