Thesis

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Contents

Introduction

Problem statement

Insomnia is the one of the most common sleep complaints in Australia, affecting up to 33% of the population and causing a significant health burden (Sweetman et al., 2021). It is associated with clinical complaints of shortened overnight sleep, difficulty with sleep initiation, and frequent overnight arousals causing clinically significant distress or dysfunction in daily life (Association, 2022a). In contrast to many other sleep disorders that are diagnosed through polysomnographic data, diagnosis of insomnia is recommended based on subjective reports of impairment through self-assessed questionnaires (Sleep Medicine, 2005). A reason for this is despite the poor subjective sleep quality experienced by this population, PSG data suggests there are several phenotypes of the disorder, being the more biologically severe insomnia with objective short sleep duration (ID-SSD) and insomnia with normal sleep duration but non-restorative sleep (ID-NRS) [Vgontzas et al. (2013);] **where do we get NRS term from?**.

The inability to identify objective markers of this **disease** through PSG may result from the inability of current methods to adequately measure sleep that are specific to individuals with NRS. - unknown how to record this sleep state mismeasurement observed in NRS. lack of clear diagnostic markers and understanding of the physiological mechanisms. **variation in definition of NRS leads to impairment of research and clinical management (Stone et al., 2008).

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

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what is the issue. impact. theoretical model. what is the solution.
is there a difference in how NRS and ID percieve daytime tiredness,
and is that related to delta power in previous nights sleep?
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Background

Current understanding of sleep

Sleep is regulated by both a homeostatic and circadian system (Borbély, 1982), wherein the homeostatic system increases the level of perceived sleepiness as waking time increases (sleep pressure) (Porkka-

Heiskanen, 2013) while the circadian system regulates internal synchrony with the environment through the suprachiasmatic nuclei (Hastings, 1997). Sleep homeostasis refers to the given amount of sleep required for an organism over a 24 hour period, increasing with time spent awake and dissipating with sleep **primarily slow wave sleep**. The best established method of measuring sleep homeostasis is the overnight dissipation of delta power (Lunsford-Avery et al., 2021)

Sleep architecture (?)

Sleep is identified through changes in EEG patterns which display the shift from wakefulness to sleep, and can be categorised into N1, N2, N3 and REM sleep stages. N1 sleep is the transitional state from wake to sleep, characterised through a reduction in alpha activity (8-12 Hz) and the appearance of theta waves (4-8 Hz). N2 sleep is identified with the emergence of K-complexes and sleep spindles, 0.5-2s bursts of high-frequency oscillatory brain activity **what do either of these have to do with drowsiness**. N3 sleep is the deepest phase of sleep, characterised by slow (delta) waves of 0.5-4 Hz and increased amplitude of 75µV, and makes up *confirm percentage of sleep* in healthy adults.

slow wave sleep

Although the function of sleep is nuclear (Sejnowski & Destexhe, 2000), a primary function may be facilitation of prophylactic cellular maintenance within individual neurons, regulated through periods of reduced synaptic input deemed slow waves requiring globally synchronised neuronal activity (Vyazovskiy & Harris, 2013). Slow wave activity (SWA) dissipates with sleep, with reduced SWA and decreased wave amplitude during late sleep compared to early sleep (Riedner et al., 2007).

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- EEG slow waves of NREM sleep occur when neurons become bistable and oscillate between two states:
a hyperpolarized down-state characterized by neuronal silence (off-period), and a depolarized up-state
during which neurons fire (on-period) [@steriade2001]. During up-state, neurons fire at high frequencies
typical of waking, and during down state there is a tonic cessation of firing activity in all cortical l
- slow oscillation is a travelling wave that originates at a definite site and travels over the scalp at
an estimated speed of 1.2-7.0 m/sec, waves originate more frequently in prefrontal-orbitofrontal regions
and propagate in an anteroposterior direction [@massimini2004].
 - We identified two clusters of delta waves with distinctive properties: (1) a frontal-central cluster
 characterized by  2.5-3.0 Hz, relatively large, notched delta waves (so-called "sawtooth waves") that
 tended to occur in bursts, were associated with increased gamma activity and rapid eye movements (EMs)
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and upon source modeling displayed an occipital-temporal and a frontal-central component and (2) a medial-occipital cluster characterized by more isolated, slower (<2 Hz), and smaller waves that were no associated with rapid EMs, displayed a negative correlation with gamma activity, and were also found in NREM sleep. Therefore, delta waves are an integral part of REM sleep in humans and the two identified subtypes (sawtooth and medial-occipital slow waves) may reflect distinct generation mechanisms and functional roles. [@bernardi2019]

ID and NRS slow wave sleep deficiencies

Insomnia is associated with dysfunction in sleep homeostasis, which may be due to decreased homeostatic drive or cortical arousal affecting the overnight dissipation of sleep pressure (Lunsford-Avery et al., 2021).

- Insomnia SSD has lower sleep duration and lower NREM delta power than HC [@kao2021]
- Insufficiency of slow-wave sleep may predict cognitive impairment and severity of chronic insomnia [@l
- insomnia patients exhibit a slower rate in overnight delta decline compared to HC, not explained by differences in total sleep time or wake after sleep onset. [@lunsford-avery2021]

Non-restorative sleep is a population experiencing objectively normal sleep as measured by PSG, however a feeling of being unrefreshed upon awakening (Stone et al., 2008). **sentence about daytime impairments and fatigue**. This population has lower NREM delta power than healthy controls, despite the same objective sleep time (Kao et al., 2021). A potential mechanism for the subjective loss of sleep is sleep-state misperception, where individuals inaccurately gauge their sleep/wake state (Edinger & Fins, 1995). However, recent research suggests that it may not actually be a misperception, but rather a mismeasurement of current methods of scoring PSG data (Stephan & Siclari, 2023).

- Definition and overview of sleep-state misperception
  - What are the neural mechanisms? [discussed in @stephan2023]
  - Why is it important?
  - How does it affect people

  **what are the neural correlates? Is it deficits in delta waves?

EEG drowsiness

Drowsiness is the experience of moving from wake to sleep, observed through reduced frequency and increased amplitude of EEG signals. During wakefulness brain activity is characterised by low amplitude, high frequency beta waves, with the appearance of alpha waves when the eyes are closed (Santamaria & Chiappa, 1987). As drowsiness increases, there is an increase in theta and delta waves. Drowsiness alpha activity is associated with a decreased amplitude in occipital regions and a slower alpha pattern in anterior cortical regions (Cantero et al., 2002).

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

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

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

increased cortical arousal in ID

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

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

`- Increased slowing ratio`

`- Higher delta and theta power`

- Associated with increased sleepiness and cognitive implications

Self-reported sleepiness

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

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

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

subjective-objective mismatch

There is a subjective-objective mismatch that is observed in people with NRS (**bianchi2013?**), however unknown if this persists in daytime drowsiness

approach

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

aim

This study aimed to examine if there are differences in how the populations experience subjective sleepiness, and if this is associated with regional differences in brain activity during resting wake. We aimed to see if there was a difference in the correlation of objective sleepiness scores to objective measures of drowsiness and if that was associated with topographical cluster differences. Finally, we examined if the regional differences was associated with delta power of previous nights sleep.

Hypotheses

1. KSS scores will be higher in the ID and NRS groups compared to healthy controls, indicating increased subjective sleepiness.
2. The correlation between KSS score and Slowing Ratio (SR) will differ significantly between the three groups. Healthy controls will have the strongest relationship between KSS score and SR, while NRS will have the weakest relationship.
3. Topography of channel-by-channel comparisons for normalised power spectral density will reveal electrode cluster differences between the ID and NRS groups and KDT conditions.
4. Clusters associated with higher SR during resting wake will be associated with lower delta power during sleep

Method

Participants

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

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

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

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

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

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

Protocol

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

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

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

Measures

KSS

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

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

KDT

The KDT was used to measure electrophysiological drowsiness as measured through HD-EEG recordings. Participants were instructed "Look at the dot in front of you and be as relaxed as possible while staying awake. Keep your head and body still and minimize blinking. After a few minutes, I'll ask you to close your

eyes and keep them closed for a few minutes. Finally, I'll ask you to open your eyes again and keep them open for a few minutes." They commence with their eyes open, close their eyes at 2m10, open eyes again at 4m40, and the test ends at 7m10.

HD-EEG

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

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

Power spectra

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

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

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

Statistical analysis

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

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

EEG processor

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

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