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RESEARCH ARTICLE

Electroencephalographic markers from routine sleep discriminate individuals who are vulnerable or resilient to sleep loss

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Summary

Sleep loss impairs cognition; however, individuals differ in their response to sleep loss. Current methods to identify an individual's vulnerability to sleep loss involve time-consuming sleep-loss challenges and neurobehavioural tests. Here, we sought to identify electroencephalographic markers of sleep-loss vulnerability obtained from routine night sleep. We retrospectively analysed four studies in which 50 healthy young adults (21 women) completed a laboratory baseline-sleep phase followed by a sleep-loss challenge. After classifying subjects as resilient or vulnerable to sleep loss, we extracted three electroencephalographic features from four channels during the baseline nights, evaluated the discriminatory power of these features using the first two studies (discovery), and assessed reproducibility of the results using the remaining two studies (reproducibility). In the discovery analysis, we found that, compared to resilient subjects, vulnerable subjects exhibited: (1) higher slow-wave activity power in channel O1 ($p < 0.0042$, corrected for multiple comparisons) and in channels O2 and C3 ($p < 0.05$, uncorrected); (2) higher slow-wave activity rise rate in channels O1 and O2 ($p < 0.05$, uncorrected); and (3) lower sleep spindle frequency in channels C3 and C4 ($p < 0.05$, uncorrected). Our reproducibility analysis confirmed the discovery results on slow-wave activity power and slow-wave activity rise rate, and for these two electroencephalographic features we observed consistent group-difference trends across all four channels in both analyses. The higher slow-wave activity power and slow-wave activity rise rate in vulnerable individuals suggest that they have a persistently higher sleep pressure under normal rested conditions.

KEYWORDS
electroencephalography, resilient, sleep loss, sleep pressure, sleep spindles, slow-wave activity, vulnerable

1 | INTRODUCTION

Sleep is essential for health and normal brain function (Irwin, 2015). Yet, a substantial proportion of the general population and active-duty Service members of the United States Armed Forces are chronically sleep deprived (Chattu et al., 2019; Good et al., 2020), resulting in impairment of cognitive functions, including attention, working memory, and decision making (Lo et al., 2012). Sleep loss does not affect

all individuals equally, as some individuals are resilient while others are vulnerable to its detrimental effects. This inter-individual variability in vulnerability to sleep loss is a trait-like characteristic, remaining consistent during repeated exposures to sleep deprivation (Rupp et al., 2012; Tkachenko & Dinges, 2018; Van Dongen et al., 2004). Given that forgoing sleep is often unavoidable, proper identification of an individual's vulnerability trait to sleep loss could help in assigning the appropriate personnel to tasks requiring sustained vigilance and in developing suitable personalised sleep-loss countermeasures (Vital-Lopez et al., 2023). However, identifying vulnerability traits to sleep loss often requires that individuals be evaluated during a sleep-loss challenge, which is time consuming, labour intensive, and not scalable. Thus, we aimed to identify potential markers of vulnerability to sleep loss that do not require sleep deprivation or behavioural tests.

Previous studies have found that, under well-rested wakefulness following one or more nights of baseline sleep, resilient and vulnerable groups differ in brain activation level (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005), structural (Cui et al., 2015; Rocklage et al., 2009) and functional connectivity (Yeo et al., 2015), psychomotor vigilance test (PVT) performance (Chua et al., 2014; Chua et al., 2019), heart rate and its variability (Chua et al., 2014), cardiovascular haemodynamic measures (Yamazaki et al., 2021), and electroencephalographic (EEG) spectral power in the high-theta frequency band (Chua et al., 2014). While these studies offer promising ways to identify vulnerability to sleep loss, they have limitations with regard to robustness and generalisability, because their results were: (1) based mostly (Chua et al., 2014) or exclusively (Mu et al., 2005) on men, with one study identifying a subset of subjects as men but providing no sex information for the remaining subjects (Caldwell et al., 2005); (2) not corrected for multiple comparisons even though multiple metrics were analysed in the same dataset (Chua et al., 2014; Yamazaki et al., 2021); (3) not re-assessed for reproducibility using an independent dataset (Caldwell et al., 2005; Chua et al., 2014; Chua et al., 2019; Cui et al., 2015; Mu et al., 2005; Rocklage et al., 2009; Yamazaki et al., 2021; Yeo et al., 2015); or (4) not replicated when assessed in a follow-up study (Chee et al., 2006; Lim et al., 2007). In addition, with the exception of functional brain connectivity (Yeo et al., 2015), all metrics examined in these studies (Caldwell et al., 2005; Chee et al., 2006; Chua et al., 2014; Cui et al., 2015; Mu et al., 2005; Rocklage et al., 2009) were based on cognitive neurobehavioural tasks, which depend on the subject's level of effort. To overcome these limitations, we aimed to identify vulnerability markers that are reproducible and independent of a subject's level of effort (i.e., do not require a neurobehavioural test). To this end, we sought markers of vulnerability to sleep loss using EEG data collected during routine nights of sleep and set aside studies not used for marker discovery to independently assess reproducibility of the markers. Obtaining markers from EEG data collected during routine sleep, as opposed to during wakefulness, has the advantage of minimal interference from endogenous factors (attention and motivation) and exogenous influences (environment) (Kitsune et al., 2015). Given that EEG signal properties have trait-like stability over time (Buckelmüller et al., 2006; Tan et al., 2000), they are suitable candidate markers for characterising vulnerability to sleep loss.

Although sleep pressure that accumulates as a function of wakefulness is known to affect cognitive performance in a dose-dependent manner (Van Dongen et al., 2003), the possibility that resilient and vulnerable groups may experience different levels of sleep pressure under baseline (non-sleep deprived) conditions has not been examined. To this end, we examined EEG features that are linked to sleep pressure. Slow-wave activity (SWA) spectral power during non-rapid-eye-movement (NREM) sleep and the rate at which it increases during the initial 20 min of sleep have been shown to be indicative of sleep pressure (Brunner et al., 1993; Dijk et al., 1990). Sleep spindles, transient EEG signal oscillations (11–15 Hz) lasting 0.5–2.0 s that are generated from thalamocortical interactions, reflect the efficiency and integrity of the thalamocortical network (Andrillon et al., 2011), which is involved in regulating sleep and arousal (McCormick & Bal, 1997). In addition, sleep spindle activity has been consistently associated with cognitive and memory-related abilities (Schabus et al., 2006), and there is an inverse relationship between sleep pressure and sleep spindle frequency (Knoblauch et al., 2003). These lines of evidence led us to hypothesise that resilient and vulnerable individuals differ in: (1) SWA power during the N2 and N3 NREM sleep stages of the first sleep cycle; (2) SWA rise rate during the first 20 min of sleep; and (3) sleep spindle frequency computed during the N2 and N3 stages for the entire night.

Therefore, the objective of our study was to determine whether we could discriminate between individuals who are resilient to sleep loss and those who are vulnerable using these EEG features measured during routine nights of sleep. To this end, we used EEG data recorded during baseline nights of sleep from four independent sleep-loss studies. To assess reproducibility of our findings, we used data from 26 subjects (13 resilient and 13 vulnerable) from two of four studies for initial marker discovery and data from 24 subjects (12 resilient and 12 vulnerable) from the remaining two studies for reproducibility analysis.

2 | METHODS

2.1 | Study design

Our dataset consisted of four previously published sleep-loss laboratory studies (Doty et al., 2017; Hansen et al., 2019; Reifman et al., 2019; Rupp et al., 2012) involving 50 healthy young adults (21 women) aged between 18 and 39 years (Table 1). In these studies, subjects slept in the laboratory for 1–7 baseline nights (8–10 h time in bed [TIB]), during which we recorded polysomnography (PSG) data, and subsequently challenged them with either total sleep deprivation (TSD; 48, 62, or 63 h) (Hansen et al., 2019; Reifman et al., 2019; Rupp et al., 2012) or chronic sleep restriction (CSR; 5 nights of 5 h TIB or 7 nights of 3 h TIB) (Doty et al., 2017; Rupp et al., 2012) (Table 1) followed by a recovery phase (1 or 3 nights of 8, 10, or 12 h TIB). Subjects performed PVTs (5-min PVT for Study D2 and 10-min PVT for

TABLE 1 Description of the four studies used to identify and independently assess discriminative electroencephalographic markers of vulnerability to sleep loss.

Study	Baseline nights, *n*	Baseline nights with PSG data, *n*	TIB during baseline nights, h	Sleep-loss protocol	Number of subjects (women)		Age, years, mean (SD)	
					R	V	R	V
D1[a]	7	1	10	63 h TSD and 3 h TIB × 7 days	6 (3)	6 (3)	28.3 (4.5)	29.7 (6.3)
D2	1	1	8	62 h TSD	7 (2)	7 (1)	26.6 (4.5)	23.9 (3.8)
R1	5	5	10	5 h TIB × 5 days	8 (5)	8 (3)	22.2 (2.8)	27.6 (2.4)
R2	3	3	10	48 h TSD	4 (1)	4 (3)	24.8 (5.0)	31.8 (5.2)
D1 + D2					13 (5)	13 (4)	27.4 (4.4)	26.5 (5.7)
R1 + R2					12 (6)	12 (6)	23.1 (3.7)	29.0 (3.9)
All					25 (11)	25 (10)	25.3 (4.5)	27.7 (5.0)

Note: studies D1 (Rupp et al., 2012) and D2 (Reifman et al., 2019) used for feature discovery; studies R1 (Doty et al., 2017) and R2 (Hansen et al., 2019) used for reproducibility analysis.

Abbreviations: PSG, polysomnography; R, resilient subject group; SD, standard deviation; TIB, time in bed; TSD, total sleep deprivation; V, vulnerable subject group.

[a]Cross-over study design with a gap of 2–4 weeks between 63 h TSD and 3 h TIB × 7 days.

studies D1, R1, and R2) during scheduled wakefulness every 1–3 h starting immediately after the baseline-sleep phase, through the sleep-loss challenge, and until the end of the recovery phase. We used two (studies D1 and D2) of the four studies for EEG marker *discovery* and the remaining two studies (R1 and R2) for *reproducibility* analysis, where we assessed whether we could independently confirm our findings. To reduce variability and minimise the 'first-night' effect (Agnew et al., 1966), for subjects for whom we had PSG recordings from multiple nights of baseline sleep, we selected the first and last nights and averaged EEG-based measures (EEG features and sleep-architecture measures) of the 2 nights. For the cross-over study D1, which had 1 baseline night with PSG recordings prior to the TSD and CSR phases, for each subject, we averaged the EEG-based measures computed from the baseline night of each of the two study phases.

2.2 | Subject classification

To classify subjects of each study into resilient and vulnerable groups, for each subject, we first normalised the PVT reaction times obtained during the sleep-loss period. To this end, separately for the baseline wake period (i.e., the first 14 or 16 h immediately following the baseline sleep) and the sleep-loss period, we obtained the mean reaction times. Then, we divided the mean reaction time of the sleep-loss period by that of the baseline period and multiplied the result by 100 to obtain the normalised reaction time (one value per subject). For the cross-over study D1, consisting of TSD and CSR challenges, we separately normalised the reaction times for each subject for each of the two phases of the study resulting in two values that we averaged to obtain a single normalised reaction time per subject. Finally, within each study, we rank ordered the subjects by their average normalised reaction times and labelled the lower third as 'resilient' (25 subjects), the upper third as 'vulnerable' (25 subjects), and the middle third as 'intermediate' (25 subjects) (Figures S1–S5).

2.3 | Sleep EEG data and preprocessing

The sampling rates of the EEG data for the four studies (D1, D2, R1, and R2) were 100 Hz, 256 Hz, 500 Hz, and 200 Hz, respectively. For studies D2, R1, and R2, we down-sampled the data to 128 Hz (D2) or 100 Hz (R1 and R2). As one of the two studies in the discovery set did not record frontal EEG channels, we did not include these channels in our analyses and only analysed the central and occipital channels (C3, C4, O1, and O2 referenced to the contralateral mastoids) that were common to all four studies. We high-pass filtered the data (6-dB cut-off frequency at 0.125 Hz) to remove slow drifts and segmented the data from each channel into 5-s epochs. We excluded from the analysis epochs in which we detected electrical or physiological artefacts (see Supplemental Materials).

2.4 | Sleep-architecture measures

We scored sleep stages in 30-s epochs following the guidelines of the American Academy of Sleep Medicine (Silber et al., 2007). Table 2 shows the sleep-architecture measures computed as described previously (Muzet et al., 2016), except that we obtained rapid-eye-movement (REM) sleep stages by joining REM sleep periods separated by <15 min and defined the number of awakenings as the number of contiguous awake periods lasting ≥30 s between sleep onset (time of first occurrence of any one stage: N1, N2, N3, or REM) and lights-on time. As sleep architecture changes with age (Ohayon et al., 2004), when performing statistical comparisons between the resilient and vulnerable groups, we age-corrected all sleep-architecture measures using a regression approach, as described previously (Wang et al., 2020).

TABLE 2 Sleep-architecture parameters of the study population.

Variable	Discovery set			Reproducibility set			Combined set		
	Resilient [$n = 13$], mean (SD)	Vulnerable [$n = 13$], mean (SD)	Group comparison p[a]	Resilient [$n = 12$], mean (SD)	Vulnerable [$n = 12$], mean (SD)	Group comparison p[a]	Resilient [$n = 25$], mean (SD)	Vulnerable [$n = 25$], mean (SD)	Group comparison p[a]
Sleep latency, min	19.0 (19.3)	15.0 (13.4)	0.837	32.2 (26.9)	18.8 (7.2)	0.285	25.3 (23.7)	16.9 (10.9)	0.393
Sleep efficiency, %	81.7 (12.6)	87.6 (7.0)	0.182	85.8 (9.3)	89.5 (5.3)	0.341	83.7 (11.1)	88.5 (6.2)	0.146
WASO, min	82.0 (61.9)	55.0 (37.5)	0.330	54.4 (40.7)	43.4 (30.6)	0.583	68.8 (53.6)	49.4 (34.1)	0.237
Number of awakenings/sleep hour	3.1 (1.1)	4.1 (1.9)	0.151	2.4 (1.1)	2.0 (1.1)	0.507	2.8 (1.2)	3.1 (1.8)	0.641
Stage N1, % TST	8.9 (3.2)	10.6 (6.0)	0.573	8.1 (4.1)	5.5 (2.8)	0.030*	8.5 (3.6)	8.2 (5.3)	0.332
Stage N2, % TST	56.6 (9.2)	48.3 (7.0)	0.027*	56.4 (6.8)	57.0 (6.8)	0.977	56.5 (8.0)	52.5 (8.1)	0.130
Stage N2, % Cyc 1	46.2 (16.8)	30.8 (8.4)	0.004*	45.7 (13.2)	43.4 (11.3)	0.665	46.0 (14.9)	36.9 (11.6)	0.019*
Stage N3, % TST	13.5 (6.0)	18.5 (6.0)	0.036*	13.7 (7.1)	16.3 (6.3)	0.341	13.6 (6.4)	17.4 (6.1)	0.030*
Stage N3, % Cyc 1	36.1 (16.2)	50.5 (9.4)	0.006*	31.6 (14.1)	39.5 (11.5)	0.157	33.9 (15.1)	45.2 (11.7)	0.003*
NREM, % TST	78.6 (4.7)	77.8 (5.2)	0.608	78.6 (4.9)	78.4 (5.7)	0.885	78.6 (4.7)	78.1 (5.3)	0.655
REM, % TST	21.4 (4.7)	22.2 (5.2)	0.608	21.4 (4.9)	21.6 (5.7)	0.885	21.4 (4.7)	21.9 (5.3)	0.655

Abbreviations: Cyc 1, first sleep cycle; NREM, non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep; SD, standard deviation; TST, total sleep time; WASO, wakefulness after sleep onset.
[a]Wilcoxon rank-sum test after age correction.
*$p < 0.05$.

2.5 | The EEG features

We extracted the following three EEG features: (1) SWA power, defined as the mean power spectral density in the frequency range of 0.2–4.0 Hz; (2) SWA rise rate, defined as the rate at which SWA power changes during the first 20 min after sleep onset; and (3) sleep spindle frequency, defined as the frequency of sinusoidal oscillations within individual sleep spindles.

To compute the SWA power for a given EEG channel, we obtained periodogram power spectral density estimates for artefact-free epochs within the N2 and N3 stages of the first sleep cycle, averaged the power spectral density within the frequency band of 0.2–4.0 Hz for each epoch, and averaged the SWA power across all epochs. The epoch-averaged SWA power was then log (base 10) transformed. To obtain the SWA rise rate, we fitted a robust linear regression to the SWA power data for epochs within the N1, N2, or N3 stages of the first 20 min of sleep. When computing the SWA power and the SWA rise rate, we required that subjects had at least one baseline night with a minimum of 30 min (cumulative) of artefact-free, N2 or N3 stage data in the first sleep cycle. Applying this criterion, we excluded one vulnerable subject from Study D2 from analyses involving SWA power and SWA rise rate. Finally, we detected sleep spindles within the frequency band of 11–15 Hz by an automated algorithm as described previously (Schabus et al., 2007), computed the period of oscillations within each detected spindle, obtained the spindle frequencies by taking the reciprocal of the mean period of oscillations within each spindle, and averaged the spindle frequencies across all spindles falling within the N2 and N3 stages over the entire night. For a few subjects (depending on the channel, two–four resilient and two–four vulnerable from D1, one resilient from R1, and one vulnerable from R2), we only used data from 1 of the 2 nights because the other night did not meet the quality criterion. Given that age is known to have an effect on sleep EEG features (Sprecher et al., 2016), we corrected the computed features using a regression model, as previously described (Wang et al., 2020).

In our dataset, the raw EEG feature values of a given subject group (resilient or vulnerable) varied across the studies for a given EEG channel likely due to study-to-study differences in recording setup, and across the channels within a given study due to recording-site differences. This variability prevented us from directly associating raw EEG feature values with sleep-loss vulnerability and from pooling them across studies. Hence, we performed within-study z-scoring normalisation that brought feature values from different studies and channels into a common scale, allowing us to pool studies together. Specifically, within a given study (D1, D2, R1, or R2), for each EEG channel, we z-scored the feature values of resilient and vulnerable subjects together, using the mean and standard deviation (SD) computed from the combined pool of subjects from both groups. Then, we pooled the z-scored feature values of the resilient subjects of studies D1 and D2 together to form the discovery set and those of studies R1 and R2 to form the reproducibility set; for the combined set, we pooled together the resilient subjects from all four studies. We repeated the same procedure to obtain the z-scored feature values for the vulnerable group.

2.6 | Secondary analyses

To examine the association between EEG-feature values and sleep-loss vulnerability, for each EEG channel, we regressed age-corrected EEG-feature values (from the resilient, intermediate, and vulnerable groups pooled together) against the normalised PVT reaction times. Accordingly, we pooled the studies together and applied multiple linear regression with a common slope, while allowing for study-specific intercepts to account for study-to-study variations.

To assess whether the discriminatory information of the SWA power came from the periodic or aperiodic component of the EEG-signal power spectrum (Buzsáki et al., 2012; He et al., 2010), we extracted each component as previously described (Wen & Liu, 2016) and analysed them separately. Specifically, for each EEG channel, we first extracted the periodic and aperiodic components from individual artefact-free 5-s epochs from stages N2 and N3 of the first sleep cycle. Next, we separately averaged the periodic component of each frequency bin over all epochs and repeated the same procedure for the aperiodic component. Then, we obtained the total power for three frequency bands (0.2–4.0, 4.0–7.5, and 0.1–25.0 Hz) by integrating the power spectral densities across the corresponding frequency range. Finally, we log-transformed the total power.

In addition to sleep spindle frequency, we also assessed whether sleep spindle amplitude or sleep spindle density could discriminate resilient and vulnerable subjects. After extracting sleep spindles, as described above in *EEG features*, we computed spindle density (counts/min) by dividing the total number of spindles within artefact-free periods in stages N2 and N3 over the entire night by the corresponding sleep duration. To compute spindle amplitude, we designated the largest peak-to-trough distance within a given spindle as its amplitude and averaged it across the spindles.

We age-corrected, z-score transformed, and pooled these additional EEG features from the secondary analysis across baseline nights and studies as described above in *EEG features*.

2.7 | Statistical analysis

For each EEG feature, subject characteristic, and sleep-architecture measure, we tested for significant statistical differences between the resilient and vulnerable groups using the non-parametric Wilcoxon's rank-sum test using the MATLAB Statistics toolbox. When assessing the statistical significance of group differences in EEG features in our primary analysis (SWA power, SWA rise rate, and spindle frequency), we conservatively accounted for multiple comparisons across the four electrodes and three EEG features by performing our statistical tests with an adjusted false-positive error rate of 0.0042, obtained by dividing the conventional false-positive error rate threshold of 0.05 by 12 (three features × four electrodes). For the secondary analysis (periodic SWA, aperiodic SWA, aperiodic broadband [0.1–25.0 Hz], spindle amplitude, and spindle density), we applied a false-positive error rate threshold of 0.0025, accounting for 20 comparisons (five features × four electrodes). Using a previously published MATLAB

package (Hentschke & Stüttgen, 2011), we computed effect sizes using the bias-corrected Cohen's *d* measure and obtained 95% confidence intervals (CIs) via bootstrap of 5000 replicates.

2.8 | Evaluation of reproducibility

We assessed whether the results obtained in the discovery set were confirmed in the reproducibility set using a combination of three statistical metrics because no single metric can comprehensively capture reproducibility (OpenScienceCollaboration, 2015). We assessed whether: (1) the group differences observed in the discovery set remained statistically significant ($p < 0.0042$) in the reproducibility set and whether the group differences were in the same direction as in the original finding; (2) the effect size computed in the reproducibility set fell within the 95% CI of the effect size in the discovery set; and (3) after we pooled the discovery and reproducibility sets into a 'combined' set, the group differences in the combined set remained statistically significant and the effect-size 95% CI excluded zero.

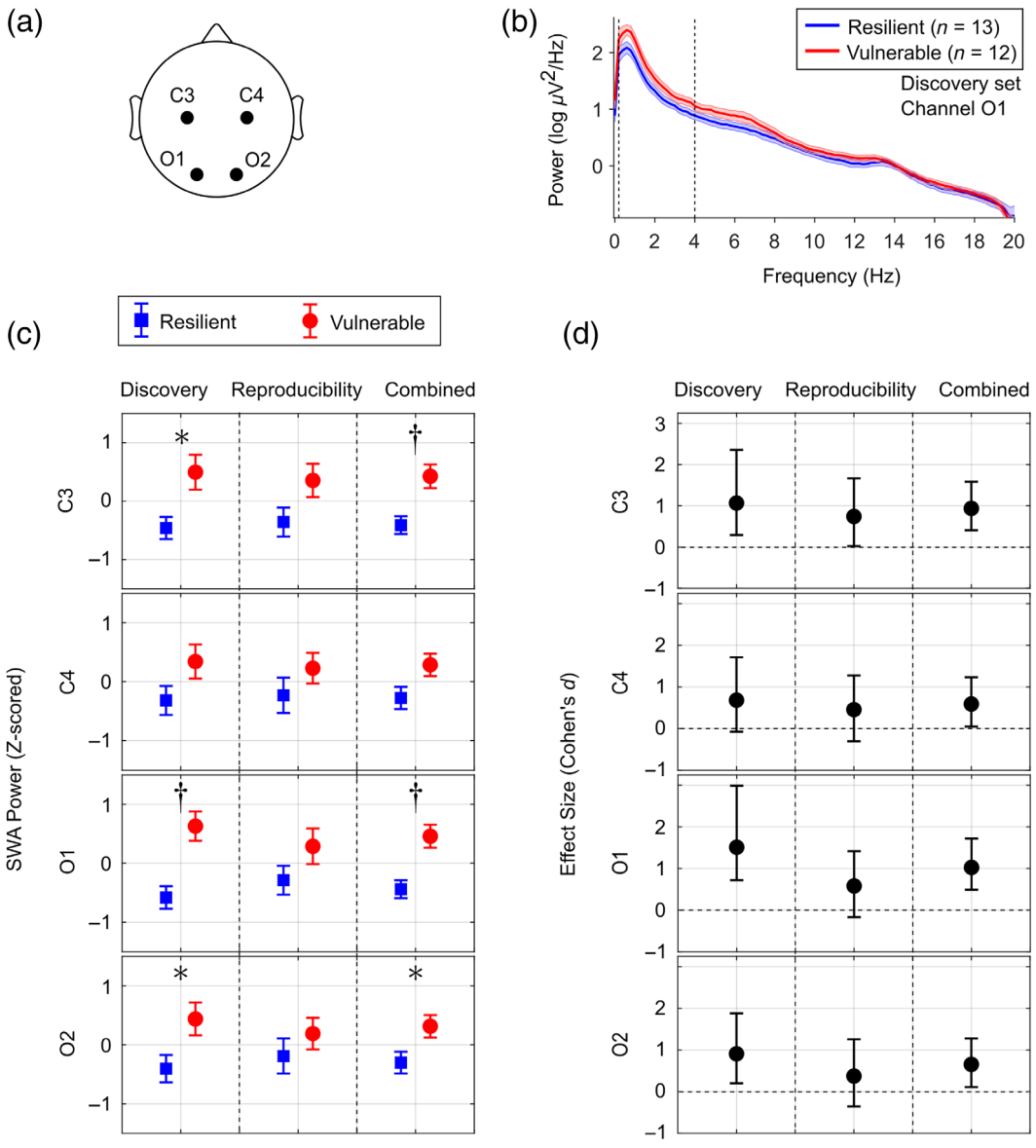

FIGURE 1 Group differences and their effect sizes for slow-wave activity (SWA) power. (a) Electroencephalogram (EEG) channel locations on the scalp. (b) Mean power spectral density computed from occipital channel O1 for the discovery set (solid line and shading indicate mean ± one standard error). Dotted vertical lines mark the boundary of the SWA frequency band (0.2–4.0 Hz). (c) Z-scored SWA power group differences for each of the four EEG channels based on the discovery, reproducibility, and combined sets. Error bar indicates one standard error. Asterisk (*) indicates $p < 0.05$ uncorrected for multiple comparisons and dagger (†) indicates $p < 0.0042$ corrected for multiple comparisons. (d) Effect size of SWA power for each of the four EEG channels based on the discovery, reproducibility, and combined sets. Positive values indicate that SWA power was higher in the vulnerable group when compared to the resilient group. Error bar indicates 95% confidence interval of the effect size.

3 | RESULTS

3.1 | Subject characteristics and sleep-architecture parameters

There was no significant age difference between the resilient and the vulnerable groups (Table 1) in either the discovery set ($p = 0.439$) or the combined set ($p = 0.104$); however, in the reproducibility set, there was a significant age difference ($p = 0.003$) between the two groups. Table 2 summarises the sleep-architecture parameters computed based on sleep scoring of the EEG data. For all three study sets (discovery, replication, and combined), most of the sleep parameters did not show a significant group difference. However, we found a significant group difference in the average percentage of sleep time in the N2 stage in the discovery set ($p = 0.027$), in the average percentage of sleep time in the N1 stage in the reproducibility set ($p = 0.030$), and in the average percentage of sleep time in the N3 stage in the discovery set ($p = 0.036$). In the combined set, we found a significant group difference in percentage of sleep time spent in stage N3 ($p = 0.030$).

3.2 | Discovery analysis of sleep EEG features

3.2.1 | The SWA power

For the resilient and vulnerable subjects in the discovery set, we computed the SWA spectral power during the N2 and N3 stages of the first sleep cycle. We found that the vulnerable group had a consistently higher SWA power than the resilient group across all EEG channels (Figure 1a–c [Discovery]). Of the four channels we examined, occipital channel O1 showed a significant group difference (Figure 1b,c [Discovery]) and a relatively large effect size (mean Cohen's $d = 1.51$; Table 3 and Figure 1d [Discovery]), with its 95% CI excluding zero. Two other channels, C3 and O2, also exhibited moderate effect sizes (mean Cohen's d of 1.07 and 0.91, respectively) with the 95% CIs excluding zero. Although these two channels showed significant group differences only in the absence of multiple-comparison correction (that is, using $\alpha = 0.05$ instead of $\alpha = 0.0042$), the group differences were in the same direction as that of channel O1, suggesting that these channels can still provide useful information for discriminating resilient from vulnerable subjects.

3.2.2 | The SWA rise rate

To compute the rate at which the SWA power changed during the initial period after sleep onset, for each EEG channel (Figure 2a) of a given subject, we fitted a regression line to the SWA power data of the first 20 min of sleep, and used its slope as an estimate of SWA rise rate. Figure 2b shows the time course of the group-averaged SWA power in channel O1, demonstrating the higher rate at which the SWA power increased in the vulnerable group. Similarly, in all four channels, we observed that the SWA power increased consistently at a higher rate for the vulnerable group (Figure 2c [Discovery]). Although none of the channels showed a significant group difference

TABLE 3 Assessment of discovery, reproducibility, and combined datasets.

	p of group differences			Effect size (95% CI)		
Sleep EEG measure	Discovery[a]	Reproducibility[b]	Combined[c]	Discovery	Reproducibility	Combined
SWA power						
C3	0.018*	0.112	0.004†	1.07 (0.29, 2.36)	0.74 (0.02, 1.66)	0.94 (0.40, 1.58)
C4	0.077	0.260	0.056	0.68 (−0.08, 1.71)	0.46 (−0.31, 1.27)	0.59 (0.05, 1.24)
O1	0.003†	0.260	0.001†	1.51 (0.72, 2.99)	0.58 (−0.17, 1.42)	1.02 (0.49, 1.72)
O2	0.028*	0.371	0.038*	0.91 (0.20, 1.88)	0.37 (−0.36, 1.26)	0.65 (0.11,1.28)
SWA rise rate						
C3	0.053	0.012*	0.001†	0.84 (0.14, 1.65)	1.10 (0.53, 1.89)	1.00 (0.54, 1.53)
C4	0.265	0.012*	0.007*	0.51 (−0.25, 1.28)	1.11 (0.43, 2.03)	0.81 (0.30, 1.40)
O1	0.005*	0.019*	0.000†	1.32 (0.69, 2.29)	0.85 (0.16, 1.68)	1.12 (0.62, 1.71)
O2	0.008*	0.012*	0.000†	1.02 (0.40, 1.85)	0.97 (0.31, 1.79)	1.03 (0.57, 1.57)
Spindle frequency						
C3	0.018*	0.977	0.081	−1.04 (−2.04, −0.36)	−0.01 (−0.80, 0.87)	−0.51 (−1.08, 0.03)
C4	0.040*	0.977	0.135	−0.83 (−1.70, −0.13)	0.01 (−0.77, 0.89)	−0.42 (−0.98, 0.11)
O1	0.065	0.624	0.107	−0.83 (−1.82, −0.13)	−0.09 (−0.96, 0.70)	−0.47 (−1.10, 0.08)
O2	0.137	0.840	0.229	−0.70 (−1.61, 0.00)	0.06 (−0.83, 0.84)	−0.33 (−0.94, 0.21)

[a]Thirteen resilient, 12 (SWA power and SWA rise rate) or 13 (spindle frequency) vulnerable.
[b]Twelve resilient, 12 vulnerable.
[c]Twenty-five resilient, 24 or 25 vulnerable.
*Values indicate $p < 0.05$, uncorrected for multiple comparisons.†Values indicate $p < 0.0042$, Bonferroni-corrected for multiple comparisons.
Abbreviations: CI, confidence interval; EEG, electroencephalography; SWA, slow-wave activity.

(Figure 2c [Discovery] and Table 3), channel O1 showed a relatively large effect size (mean Cohen's $d = 1.32$; Figure 2d [Discovery]) and a group difference that approached statistical significance ($p = 0.005$). Occipital channel O2 also exhibited a moderate effect size (mean Cohen's $d = 1.02$) and a significant group difference in the absence of multiple-comparison correction. Of the two central channels, only C3 exhibited a moderate effect size (mean Cohen's $d = 0.84$). Overall, all four channels showed group differences in the same direction, and three of them (C3, O1, and O2) exhibited moderate to large effect sizes with their 95% CIs excluding zero.

3.2.3 | Sleep spindle frequency

We detected sleep spindles in each channel (Figure 3a,b), computed a frequency value for each spindle, and averaged the frequencies across the spindles detected during the N2 and N3 stages for the entire night. We found a consistent trend across all four channels, with a lower spindle frequency for the vulnerable group (Figure 3c [Discovery] and Table 3). Although this effect was not significant in any of the channels, central channels C3 and C4 and occipital channel O1 showed moderate effect sizes (mean Cohen's d of −1.04, −0.83, and

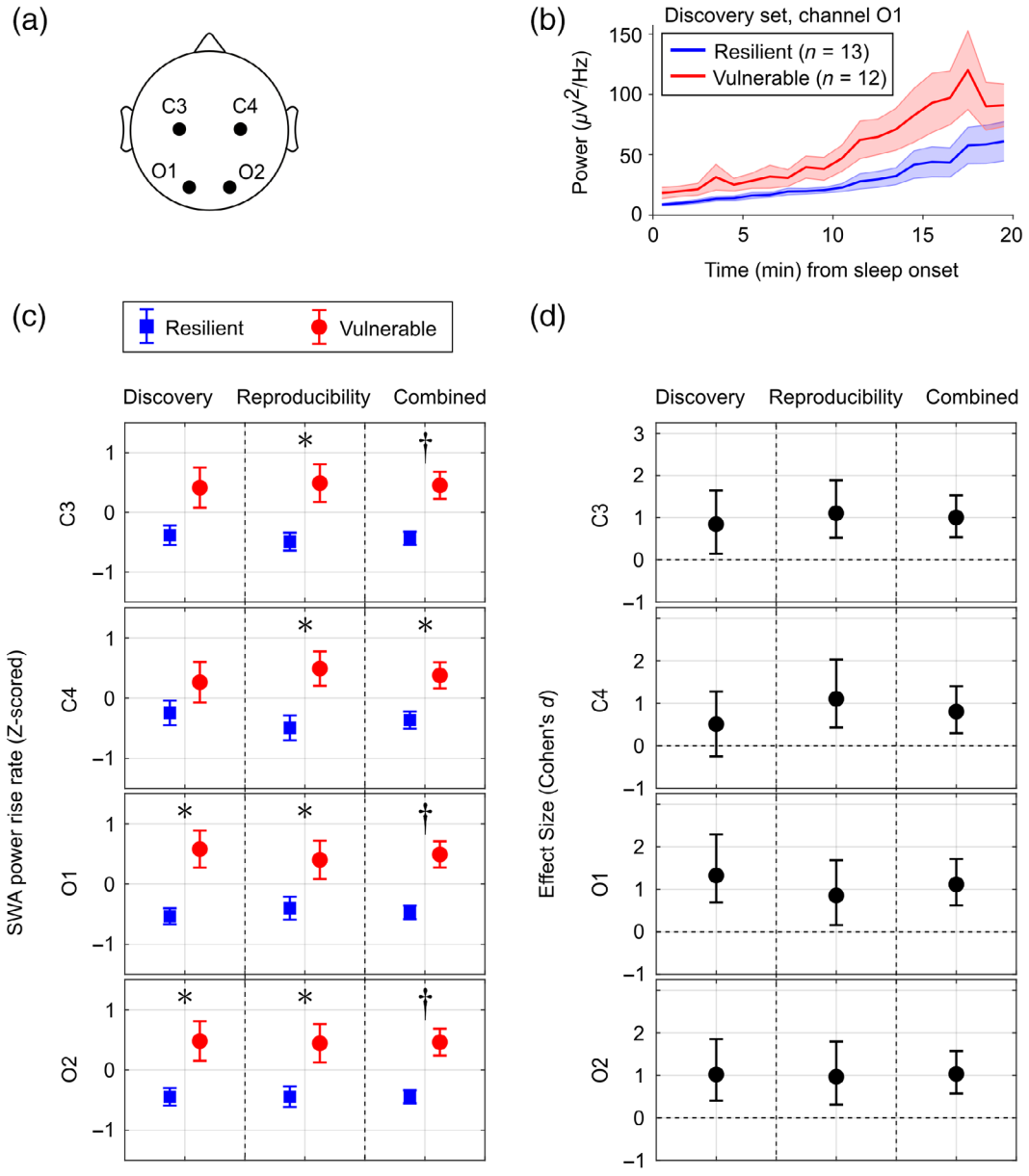

FIGURE 2 Group differences and their effect sizes for slow-wave activity (SWA) power rise rate. (a) Electroencephalogram (EEG) channel locations on the scalp. (b) Time course of mean SWA power computed from occipital channel O1 for the discovery set (solid line and shading indicate mean ± one standard error). (c) Z-scored SWA slope group differences for each of the four EEG channels based on the discovery, reproducibility, and combined sets. SWA slope was computed from line fits to the SWA power time course for individual subjects. Error bar indicates one standard error. Asterisk (*) indicates $p < 0.05$ uncorrected for multiple comparisons and dagger (†) indicates $p < 0.0042$, corrected for multiple comparisons. (d) Effect size of SWA slope for each of the four EEG channels based on the discovery, reproducibility, and combined sets. Positive values indicate that SWA slope was larger in the vulnerable group when compared to the resilient group. Error bar indicates 95% confidence interval of the effect size.

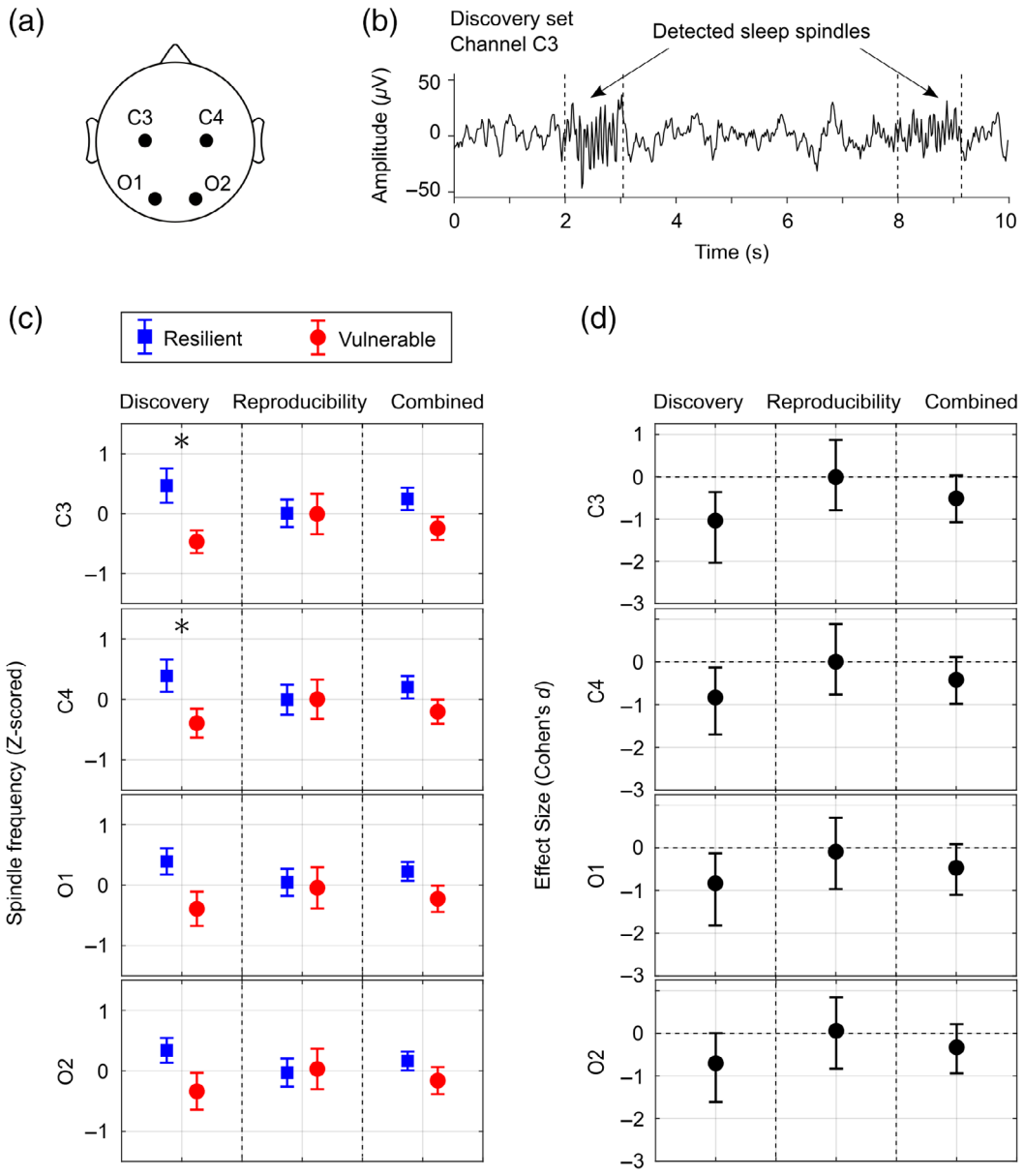

FIGURE 3 Group differences and their effect sizes for sleep spindle frequency. (a) Electroencephalogram (EEG) channel locations on the scalp. (b) Example of sleep spindles detected in central channel C3 in one of the subjects of the discovery set. (c) Z-scored sleep spindle frequency group differences for each of the four EEG channels based on the discovery, reproducibility, and combined sets. Error bar indicates one standard error. Asterisk (*) indicates $p < 0.05$, which is uncorrected for multiple comparisons. (d) Effect size of spindle frequency for each of the four EEG channels based on the discovery, reproducibility, and combined sets. Negative values indicate that the vulnerable group's spindle frequency was lower than that of the resilient group. Error bar indicates 95% confidence interval of the effect size.

−0.83, respectively; Figure 3d [Discovery] and Table 3) with 95% CIs excluding zero. Channels C3 and C4 also showed significant group differences in the absence of multiple-comparison correction (for channel C3 that had the largest effect size of all channels, group mean values [1 SD] for spindle frequency were 13.24 [0.35] Hz for the resilient group and 12.94 [0.28] Hz for the vulnerable group in Study D1; and 12.91 [0.45] Hz for the resilient group and 12.50 [0.24] Hz for the vulnerable group in Study D2).

The results presented in Figures 1–3 (Discovery columns of panels C and D) show that each of the three EEG features showed consistent trends across all four EEG channels. To determine the most promising candidates of the 12 EEG feature-channel combinations (three features × four channels), we aimed to select feature-channel combinations for which we observed statistically significant group differences (with or without correction for multiple comparisons) and effect size 95% CIs that excluded zero. Applying these criteria, we selected seven EEG feature-channel combinations for reproducibility analysis: SWA power from channels C3, O1, and O2; SWA rise rate from channels O1 and O2; and sleep spindle frequency from channels C3 and C4.

3.3 | Reproducibility analysis

Because no single metric can comprehensively capture reproducibility, we used three complementary statistical metrics in our assessment of reproducibility (Table 4). For the SWA power, none of the channels met all three statistical metrics. However, channel C3 met two of the metrics: the reproducibility effect size fell within the 95% CI of the discovery set (metric 2) and, for the combined set, the group differences were statistically significant, and the 95% CI of the effect size excluded zero (metric 3). For SWA rise rate, although none of the channels met all three statistical metrics, channels O1 and O2 met two of them (metrics 2 and 3); channel C3 also met metrics 2 and 3; however, we did not consider this channel further because it did not show a significant group difference in the discovery set. For sleep spindle frequency, none of the channels met any of the three metrics, indicating poor reproducibility. Although none of the EEG feature-channel combinations showed significant group differences (with multiple-comparison correction) in the reproducibility set (metric 1), the group differences for SWA power and SWA rise rate were in the same direction as that of the discovery set. Taken together, these results suggest that, of the three EEG features we assessed, SWA power in channel C3 and SWA rise rate in channels O1 and O2 showed the ability to discriminate between subjects who were resilient and those who were vulnerable to sleep loss.

3.4 | Secondary analyses

In addition to the primary analyses discussed above, we also performed secondary analyses. For the three promising EEG feature-channel combinations (SWA power from channel C3 and SWA rise rate from channels O1 and O2) from our primary analysis, we also examined the association between sleep-loss vulnerability (as measured by the normalised PVT reaction times) and EEG-feature values after pooling together subjects from the resilient, intermediate, and vulnerable groups. Linear regression analysis of the combined set showed that both SWA power and SWA rise rate increased with vulnerability to sleep loss (Figure S6; C3 SWA power: $p = 0.0008$ and $F_{4,69} = 5.37$; O1 SWA rise rate: $p = 0.0001$ and $F_{4,69} = 6.86$; and O2 SWA rise rate: $p = 0.00001$ and $F_{4,69} = 8.65$). These results suggest that SWA power and SWA rise rate are indicators of sleep-loss vulnerability. To further assess whether these two features provide independent information, we examined the correlation between the z-scored SWA power and the z-scored SWA rise rate for each EEG channel for the combined set with all three subject groups pooled together. The results showed that SWA power and SWA rise rate were significantly correlated in all four EEG channels (Pearson's product–moment correlation coefficient [r] range: 0.53–0.62; $p < 0.001$ for all channels; range of $1 - r^2$: 0.62–0.72; $n = 74$ subjects), suggesting that a partial overlap of information provided by these two EEG features. However, 62%–72% of the variance in one feature was

TABLE 4 Summary of the reproducibility analyses.

Sleep EEG feature-channel pair	Metric 1: Reproducibility set $p < 0.0042^{\dagger}$ ($p < 0.05^{*}$)	Metric 2: Reproducibility set effect size within 95% CI of discovery set	Metric 3: Combined set $p < 0.0042^{\dagger}$ and effect-size 95% CI excludes zero
SWA power			
C3[a]	No (No)	Yes	Yes
C4	No (No)	Yes	No
O1[a]	No (No)	No	Yes
O2[a]	No (No)	Yes	No
SWA rise rate			
C3	No (Yes)	Yes	Yes
C4	No (Yes)	Yes	No
O1[a]	No (Yes)	Yes	Yes
O2[a]	No (Yes)	Yes	Yes
Spindle frequency			
C3[a]	No (No)	No	No
C4[a]	No (No)	No	No
O1	No (No)	No	No
O2	No (No)	No	No

Abbreviations: CI, confidence interval; EEG, electroencephalography; SWA, slow wave activity.
[a]Discovery set group difference statistically significant (with or without multiple-comparison correction) with effect size 95% CI excluding zero.
[†]Bonferroni corrected for multiple comparisons.
*Uncorrected for multiple comparisons.

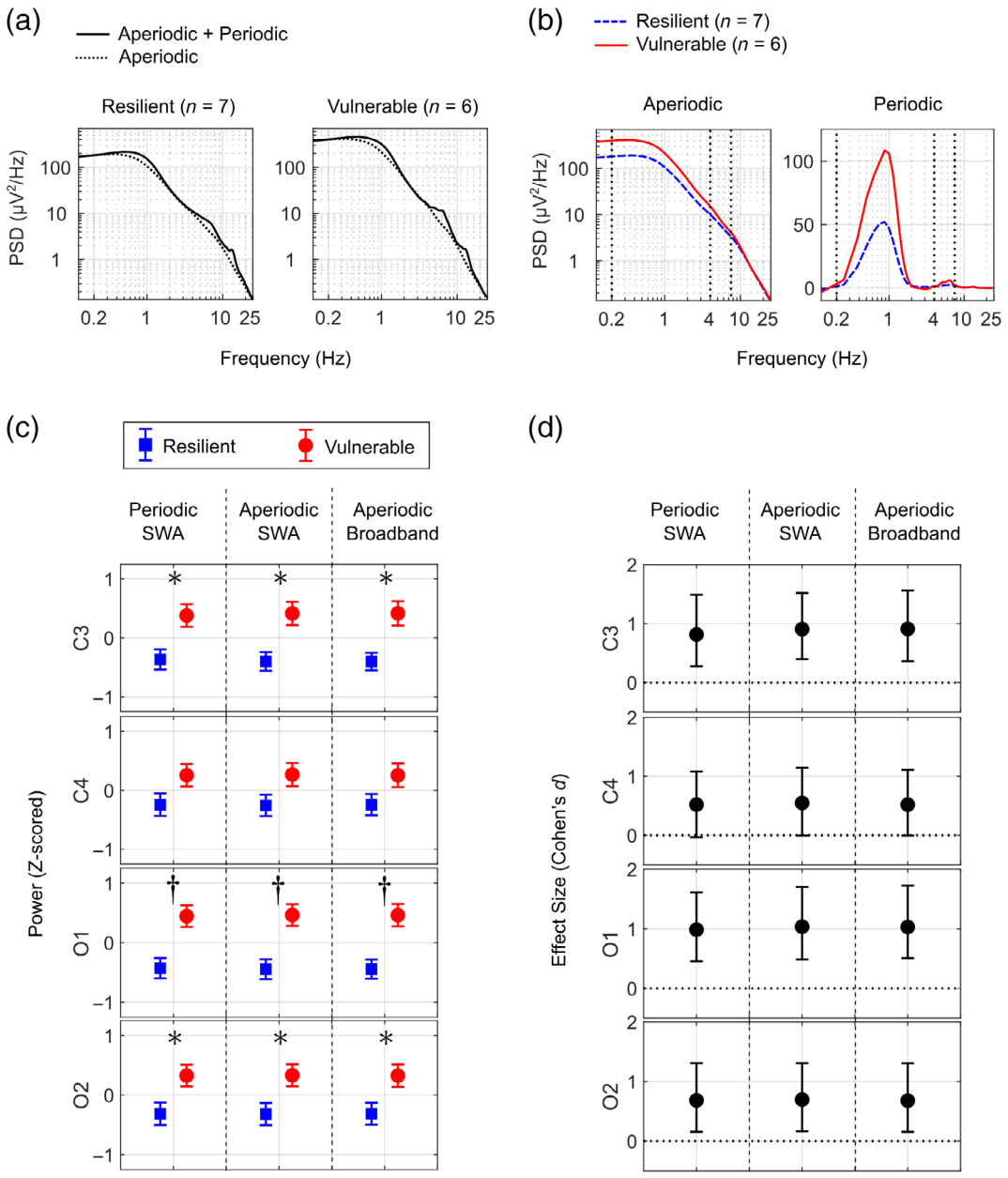

FIGURE 4 Group differences and effect sizes for the periodic and aperiodic components of the power spectrum in N2 and N3 sleep stages of the first sleep cycle. (a, b) Example data (averaged across subjects in each group) from channel O1 in Study D2, demonstrating the procedure of separating the periodic and aperiodic components. (a) Log–log plots showing the mean aperiodic (dotted trace) and mean total (aperiodic plus periodic, continuous trace) power spectral densities (PSD). (b) Left, log–log plot of the aperiodic component of the total PSD. Right, semi-log plot of the periodic component of total PSD, obtained by subtracting the aperiodic component from the total PSD. The first two (from left) vertical dotted lines mark slow-wave activity (SWA) band (0.2–4.0 Hz), and the last two vertical dotted lines mark the theta frequency band (4.0–7.5 Hz). (c, d) Results from the combined study set (studies D1, D2, R1, and R2 pooled together; $n = 25$ resilient, 24 vulnerable). (c) Z-scored band-power group differences for the aperiodic and periodic components of the SWA band, and the broadband (0.1–25.0 Hz) aperiodic component, for each of the four EEG channels (C3, C4, O1, and O2). Error bar indicates one standard error. Asterisk (*) indicates $p < 0.05$ uncorrected for multiple comparisons and dagger (†) indicates $p < 0.0025$, corrected for multiple comparisons. (d) Effect size of the aperiodic and periodic components of the power spectrum. Positive values indicate that band power was larger in the vulnerable group relative to the resilient group. Error bar indicates 95% confidence interval of the effect size.

still not accounted for by the other feature, suggesting a benefit of using both features for discriminating the resilient from the vulnerable group.

It is well documented that the power spectrum of neurophysiological signals is composed of periodic (rhythmic) and aperiodic (arrhythmic) components, with the aperiodic component exhibiting power-law scaling ($P \propto \frac{1}{f^{\alpha}}$), where power ($P$) drops off exponentially as frequency (f) increases, with its rate controlled by the exponent α (Buzsáki et al., 2012; He et al., 2010). In the primary analyses, we computed SWA power from the power spectrum consisting of both

TABLE 5 Statistical analysis of the periodic and aperiodic components of the electroencephalography channel power spectra.

EEG channel	*p* of group differences[a]			Effect size (95% CI)		
	Periodic–SWA	Aperiodic–SWA	Aperiodic–broadband	Periodic–SWA	Aperiodic–SWA	Aperiodic–broadband
C3	0.009*	0.008*	0.006*	0.82 (0.26, 1.49)	0.91 (0.35, 1.55)	0.91 (0.38, 1.53)
C4	0.121	0.116	0.126	0.52 (−0.01, 1.10)	0.55 (0.02, 1.12)	0.52 (−0.00, 1.09)
O1	0.002†	0.001†	0.002†	0.99 (0.44, 1.64)	1.04 (0.51, 1.70)	1.03 (0.49, 1.70)
O2	0.027*	0.024*	0.026*	0.68 (0.16, 1.29)	0.70 (0.16, 1.28)	0.68 (0.14, 1.34)

Abbreviations: broadband, 0.1–25.0 Hz; CI, confidence interval; EEG, electroencephalography; SWA, slow-wave activity (0.2–4.0 Hz).
[a]Twenty-five resilient, 24 vulnerable.
*Values indicate $p < 0.05$, uncorrected for multiple comparisons.†Values indicate $p < 0.0025$, Bonferroni-corrected for multiple comparisons.

the periodic and aperiodic components, making it unclear which component(s) contributed to the observed effects. To address this issue, we decomposed the power spectrum into its periodic and aperiodic components and extracted the power in each of the components within the SWA band (Figure 4a,b). Pooling the data across the four studies, we found that power in the periodic component of the SWA band (0.2–4.0 Hz), which reflects pure oscillatory activity, showed a significant group difference (with or without multiple-comparison corrections) in three out of four EEG channels (Figure 4c, Table 5). Interestingly, power in the aperiodic component for both the SWA band as well as the broadband (0.1–25.0 Hz) also showed the same pattern of results, where the same three EEG channels showed significant group differences (with or without multiple-comparison corrections), with effect sizes similar to those of the periodic component of the SWA band (Figure 4c,d, Table 5). We also found that the periodic component power in the theta band (4.0–7.5 Hz), which is adjacent to the SWA band, had poor discriminatory power (three out of four channels did not show a significant group difference with or without multiple-comparison corrections; the remaining channel [channel O1, $p = 0.005$] showed a significant group difference only in the absence of multiple-comparison corrections). Taken together, these results suggest that most of the discriminatory power resides within the SWA band, and within this band, both the periodic and aperiodic components are discriminatory.

4 | DISCUSSION

With the goal of identifying potential discriminatory markers of vulnerability to sleep loss, we examined three EEG features (SWA power, SWA rise rate, and sleep spindle frequency) extracted from data recorded during baseline nights of sleep. To this end, using data from four sleep studies, each with its own sleep-loss challenge, experimental design, and set of participants, we discovered potential markers using the data from the first two studies and independently assessed reproducibility using the data from the remaining two studies. From this two-step analysis, we determined that, although sleep spindle frequency may not be a reliable discriminatory marker, SWA power during the N2 and N3 stages of the first sleep cycle and SWA rise rate during initial sleep are promising candidate markers of vulnerability to sleep loss. These results are encouraging because we corroborated them using independent studies involving different experimental conditions, which strengthens our conclusions.

Previous studies that investigated physiological markers of vulnerability to sleep loss analysed features during periods of wakefulness that followed baseline nights of sleep (Caldwell et al., 2005; Chee et al., 2006; Chua et al., 2014; Cui et al., 2015; Mu et al., 2005; Yamazaki et al., 2021; Yeo et al., 2015), with the exception of one study (Chua et al., 2014) that, as in our study, assessed potential EEG markers during a baseline night. In that study, Chua et al. (2014) found that there were no significant differences between resilient and vulnerable groups when considering EEG spectral power of NREM and REM episodes over the entire night or SWA (0.75–4.5 Hz) computed in 2-h bins throughout the night. Their finding that the SWA power during a baseline night is not discriminatory contradicts our results, which showed a higher SWA power in the vulnerable group. We can reconcile this discrepancy by noting that our definition of SWA (0.2–4.0 Hz) included more low-frequency components than that used by Chua et al. (2014), which is shifted by ~0.5 Hz towards higher frequencies compared to our definition of SWA. In addition, the composition of the NREM stage signals we used to compute SWA was different from that used by Chua et al. (2014). While they included all NREM stages (N1, N2, and N3) for the first 2 h of sleep irrespective of sleep-cycle identity, we restricted our SWA power analysis to the N2 and N3 stages of the first sleep cycle. When we repeated our SWA power calculations using the SWA frequency range, NREM stages, and the 2-h time window used by Chua et al. (2014), indeed we found that the effect size of all EEG channels was reduced by an average of 20%, partially explaining the lack of effect of SWA power in their study. These results suggest that spectral power at frequencies as low as 0.2 Hz may have discriminative information and that a sleep-cycle-based analysis may be necessary to obtain useful information for discriminating resilient from vulnerable individuals.

In addition to EEG spectral feature differences, we also found differences in the sleep architecture measures of the resilient and vulnerable groups. Specifically, the percentage of sleep time spent in the relatively lighter sleep stages N1 and N2 was higher in the resilient group compared to the vulnerable group, although this effect was not consistent across the discovery and reproducibility sets. However, we

found that the percentage of sleep time spent in deep sleep (stage N3) was higher in the vulnerable group compared to the resilient group and the effect was consistent across the discovery, reproducibility, and combined sets. A previous study (Chua et al., 2014) that examined sleep architecture during a baseline night found that the resilient group spent more time in the N1 stage, as we found in our reproducibility set. However, contrary to our findings, they reported a lack of group differences in the percentage of sleep time spent in the N2 or N3 stages. While we do not know the source of these contradictions, the findings from their work and our study both indicate that, compared to vulnerable subjects, resilient subjects spend more time in a relatively lighter sleep (that is, in stage N1 or N2), potentially indicating a lesser sleep need. This observation and our finding that vulnerable subjects spent more time in a deeper sleep stage (N3) than resilient subjects support the notion that the need for sleep is comparatively higher in vulnerable individuals.

Group differences in EEG signal power in a narrow frequency band, such as the SWA band, could result from differences in the periodic activity in that band, a shift in the aperiodic component, or both (Donoghue et al., 2020). We found that the resilient and vulnerable groups differed in both the periodic activity in the SWA band and in the broadband aperiodic activity. While the periodic activity difference could be attributed to sleep pressure, it is unclear what underlies the broadband aperiodic activity difference. A previous EEG study (Miskovic et al., 2019) found that the power spectrum in stage N3 (in the log–log space) is more negatively sloped than that of stage N2. Although the authors of the study did not decompose the power spectrum into periodic and aperiodic components, their slope estimation procedure was largely tuned to capture the aperiodic component, suggesting that the aperiodic activity is higher in N3 than in N2, with a steeper negative slope. Given that, in the combined set, during the first sleep cycle, vulnerable subjects spent significantly more of their sleep time in stage N3 (Table 2) compared to resilient subjects, the higher aperiodic activity (which is the dominant component of the power spectrum) in the vulnerable subjects can be partly attributed to the sleep-stage differences between the two groups.

The rate at which SWA power rises during initial sleep has been surmised to indicate sleep pressure (Dijk et al., 1990). While a few studies have used SWA rise rate as a measure to assess sleep pressure differences between groups of subjects with different ages (Chinoy et al., 2014), disease states (Khatami et al., 2008), or gene variants implicated in sleep (Bachmann et al., 2012), our study is unique in that we examined the relationship between baseline night SWA rise rate and vulnerability to sleep loss. Given that a faster SWA rise rate has been shown to be indicative of a higher sleep pressure (Dijk et al., 1990), our finding of a higher SWA rise rate at the beginning of sleep in the vulnerable group suggests that these individuals normally have a higher accumulated sleep pressure compared to resilient individuals.

Although we did not observe significant group differences in spindle frequency, the vulnerable group had a lower spindle frequency consistently across all EEG channels in the discovery and combined study sets. A previous sleep-loss study (Knoblauch et al., 2003) indicated that sleep spindle frequency is inversely related to sleep pressure based on observations that sleep spindle frequency is lower during recovery nights when sleep pressure is higher relative to baseline nights. Therefore, the trend of lower spindle frequency in the vulnerable group may be indicative of a persistently higher sleep pressure in these individuals. However, further studies are necessary to confirm this conclusion. Although spindle amplitude and density have also been shown to be related to sleep pressure (Knoblauch et al., 2003), in a secondary analysis of the spindle data, we did not find any significant group differences for either of these additional spindle features (with or without multiple-comparison corrections).

The biological basis for vulnerability to sleep loss includes inter-individual differences in genetics, brain structure and function, sleep homeostasis, and circadian influence (Tkachenko & Dinges, 2018). Because SWA power and its rise rate during initial sleep are established markers of homeostatic sleep pressure (Brunner et al., 1993; Dijk et al., 1990), our results suggest that vulnerable individuals have a higher accumulated sleep pressure despite the same time spent awake prior to the sleep period analysed, compared to resilient individuals, suggesting that the vulnerable group accumulates homeostatic sleep drive at a faster rate than the resilient group. Thus, we speculate that during periods of sleep loss, the lingering higher sleep pressure in the vulnerable individuals interferes more adversely with attention processes, leading to a greater degradation of performance in PVTs in the vulnerable group. In other words, sleep, which dissipates sleep pressure, is more important for vulnerable individuals, for whom lack of sleep leads to a greater impairment on vigilance tasks. Supporting this conjecture, Viola et al. (2007) have shown that individuals with a period circadian regulator 3 gene ($PER3^{5/5}$) allele as opposed to the $PER3^{4/4}$ allelic version of the circadian clock gene *PER3* have a higher SWA power (indicating a higher sleep pressure) during the first quarter of sleep periods and show a greater impairment of neurobehavioural task performance with sleep loss. Taken together, these results suggest that a higher persistent sleep pressure may contribute to a greater vulnerability to sleep loss.

4.1 | Limitations

Our study has limitations. First, sleep loss leads to several cognitive deficits (Pilcher & Huffcutt, 1996), whereas the PVT mainly reveals the level of sustained attention (Drummond et al., 2005). Thus, the EEG features we found may not be predictive of changes in other cognitive functions, such as working memory or decision-making (Schnyer et al., 2009), due to sleep loss. However, sustained attention (as measured by the PVT) is essential for a wide variety of tasks, including driving, night watch, and air traffic control, in both civilian and military settings. Therefore, our discovery of EEG features associated with sleep-loss vulnerability as identified by the PVT applies to a broad set of tasks. Second, in the discovery set, we only found a significant effect on SWA rise rate when we omitted multiple-comparison corrections. However, we observed moderate to high effect sizes and the feature values had a consistent trend across all

EEG channels. This cumulative evidence, which is an important aspect of reproducibility (Goodman et al., 2016), suggests that SWA rise rate is a potentially valuable predictor of vulnerability to sleep loss. Third, we applied z-score transformation within each study to bring the EEG-feature values from the different studies into a common scale. However, z-score-based prediction requires a group of test subjects and cannot be used at the single-subject level. For group-level assessment performed herein, this is likely not a severe limitation because predicting vulnerability or resilience to sleep loss in many settings (such as in the Armed Forces) is done at the group level. Finally, our results are based on data from healthy young adults, limiting their extendibility to heterogeneous and older populations.

5 | CONCLUSIONS

Although the adverse effects of compromised sleep are well established, in many circumstances sleep loss is unavoidable. The ability to identify an individual's vulnerability to sleep loss will not only help in choosing resilient individuals for tasks requiring sustained attention but will also aid in the development of appropriate countermeasures to improve the performance and sleep hygiene of vulnerable individuals, minimising fatigue-related accidents. Our findings that SWA power and SWA rise rate computed from routine nights of sleep are promising markers of vulnerability to sleep loss at the group level provide the first step in building machine-learning algorithms to determine individual-level discrimination. Importantly, because our findings are based on a reproducibility analysis, we expect that our results will be valid under different experimental conditions and will be independently confirmed in future studies. With sleep loss being widespread in modern society (Léger et al., 2008), our results have broad applicability for identifying vulnerable individuals in a more effective manner, as they obviate the need for time-consuming and costly sleep-loss challenges.

AUTHOR CONTRIBUTIONS

Manivannan Subramaniyan: Methodology; formal analysis; data curation; writing – original draft; writing – review and editing. **Chao Wang:** Conceptualization; methodology; data curation; writing – review and editing. **Srinivas Laxminarayan:** Methodology; data curation; writing – review and editing. **Francisco G. Vital-Lopez:** Methodology; formal analysis; data curation; writing – review and editing. **John D. Hughes:** Investigation; data curation; writing – review and editing. **Tracy J. Doty:** Conceptualization; writing – review and editing. **Jaques Reifman:** Conceptualization; methodology; writing – original draft; writing – review and editing; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used in this article cannot be shared publicly because the protocols and informed consent documents for these older, legacy studies do not support data sharing outside of entities defined in the original documentation.

DISCLOSURE STATEMENTS

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