

CLINICAL INVESTIGATIONS

Static postural stability and neuropsychological performance after awakening from REM and NREM sleep in patients with chronic insomnia: a randomized, crossover, overnight polysomnography study

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Study Objectives: Chronic insomnia disorder (CID) is a common sleep disorder, with a prevalence ranging from 6%–10% worldwide. Individuals with CID experience more fragmented sleep than healthy control patients do. They awaken frequently during the night and have a higher risk of injury from falling. Awakening from different sleep stages may have different effects on postural stability and waking performance. However, limited research has been conducted on this topic.

Methods: This prospective randomized crossover study was conducted between January 2015 and January 2017. We included 20 adults aged 20–65 years who fulfilled the diagnosis criteria for CID. Participants underwent 2 overnight polysomnography studies with an interval of at least 7 days. They were awakened during either rapid eye movement (REM) sleep or stage N1/N2 sleep alternatively. We compared measurements of static postural stability, vigilance scores, and neuropsychological tests between REM sleep and stage N1/N2 sleep awakening.

Results: Polysomnography parameters between the 2 nights were comparable. Participants who were awakened from REM sleep had worse static postural stability than those with stage N1/N2 sleep awakening. Compared with stage N1/N2 sleep awakening, larger mean sway areas of center of pressure ($P = .0413$) and longer center-of-pressure mean distances ($P = .0139$) were found in REM sleep awakening. There were no statistically significant differences in vigilance scores or neuropsychological tests between the 2 nights.

Conclusions: REM sleep awakening was associated with worse static postural stability than was stage N1/N2 sleep awakening. No statistically significant differences were found in waking performance in alertness or in neuropsychological tests between stage N1/N2 and REM sleep awakening.

Keywords: insomnia, polysomnography, postural stability, rapid eye movement sleep, waking performance

Citation: Yeh W-C, Chuang Y-C, Yen C-W, et al. Static postural stability and neuropsychological performance after awakening from REM and NREM sleep in patients with chronic insomnia: a randomized, crossover, overnight polysomnography study. *J Clin Sleep Med.* 2022;18(8):1983–1992.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Individuals with chronic insomnia disorder awaken frequently during the night and have a higher risk of injury from falling. Awakening from different stages of sleep may have different effects on postural stability and waking performance.

Study Impact: Rapid eye movement sleep awakening was associated with worse static postural stability than stage N1/N2 awakening was. No statistically significant difference in vigilance or neuropsychological scores was found between these 2 types of awakening.

INTRODUCTION

Chronic insomnia disorder (CID) is one of the most common sleep disturbances in the general population, with a prevalence of 10% worldwide.¹ People with CID experience a decline in daily performance and cognitive function,² and they may experience more medical comorbidities and mood disorders with higher risks of traffic accidents.³ Moreover, chronically poor sleep quality impairs postural stability, which is similar in extent to total sleep deprivation.⁴ Older adults with insomnia have a higher risk of falls as compared with those without insomnia of the same age.⁵ Our previous studies showed that

patients with CID carry a higher risk of not only falls but also hospitalization because of the use of hypnotic agents.^{6,7}

Sleep is tightly regulated by the circadian rhythm and homeostasis.⁸ The suprachiasmatic nucleus maintains the internal synchronization of the sleep–wake cycle.⁹ Misalignment between the circadian rhythm and sleep–wake cycle results in circadian rhythm sleep disorders.¹⁰ Phototherapy is effective in enhancing the alignment of the circadian rhythm and the sleep–wake cycle and has been used frequently in circadian rhythm sleep disorders.¹¹ Compared with pharmacologic interventions, phototherapy is associated with fewer adverse effects and avoids the risk of drug–drug interactions. Furthermore,

sunlight is convenient and available everywhere. At sunrise, the color temperature of sunlight is approximately 3,000K and gradually increases to 5,000K before noon. The illumination of sunlight is approximately 400 lux at sunrise.¹² Sunlight exposure in the morning corrects a delayed-phase sleep–wake disorder, and sunlight exposure in the evening can correct an advanced-phase disorder.¹³

However, the importance of the internal alignment of the circadian rhythm and sleep–wake cycle through light exposure has often been overlooked in the treatment of chronic insomnia. Some hypnotic agents may affect sleep architecture and the sleep–wake cycle and waking alertness.¹⁴ For example, benzodiazepines cause a decrease in rapid eye movement (REM) sleep and slow-wave sleep and may induce residual effects on waking performance.¹⁵ Furthermore, hypnotics and benzodiazepines significantly increase the risk of falls.¹⁶

We supposed that in people with CID, light awakening might be a better alternative than an alarm clock. Compared with alarm clock awakening, which suddenly disrupts sleep, light awakening with a gradual change in color temperature and illumination prevents the abrupt disruption of sleep architecture and may have a smaller impact on waking performance.

There is only limited research assessing postural stability and waking performance after awakening at different sleep stages. CID is considered a disorder of hyperarousal, and patients with insomnia may have frequent awakening either during nonrapid eye movement (NREM) or REM sleep and have a higher risk of injury from falling. Compared to NREM sleep, which is characterized by a period of relative autonomic stability, REM sleep is characterized by a fluctuating heart rate, surge in blood pressure, and irregular respiratory pattern. In addition, there is generalized skeletal muscle atonia during REM sleep. Therefore, we hypothesized that awakening from REM sleep might have a worse effect on vigilance performance and postural stability compared to awakening from NREM sleep.

In the present study, we aimed to evaluate the difference in waking performance after patients were awakened by light exposure at different sleep stages. Specifically, we evaluated differences in waking static postural stability, vigilance, and cognitive performance between participants awakened during REM sleep and stage N1/N2 sleep.

METHODS

Preliminary study

To decide the optimal length of light exposure, we conducted a preliminary randomized crossover study to compare 2 modes of light awakening: the “fast light-on mode” (gradual illuminance change from 0 lux–2,500 lux and color temperature change from 3,000K–6,500K within 2 minutes 30 seconds) and the “slow light-on mode” (gradual illuminance change from 0 lux–2,500 lux and color temperature change from 3,000K–6,500K within 30 minutes) in 20 healthy volunteers (mean age 23.3 years, 100% male). The results of the preliminary study suggested that volunteers awakened with the fast light-on mode had worse performance in the Symbol Searching Test and the Digit

Symbol Substitution Test ($t = -3.766$, $P = .004$ and $t = -3.130$, $P = .012$). Therefore, to avoid the negative effects of fast light-on mode on the vigilance test, we decided to use the slow light-on mode in the present study.

We also assessed the differences in postural stability between REM sleep and stage N1/N2 sleep awakening in healthy volunteers (people without any sleep problem) in the preliminary study. Twelve healthy volunteers (mean age 22.2 years, 33.3% female) completed the preliminary crossover study. There were no significant differences in all center-of-pressure (COP) parameters between the types of awakenings (REM sleep and stage N1/N2 sleep). However, there was a trend of worse postural stability after patients were awakened from REM sleep than after they were awakened from stage N1/N2 sleep (Table 1). Therefore, we supposed that REM sleep awakening may negatively affect postural stability; this negative effect may be augmented in patients with chronic insomnia disorder.

Participants

This was a prospective randomized crossover study conducted at the Sleep Disorders Center, Kaohsiung Medical University Hospital (Kaohsiung City, Taiwan), between January 2015 and January 2017. The inclusion criteria were as follows: fulfilling the *International Classification of Sleep Disorders*, third edition (ICSD-3) criteria for CID; age 20–65 years; nonsmoker; body mass index between 18.5 and 24.9 kg/m²; and a score of 0 on the Berlin Questionnaire for sleep apnea. According to the ICSD-3, CID is defined as (1) a report of sleep initiation or maintenance problems, (2) adequate opportunity and circumstances to sleep, and (3) daytime consequences, at least 3 times per week for 3 months.¹⁷

We excluded individuals with primary sleep disorders, including obstructive sleep apnea (apnea-hypopnea index ≥ 10 events/h), periodic limb movement disorder (measured using the Periodic Limb Movement Index; ≥ 10 events/h), narcolepsy, circadian rhythm sleep disorder, and restless legs syndrome. Patients with chronic obstructive pulmonary disease, end-stage renal disease, epilepsy, heart failure, malignancy, neurocognitive disorders, or psychiatric disorders were excluded. People employed in shift work or who had taken trans-meridian flights within the past 2 weeks were also excluded. All participants were asked to stop benzodiazepine or hypnotic use 2 weeks before the study.

All participants signed an informed consent and were notified that such informed consent could be withdrawn without any reason, as participation was voluntary. This study protocol followed the ethical principles outlined by the Declaration of Helsinki for medical research and was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (approval KMHIRB-G(I)-20160056).

Study design

Participants recorded their own habitual hours of sleep and awake (sleep diary) during the 2 weeks before the polysomnography (PSG) study. They arrived at the sleep center at least 90 minutes before their habitual bedtime. All participants underwent 2 overnight PSG studies. Participants were awakened by

Table 1—COP parameters between light awakening at stage N1/N2 sleep and REM sleep in healthy volunteers.

| | COP Parameters | Stage N1/N2 Sleep Awakening (n = 12) | REM Sleep Awakening (n = 12) | P |
|-------------|----------------|--------------------------------------|------------------------------|-------|
| Eyes open | SA | 9.22 ± 5.48 | 9.06 ± 4.69 | .9504 |
| | Distance | 4.65 ± 1.62 | 4.74 ± 2.02 | .8846 |
| | Frequency | 0.32 ± 0.09 | 0.32 ± 0.08 | .9102 |
| | Velocity | 7.06 ± 2.11 | 8.49 ± 2.99 | .2909 |
| | Velocity (AP) | 5.45 ± 1.71 | 7.02 ± 2.59 | .1760 |
| | Velocity (ML) | 3.62 ± 1.08 | 4.12 ± 1.49 | .4561 |
| Eyes closed | SA | 7.75 ± 5.15 | 9.33 ± 7.34 | .6117 |
| | Distance | 3.43 ± 1.15 | 4.21 ± 2.29 | .3609 |
| | Frequency | 0.37 ± 0.10 | 0.36 ± 0.06 | .9110 |
| | Velocity | 7.35 ± 2.29 | 9.27 ± 5.06 | .3243 |
| | Velocity (AP) | 6.02 ± 1.86 | 7.96 ± 4.49 | .2674 |
| | Velocity (ML) | 3.34 ± 1.12 | 4.19 ± 2.34 | .3567 |

Paired-samples *t* test. AP = anteroposterior, COP = center of pressure, ML = median-lateral, REM = rapid eye movement, SA = sway area.

LED light in the morning according to a scheduled window of wake-up time at the end of the PSG study. The 1-hour wake-up time window was defined as 30 minutes before and after the habitual wake-up time, which was set according to each participant's sleep diary. After reaching their individualized wake-up time window, the participants were awakened by the light equipment with a remote control following one 30-second epoch of either stable REM sleep or stage N1/N2 sleep, determined by certificated sleep technicians. The order of awakening during REM sleep or stage N1/N2 sleep was randomized in a 1:1 ratio using a computer algorithm. Each participant was assigned randomly to be awakened during REM sleep or stage N1/N2 sleep on the first recorded night, then to cross over to be awakened during stage N1/N2 sleep or REM sleep on the second recorded night, with a washout period of at least 7 days (Figure 1). We did not choose stage N3 sleep awakening as the NREM sleep control, because we supposed that participants may be less likely to wake up solely by light during N3 sleep.

All participants underwent kinetic measurement of static postural stability before each PSG study (baseline measure) and then repeated the measurement within 20 minutes after REM sleep awakening and stage N1/N2 sleep awakening. Sleep technicians maintained electroencephalogram (EEG) monitoring after the wake-up light had been switched on. We obtained data from only participants who were awakened at the same sleep stage during which we attempted to wake them—that is, during either REM sleep or stage N1/N2 sleep. Postural stability and neuropsychological test (NPT) data were not included in the final analysis from participants awakened at a different stage of sleep from which the wake-up light had been initiated.

Sleep questionnaires

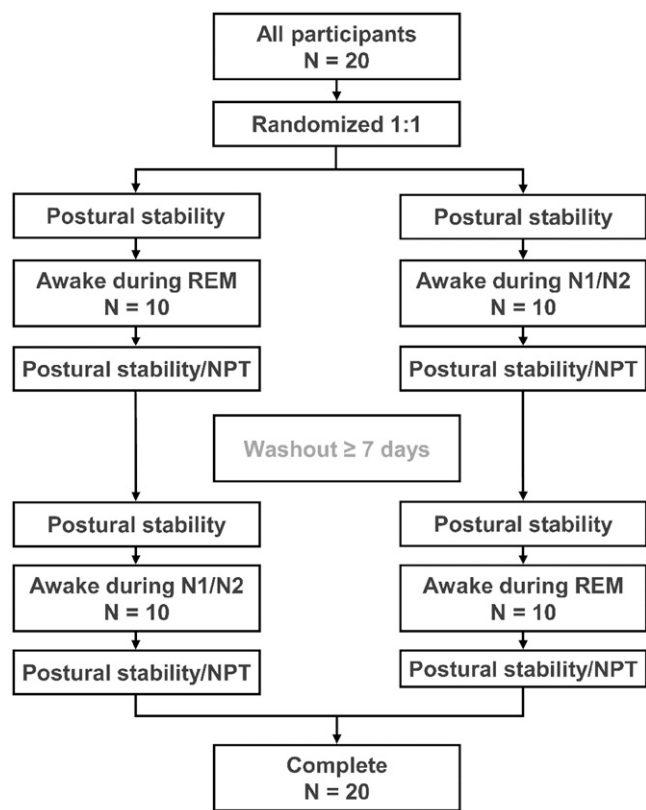
All participants completed validated sleep questionnaires and sleep scales using the Chinese versions of the Athens Insomnia Scale (AIS), the Epworth Sleepiness Scale (ESS), the Morningness–Eveningness Questionnaire, and the Pittsburgh Sleep Quality Index

(PSQI). The AIS consists of 8 items, with a total score of 0–24; a higher AIS score indicates more severe insomnia.¹⁸ The ESS is composed of 8 items, with a total score of 0–24, with a higher ESS score (> 10) indicative of worse daytime sleepiness.¹⁹ The Morningness–Eveningness Questionnaire consists of 19 items, with a total score of 16–86. Scores of 41 and below indicate “evening types,” with a total score of 16–30 indicating “definite evening types” and a total score of 31–41 indicating “moderate evening types.” Scores of ≥ 59 indicate “morning types,” with a score of 70–86 indicating “definite morning types” and 59–69 indicating “moderate morning types.” Scores between 42 and 58 indicate “intermediate types.”²⁰ The PSQI consists of 9 items, with a total score of 0–21, and assesses the following subscales: (1) self-reported sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbance, (6) use of hypnotics, and (7) daytime dysfunction. A higher PSQI score indicates poorer self-reported sleep quality. Its cutoff score is 5, with a sensitivity of 89.6% and a specificity of 86.5% for patients with sleep disturbance.²¹

Instruments

In-laboratory overnight PSG

All eligible participants underwent 2 overnight in-laboratory PSGs. The overnight full-channel PSG, including 6 EEG referential channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, and O2-A1), 2 electrooculogram channels recorded on bilateral canthi, and 3 electromyogram channels recorded on the submentalis and bilateral tibialis anterior muscles, was recorded by a validated machine (Nicolet Ultrason, Madison, WI). Thoracic and abdominal respiratory inductive plethysmography was used to record respiratory effort. Nasal airflow was recorded by a thermistor and a nasal airway pressure transducer. Oxyhemoglobin saturation was recorded by pulse oximetry, with the probe placed on the participants' index finger. Sleep stages and

Figure 1—Participant flowchart.

Each participant was randomly assigned to be awakened during REM sleep or stage N1/N2 sleep on the first recorded night and then to cross over to be awakened during stage N1/N2 sleep or REM sleep on the second recorded night, with a washout period of at least 7 days. The order of awakening during REM sleep or stage N1/N2 sleep was randomized in a 1:1 ratio using a computer algorithm. All participants underwent kinetic measurement of static postural stability before each PSG study and then repeated the measurement within 30 minutes after REM sleep awakening and stage N1/N2 sleep awakening. Vigilance tests and NPTs were performed after awakening in each PSG record. NPT = neuropsychological test, PSG = polysomnography, REM = rapid eye movement.

sleep-related events were scored based on American Academy of Sleep Medicine criteria.²²

The parameters obtained from the PSG study included total sleep time, sleep efficiency, percentage of each stage of sleep (percentage of total sleep time), sleep latency, and REM sleep latency. Arousal on the EEG was defined as an abrupt change in electroencephalographic frequency of at least 3 seconds followed by at least 10 seconds of sleep on any of the referential EEG channels. The frequency of arousals was represented as the arousal index, calculated as arousal events per hour of total sleep time.

Light awakening

The LED was placed on the wall 50 cm directly above the pillow. We intended to simulate the sunrise light exposure using a gradual illuminance change from 0–2,500 lux and a gradual color temperature change from 3,000–6,500K within 30 minutes.

The light equipment was turned on with a remote control during either stable REM sleep or stage N1/N2 sleep within the individually scheduled wake-up time window.

Static postural stability: kinetic measures during quiet standing

The kinetic measures during quiet standing consisted of force-plate posturography measurement of COP, the weighted average of pressures distributed over the surface of the area in contact with the ground. Participants stood in a comfortable stance near the center of the force plate, looking straight ahead at a visual reference with arms relaxed at their sides. Each measurement on the platform lasted 80 seconds: 40 seconds with eyes open and 40 seconds with eyes closed. Measurements were repeated 3 times with a 60-second interval. We analyzed the following COP parameters: COP sway area (SA), COP mean distance, COP mean frequency, COP mean velocity, medial–lateral velocity, and anteroposterior velocity. Lower COP values indicated better postural stability during quiet standing. Static postural stability was measured before and after each recorded night, and we compared the measurements before sleep and after awakening.

The measurement system consisted of a force plate (9286AA, Kistler Instrumente AG, Winterthur, Switzerland) connected to a computer-based data acquisition system. The force-plate measurements were sampled at 512 Hz with a 14-bit analog-to-digital data acquisition card (USB-6009, National Instruments, Austin, TX) connected to a desktop computer. For data processing, we used a custom-developed program written in LabVIEW (National Instruments, Austin, TX). The signals were filtered using a zero-phase sixth-order low-pass Butterworth filter with a cutoff frequency of 5 Hz.^{23,24} The COP parameter units were as follows: COP SA in square millimeters, COP mean distance in millimeters, COP mean frequency in seconds, and COP mean velocity in millimeters per second.

Evaluation of vigilance

We used the Multiple Unprepared Reaction Time test to assess the participants' vigilance.²⁵ The Oxford Sleep Resistance Test device (Stowood Scientific Instruments, Oxford, UK) was used. Over a 10-minute period, participants responded by hitting a button on a portable device each time a dim light randomly flashed at 2- to 10-second intervals.

Neuropsychological tests

We used the Digit Symbol Substitution Test, Symbol Searching Test, and the Trail Making Test (TMT) to assess the participants' attention and concentration. The Digit Symbol Substitution Test and Symbol Searching Test measure a range of cognitive operations. Good performance on the Digit Symbol Substitution Test requires intact motor speed, attention, and visuo-perceptual functions, including scanning and the ability to write or draw.²⁶

The TMT consists of 25 circles distributed over a sheet of paper. The circles are numbered 1–25 in TMT part A. In TMT part B, the circles include both numbers (1–13) and letters (A–L). The participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters in part B (ie, 1-A-2-B-3-C).

The participants were instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper.²⁷ The TMT is scored by how long it takes to complete the test.²⁸

Statistical analysis

We carried out statistical analyses using JMP 12.0 (SAS Institute Inc., Cary, NC). Continuous variables (ie, age, PSG parameters, sleep questionnaire/scale scores, indices of sleep-related events, COP measures, and score of neuropsychological tests) were expressed as mean \pm standard deviation. Binary variables were expressed as number and percentage.

The present study did not include sleep deprivation or restriction, and there was a washout period of at least 7 days between the 2 PSG studies. We believed that the carryover effects or period effects were limited and would not affect our results. Therefore, we used the paired-sample *t* test to compare continuous variables between the 2 measurements in this study. Statistical significance was set at $P < .05$.

RESULTS

Background information

Twenty-one volunteers were eligible and included in the present study. One participant was not awakened at the same stage of sleep from which the wake-up light was switched on. Twenty participants completed the study of light awakening during stage N1/N2 sleep and during REM sleep (Figure 1). The mean participant age was 46.1 years (range, 26–65 years). Fifteen participants were female (75%). The mean BMI was 23.8 (16.9–33.2) kg/m² (Table 1).

Sleep questionnaires

Morningness–Eveningness Questionnaire

Based on the total Morningness–Eveningness Questionnaire score, 8 participants (40%) were classified as moderate morning types, 8 (40%) as intermediate types, 3 (15%) as moderate evening types, and 1 (5%) as evening type.

AIS

Eighteen participants (90%) had an AIS score ≥ 8 , indicating self-reported insomnia.

PSQI

Of the participants, 95% had a PSQI score > 5 , indicating self-reported poor sleep.

ESS

Eight participants (40%) had an ESS score > 10 , and 12 participants (60%) did not have self-reported daytime sleepiness.

Sleep macrostructure: PSG parameters

There were no statistically significant differences in any of the PSG parameters (total sleep time, sleep efficiency, sleep latency, REM sleep latency, and percentage of stage N1, stage

N2, slow-wave sleep, and REM sleep) between the first and the second night among all participants. We observed no statistically significant differences in apnea-hypopnea index, oxygen desaturation index, and periodic leg movement index, respectively (Table 2).

Static postural stability: kinetic measures during quiet standing

Before and after sleep

All COP parameters decreased after stage N1/N2 sleep awakening. There was a statistically significant difference in 6 parameters: COP mean frequency with eyes open and eyes closed ($P = .0096$ and $P = .0163$), COP mean velocity with eyes open and eyes closed ($P = .0224$ and $P = .0287$), and anteroposterior velocity with eyes open and eyes closed ($P = .0254$ and $P = .0263$) after being awakened from stage N1/N2 sleep (Table 3).

On the other hand, we found a statistically significant decrease in only 3 parameters (COP mean frequency with eyes open and eyes closed [$P = .0282$ and $P = .0138$] and anteroposterior velocity with eyes closed [$P = .0402$]) after being awakened from REM sleep. Conversely, we noted a statistically significant increase in mean sway distance with eyes closed ($P = .0459$) after REM sleep awakening (Table 4).

REM sleep awakening and stage N1/N2 sleep awakening

Statistically significant differences were found in COP SA (eyes closed) and COP mean distance (eyes closed) between the 2 records. Participants who were awakened from stage N1/N2 sleep had a smaller COP SA ($P = .0413$) and a shorter COP mean distance ($P = .0139$) than those awakened from REM sleep (Table 5).

Evaluation of vigilance and the NPTs

There was no statistically significant difference between the 2 records in the Multiple Unprepared Reaction Time test results. The Digit Symbol Substitution Test, Symbol Searching Test, TMT part A, and TMT part B scores were not statistically different between awakening from REM sleep and from stage N1/N2 sleep (Table 6).

DISCUSSION

We found significant differences in static postural stability during quiet standing between REM sleep awakening and stage N1/N2 sleep awakening. Stage N1/N2 sleep awakening was associated with statistically significant improvements in more COP parameters than REM sleep awakening was. Furthermore, we found that as compared with stage N1/N2 sleep awakening, REM sleep awakening was associated with a statistically significant larger COP SA and longer COP mean distances with eyes closed. On the other hand, there were no statistically significant differences in the measures of postural stability with eyes open between REM sleep awakening and stage N1/N2 sleep awakening, suggesting that visual aid may compensate for postural instability after REM sleep awakening. No statistically significant

Table 2—PSG parameters between the 2 nights.

| PSG Parameter | Stage N1/N2 Sleep Awakening (n = 20) | REM Sleep Awakening (n = 20) | P |
|-----------------------|--------------------------------------|------------------------------|-------|
| Total sleep time, min | 384.4 ± 84.5 | 401.9 ± 96.6 | .5036 |
| Sleep latency | 19.5 ± 32.2 | 19.6 ± 19.2 | .9841 |
| Sleep efficiency, % | 80.7 ± 14.4 | 77.3 ± 15.8 | .3751 |
| Arousal index | 7.49 ± 12.6 | 7.48 ± 6.93 | .9949 |
| REM sleep latency | 145.6 ± 80.7 | 154.9 ± 70.7 | .6560 |
| Stage N1 sleep, % | 10.7 ± 16.4 | 11.1 ± 7.5 | .9187 |
| Stage N2 sleep, % | 48.2 ± 13.4 | 51.7 ± 11.0 | .2242 |
| Stage N3 sleep, % | 21.5 ± 14.1 | 18.0 ± 10.8 | .1938 |
| REM sleep, % | 19.6 ± 5.77 | 19.2 ± 5.98 | .7794 |
| AHI | 5.16 ± 15.3 | 4.74 ± 11.3 | .6738 |
| ODI | 4.28 ± 14.7 | 3.47 ± 9.94 | .4747 |
| PLMI | 1.63 ± 3.94 | 4.26 ± 12.1 | .3077 |

Paired-samples *t* test. AHI = apnea-hypopnea index, ODI = oxygen desaturation index, PLMI = periodic limb movement index, PSG = polysomnography, REM = rapid eye movement.

differences were found in the vigilance test or NPT scores between stage N1/N2 sleep awakening and REM sleep awakening. Among all participants, there were no statistically significant differences in sleep macrostructure or indices of sleep-related events between the first and second PSG record.

Sleep and postural stability

General improvement in postural stability after sleep was noted in this study, and most parameters of COP decreased after sleep. The maintenance of postural stability depends on the interaction between the visual, proprioception, and vestibular system.²⁹ The main clinical phenomena of patients with CID is chronic sleep deprivation. Sleep deprivation is believed to have damaging effects on postural stability, and the mechanism is complex.

According to Aguiar and Barela, impairment of sensorimotor coupling is the main cause of postural instability after sleep deprivation.^{30,31} On the other hand, other research has suggested that reduced adaptation ability and lapses in attention are the main causes.^{32,33} In the study by Martin et al, the decline in vertical perception after sleep deprivation was associated with postural instability.³⁴ Nevertheless, the lack of integration of any 1 of the 3 systems (visual, proprioception, and vestibular) can lead to reduced postural stability.³⁵

REM sleep awakening and postural stability

REM sleep is characterized by rapid eye movements, desynchronized EEG, and generalized muscle atonia.³⁶ The pedunculopontine nucleus (PPN) is the central neural network that controls REM

Table 3—COP parameters before sleep and after light awakening at N1/N2 sleep.

| | COP Parameter | Before Sleep (n = 20) | Stage N1/N2 Sleep Awakening (n = 20) | P |
|-------------|---------------|-----------------------|--------------------------------------|--------|
| Eyes open | SA | 12.28 ± 7.69 | 9.69 ± 6.24 | .1685 |
| | Distance | 4.67 ± 1.45 | 4.44 ± 1.61 | .4824 |
| | Frequency | 0.35 ± 0.14 | 0.28 ± 0.08 | .0096* |
| | Velocity | 9.35 ± 4.05 | 7.18 ± 2.25 | .0224* |
| | Velocity (AP) | 7.28 ± 3.23 | 5.51 ± 2.16 | .0254* |
| | Velocity (ML) | 4.56 ± 2.78 | 3.46 ± 1.16 | .0601 |
| Eyes closed | Sway area | 12.39 ± 10.66 | 8.58 ± 4.81 | .1271 |
| | Distance | 4.27 ± 1.59 | 3.92 ± 1.14 | .3591 |
| | Frequency | 0.41 ± 0.15 | 0.34 ± 0.07 | .0163* |
| | Velocity | 10.59 ± 5.33 | 8.07 ± 2.46 | .0287* |
| | Velocity (AP) | 8.52 ± 4.04 | 6.47 ± 2.55 | .0263* |
| | Velocity (ML) | 4.76 ± 3.67 | 3.49 ± 1.23 | .0861 |

Paired-samples *t* test. **P* < .05. AP = anteroposterior, COP = center of pressure, ML = median-lateral, SA = sway area.

Table 4—COP parameters before sleep and after light awakening at REM sleep.

| | COP Parameter | Before Sleep (n = 20) | REM Sleep Awakening (n = 20) | P |
|-------------|---------------|-----------------------|------------------------------|--------|
| Eyes open | SA | 10.27 ± 5.94 | 9.29 ± 4.52 | .3203 |
| | Distance | 4.48 ± 1.59 | 4.51 ± 1.29 | .9027 |
| | Frequency | 0.32 ± 0.10 | 0.28 ± 0.07 | .0282* |
| | Velocity | 8.13 ± 2.66 | 7.48 ± 2.12 | .1287 |
| | Velocity (AP) | 6.29 ± 2.36 | 5.92 ± 1.95 | .3002 |
| | Velocity (ML) | 3.99 ± 1.58 | 3.51 ± 1.16 | .0532 |
| Eyes closed | SA | 10.28 ± 5.04 | 10.31 ± 5.27 | .9714 |
| | Distance | 4.30 ± 1.42 | 4.61 ± 1.53 | .0459* |
| | Frequency | 0.37 ± 1.24 | 0.32 ± 0.07 | .0138* |
| | Velocity | 9.44 ± 3.33 | 8.79 ± 2.82 | .0807 |
| | Velocity (AP) | 7.79 ± 3.09 | 7.21 ± 2.63 | .0402* |
| | Velocity (ML) | 3.98 ± 1.64 | 3.75 ± 1.65 | .3410 |

Paired-samples *t* test. **P* < .05. AP = anteroposterior, COP = center of pressure, ML = median–lateral, REM = rapid eye movement, SA = sway area.

sleep, locomotor function, and postural stability,³⁷ which is crucial in coordinating between the basal ganglia, the cerebellum, and the spinal cord to control muscle tone during REM sleep.^{38,39} Cholinergic neurons at the PPN induce REM sleep,⁴⁰ and REM sleep maintenance depends on the balance between the REM-on and REM-off neuron centers.⁴¹

The PPN also plays a vital role in postural and locomotor control, which have been widely investigated in neurodegenerative diseases such as Parkinson's disease and REM sleep behavior disorders. Microstructural lesions in the PPN significantly impair postural and gait stability in Parkinson's disease,⁴² and PPN deep brain stimulation is effective for postural and gait stability in these patients.^{43,44} Moreover, PPN deep brain stimulation in patients with Parkinson's disease has also been found to cause a significant increase in REM sleep.⁴⁵

Different PPN neurons show different activity across the sleep–wake cycle. Studies in the literature have reported that the vestibular system and cerebellum vermis, which mediate the adaptation to inertia of gravity, spatial orientation, and postural stability, have increased activity during REM sleep.^{46,47} In addition, generalized skeletal muscle atonia occurs during REM sleep.⁴⁸ Awakening from REM sleep may transiently alter the activity of the PPN and delay the regain of muscle tone upon awakening. Therefore, in the present study, we assumed that awakening from REM sleep could disrupt REM sleep consolidation and contribute to worse postural stability and increased fall risk.

Sleep, vigilance, and NPTs

We found no significant differences in the alertness test or NPT scores between REM sleep awakening and stage N1/N2 sleep

Table 5—COP parameters between light awakening at stage N1/N2 sleep and REM sleep.

| | COP Parameter | Stage N1/N2 Sleep Awakening (n = 20) | REM Sleep Awakening (n = 20) | P |
|-------------|---------------|--------------------------------------|------------------------------|--------|
| Eyes open | SA | 9.69 ± 6.24 | 9.29 ± 4.52 | .7394 |
| | Distance | 4.44 ± 1.61 | 4.51 ± 1.29 | .7532 |
| | Frequency | 0.28 ± 0.08 | 0.28 ± 0.07 | .6781 |
| | Velocity | 7.18 ± 2.25 | 7.48 ± 2.12 | .3361 |
| | Velocity (AP) | 5.51 ± 2.16 | 5.92 ± 1.95 | .2151 |
| | Velocity (ML) | 3.46 ± 1.16 | 3.51 ± 1.16 | .7911 |
| Eyes closed | SA | 8.58 ± 4.81 | 10.31 ± 5.27 | .0413* |
| | Distance | 3.92 ± 1.14 | 4.61 ± 1.53 | .0139* |
| | Frequency | 0.34 ± 0.07 | 0.32 ± 0.07 | .1365 |
| | Velocity | 8.07 ± 2.46 | 8.79 ± 2.82 | .0784 |
| | Velocity (AP) | 6.47 ± 2.55 | 7.21 ± 2.63 | .0773 |
| | Velocity (ML) | 3.49 ± 1.23 | 3.75 ± 1.65 | .3022 |

Paired-samples *t* test. **P* < .05. COP = center of pressure, AP = anteroposterior, ML = median–lateral, REM = rapid eye movement, SA = sway area.

Table 6—Vigilance test and NPT between stage N1/N2 sleep and REM sleep awakening.

| Test | Parameter | Stage N1/N2 Sleep Awakening (n = 20) | REM Sleep Awakening (n = 20) | P |
|---------|-----------------------|--------------------------------------|------------------------------|-------|
| MURT | Valid reactions | 96.4 ± 0.74 | 96.4 ± 0.52 | > .99 |
| | Invalid reactions | 1.0 ± 0.53 | 0.87 ± 0.83 | .7318 |
| | Mean reaction time | 214.4 ± 46.2 | 219.8 ± 37.7 | .6376 |
| | Maximum reaction time | 482.3 ± 138.2 | 494.8 ± 315.6 | .9212 |
| | Minimum reaction time | 152.7 ± 20.1 | 154.5 ± 15.7 | .7627 |
| DSST | Mean score | 73.7 ± 20.1 | 72.8 ± 14.7 | .6682 |
| SST | Mean score | 32.2 ± 9.91 | 33.15 ± 9.86 | .3631 |
| Trail A | Mean score (second) | 42.0 ± 16.55 | 40.35 ± 14.14 | .5962 |
| | Total error | 0.20 ± 0.52 | 0.10 ± 0.31 | .4283 |
| Trail B | Mean score (second) | 85.35 ± 34.33 | 76.65 ± 28.55 | .1861 |
| | Total error | 0.85 ± 1.09 | 0.60 ± 0.75 | .4703 |

Paired-samples *t* test. DSST = Digit Symbol Substitution Test, MURT = Multiple Unprepared Reaction Time, NPT = neuropsychological test, REM = rapid eye movement, SST = Symbol Searching Test.

awakening. Della Monica et al⁴⁹ evaluated the relationships between the performance of NPTs and the amount of REM sleep and slow-wave sleep among 206 healthy adults aged 20–84 years. They found that REM sleep was associated with the accuracy of waking performance and that slow-wave sleep was associated with the speed of waking performance. In addition, a longer REM sleep duration was associated with better performance on an auditory verbal learning test.⁵⁰

The sleep macrostructure between the 2 PSG records was comparable in the present study. Our results suggest that awakening from different stages of sleep (REM sleep awakening vs stage N1/N2 sleep awakening) may not affect waking vigilance or neuropsychological performance. To elucidate the interactions between waking performance and specific sleep stage, further studies are needed.

Summary remarks

Patients with CID experienced frequent awakenings during the night. Partial and total sleep deprivation could both impair postural stability and increase the risk of fall. The present study further evaluated the differences in postural stability after awakening from different sleep stages. We want to emphasize that REM sleep awakening may carry an increased risk of fall as compared to stage N1/N2 sleep awakening. Therefore, medications such as benzodiazepines that disrupt REM sleep should be used with caution in patients with CID. Furthermore, the results suggested that visual aid may compensate for postural instability after REM sleep awakening. Therefore, an environment with adequate illumination may decrease the risk of fall when patients with CID are awakened at night.

Limitations

First, the number of participants in this study was small, and the single-center design may limit the generalizability of the results. Second, we assessed the difference in postural instability in patients between stage N1/N2 sleep and REM sleep

awakening; however, the first-night effect could have had an effect on sleep stage stability. Finally, we assessed only postural stability during quiet standing after awakening; measuring dynamic postural stability may also provide valuable information for predicting fall risk. Furthermore, postural stability was measured within 10 minutes after REM sleep or stage N1/N2 sleep awakening, which can reflect only the physical condition immediately after awakening, and whether the effect will last for the rest of the day remains unknown. Finally, our study design was based on common physiological experiences that humans normally wake up from either light sleep (stage N1/N2 sleep) or REM sleep. Awakening from deep sleep (stage N3 sleep) may cause a pathological condition, such as sleep inertia or disorders of arousal (sleep terror, somnambulism, confusional arousal), which is not the focus of the present study.

CONCLUSIONS

In the present study, REM sleep awakening was associated with worse static postural stability than stage N1/N2 sleep awakening was. However, no statistically significant difference in vigilance or neuropsychological scores was found between these 2 types of awakening. This study sheds better light on the association between postural stability and awakening from specific stages of sleep. The prevention of REM sleep disruption and an environment with adequate illumination may both decrease the risk of fall at night in patients with CID. Further investigation is required to determine the underlying mechanisms and to evaluate how long the effect lasts during the rest of the day.

ABBREVIATIONS

AIS, Athens Insomnia Scale
CID, chronic insomnia disorder

COP, center of pressure
 EEG, electroencephalogram
 ESS, Epworth Sleepiness Scale
 NPT, neuropsychological test
 PPN, pedunculopontine nucleus
 PSG, polysomnography
 PSQI, Pittsburgh Sleep Quality Index
 REM, rapid eye movement
 SA, sway area
 TMT, Trail Making Test

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ACKNOWLEDGMENTS

The authors are grateful to Jia-Chi Juang, Yen-Ju Chuang, Fu-Hui Tsai, Chih-Yang Hsu, and Ming-Hung Sun from the Sleep Center of Kaohsiung Medical University Hospital for their assistance in data collection. This study was supported by the Ministry of Science and Technology Grant (106-2314-B-037-026), Kaohsiung Medical University Research Center (KMUH106-6R65), and the Industrial Technology Research Institute (ST104020).

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication November 3, 2021

Submitted in final revised form April 8, 2022

Accepted for publication April 8, 2022

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the Sleep Disorders Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. The authors report no conflicts of interest.