Received: 31 October 2021 | Revised: 29 April 2022 | Accepted: 10 May 2022

DOI: 10.1111/ina.13055

ORIGINAL ARTICLE

WILEY

Carbon dioxide effects on daytime sleepiness and EEG signal: A combinational approach using classical frequentist and Bayesian analyses

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Funding information
This work was supported by the Center of Innovation Program from the Japan Science and Technology Agency, JST COI Grant Number: JPMJCE1303.

Abstract

Environmental carbon dioxide (CO_2) could affect various mental and physiological activities in humans, but its effect on daytime sleepiness is still controversial. In a randomized and counterbalanced crossover study with twelve healthy volunteers, we applied a combinational approach using classical frequentist and Bayesian statistics to analyze the CO_2 exposure effect on daytime sleepiness and electroencephalogram (EEG) signals. Subjective sleepiness was measured by the Japanese Karolinska Sleepiness Scale (KSS-J) by recording EEG during CO_2 exposure at different concentrations: Normal (C), 4000 ppm (Moderately High: MH), and 40 000 ppm (high: H). The daytime sleepiness was significantly affected by the exposure time but not the CO_2 condition in the classical statistics. On the other hand, the Bayesian paired *t*-test revealed that the CO_2 exposure at the MH condition might induce daytime sleepiness at the 40-min point compared with the C condition. By contrast, EEG was significantly affected by a short exposure to the H condition but not exposure time. The Bayesian analysis of EEG was primarily consistent with results by the classical statistics but showed different credible levels in the Bayes' factor. Our result suggested that the EEG may not be suitable to detect objective sleepiness induced by CO_2 exposure because the EEG signal was highly sensitive to environmental CO_2 concentration. Our study would be helpful for researchers to revisit whether EEG is applicable as a judgment indicator of objective sleepiness.

KEYWORDS
Bayes factor, Bayesian statistics, carbon dioxide, daytime sleepiness, electroencephalogram

1 | INTRODUCTION

Carbon dioxide (CO_2) is an odorless, tasteless, and colorless gas that affects humans' physiological conditions.[1] The average indoor CO_2 concentration typically ranges from 600 to 1000 ppm (parts per million)[2,3] although it could often reach over 4500 ppm by occupation with insufficient ventilation.[4–6] Prolonged passive exposure to elevated CO_2 concentrations could have adverse effects on human health. Therefore, common indoor air quality standards have been defined as an acceptable concentration and duration of CO_2

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exposure in an average range of 800–1000 ppm for 8–24 h by international agencies. Several standards were proposed as the optimal indoor space CO_2 concentration. More specifically, ≤1000 ppm by the Ministry of Health Labor and Welfare (MHLW, Japan)[7]; ≤0.10% (2000 mg/m^3) by Administration of Quality Supervision Inspection and Quarantine (AQSIQ, China Standard CS GB/T17094-1997)[8]; ≤800 ppm (excellent class/non-residential) by the Hong Kong Special Administrative Region (HKSAR, China)[9]; ≤1000 ppm by Department of Occupational Safety and Health (DOSH, Malaysia)[10]; ≤1000 ppm by Guideline development for evaluation and management of office air quality (II) by Korea Occupational Safety and Health Agency (KOSHA)[11]; ≤1000 ppm by Singapore Institute of Environmental Epidemiology (SAIQG)[12]; and <550 ppm (good indoor air quality) by The Finnish Society of Indoor Air Quality and Climate (FiSIAQ).[13]

Exposure to CO_2 could result in various mental and physiological changes in humans, even at relatively low concentrations. When the environmental CO_2 concentration reaches in the range of 1000–4000 ppm, people start feeling uncomfortable[14,15] and show changes in sleepiness, heart rate variation, headaches symptoms,[16] and declined cognitive capacities.[15,17] However, the relationship between CO_2 concentration and exposure time on daytime sleepiness, which critically reduces office workers' work efficiency, is still controversial. The earliest study by Vehviläinen et al. reported CO_2 at around 3000 ppm resulted in changes in heart rate variability with increased sleepiness.[16] By contrast, Bloch - Salisbury et al.[18] reported no association between CO_2 inhalation and cognitive performance or alertness. In the past few years, moreover, researchers hold different views on whether carbon dioxide causes cognitive decline and induces daytime sleepiness.[19] A possible reason for the discrepancy is that daytime sleepiness was mainly measured by Karolinska Sleepiness Scale (KSS) or Stanford Sleepiness Scale scores, which indicate subjective sleepiness, resulting in considerable variation among the participants.

Electroencephalogram (EEG) has often been used as a valid indicator to detect objective sleepiness in the physiological approach.[20] In the eyes-open condition, increased powers in the low-frequency bands such as delta (1–3 Hz), theta (4–7 Hz), and alpha (8–13 Hz), especially increased alpha and theta bands, are thought to be a sign for sleepiness.[21,22] However, environmental CO_2 has been rarely considered a source of the factors causing physiological artifacts in most previous studies,[23–25] even though the low concentration of CO_2 could affect the physiological parameters, including EEG signals.[15,26] Recently, Snow et al. have attempted to analyze EEG signals as an objective indication of sleepiness, but their report still showed a discrepancy in the relationship between sleepiness and CO_2.[27] In their study, "participants who had slept less the previous night appeared more susceptible to becoming sleepier as a result of the increased CO_2," but no significant correlation between the levels of sleepiness (self-reported sleepiness) and CO_2 exposure was found, although the significant correlations between hours of sleep in the previous night and EEG signals were observed.[27]

Collectively, the relationship between CO_2 concentration and daytime sleepiness induction or EEG signals is still controversial.

Practical Implication

1. Our study combining Bayesian and conventional statistics provides a practical procedure to measure the degree of the effect of CO_2 exposure on daytime sleepiness and EEG signals.
2. The environmental CO_2 level should be considered in future studies using EEG measurements because EEG signals could be sensitive to environmental CO_2 levels.
3. Our combinational approach would enable researchers a more flexible and reasonable interpretation even if there is no statistically significant difference in the classical statistical analysis.

Therefore, this study aimed to analyze the CO_2 exposure effects on daytime sleepiness and EEG signal in a well-regulated environment. We also used a combined analysis using classical frequentist and Bayesian statistics to compensate for each other for a few reasons. Since subjective sleepiness could highly depend on the mental and physiological conditions of the participants resulting in a considerable variation among participants, it is often difficult to estimate an appropriate sample size required for classical statistics in advance. Bayesian statistics allows to inclusion of additional data as Bayesian updating, which is usually restricted or not permitted in classical statistics. While the classical statistical approach often needs a relatively large sample size to obtain enough statistical power if the data show a considerable variation among individuals, Bayesian statistics accept a relatively small sample size.[28,29] Most importantly, classical statistics give clear criteria by determining a threshold of the *p*-value ($p < 0.05$ is generally used), but it does not tell confidence of the obtained result. However, the Bayesian statistics would give us a certain degree of confidence and insight on the *p*-values by the classical analysis even if it indicated no significance in the results because the Bayesian statistics uses Bayes' factor, odds of confidence for the alternative hypothesis instead of the *p*-value.[30]

Advantages of our combinational approach are as follows: (1) Levels of significance and confidence in the null- and alternative hypotheses could be obtained simultaneously, allowing a more flexible interpretation. (2) Bayesian analysis would provide the effect size with credible intervals, estimating a range of effect size. By contrast, the classical procedure could give a sole value of effect size. (3) Bayesian analysis could provide a level of credibility to the classical frequentist analysis, while the classical analysis could give the other a clear criterion or standard.

In the present study, subjective sleepiness was measured by the KSS-J score with EEG recording during CO_2 exposure at different concentrations. Our result suggested that the EEG recording may not be suitable for the detection of objective sleepiness induced by CO_2 exposure because the EEG signal is highly sensitive to the level of environmental CO_2 concentration. Our combinational approach would also provide a solution to judge "confidence" in obtained

results. The study presented here would provide a helpful guide for researchers to revisit whether EEG is applicable as a judgment indicator of objective sleepiness.

2 | METHODS

2.1 | Participants and ethical approval

The sample size was determined according to a previous study by Vehviläinen et al.[16] using G*Power 3.1.9,[31] assuming a type I error of 0.05 and power of 0.80. In the study, they used a similar study design, in which each participant was exposed to a "Ventilated room" and "Non-ventilated room" (i.e., the conditions of CO_2 corresponding to "Normal (C)" and "CO_2 (Moderately High (MH))" in this study) and the subjective sleepiness was measured repeatedly by KSS. The sample size in the present study was calculated as 10 using the number of groups = 2 (C vs. MH) and the number of measurements = 7 (0–60 min) and assuming a 10% drop-out rate. The 6-minute continuous exposure to high (H) CO_2 conditions was also included as a positive control to confirm the CO_2 effect on the physiological parameters. The study protocol was approved by the Research Ethics Committee of Tohoku University (Approval No. 2018-1-862), after signing informed consent. The exclusion criteria for the study participants were to have a history of sleep disorders, neurological, cardiovascular, respiratory, or other diseases. After inclusion, all participants were asked to avoid coffee (including caffeinated beverages), medication (including sleeping pills or melatonin), and alcohol for at least a week before the first visit and through the entire period of the experiment.

2.2 | Experimental procedures

In a randomized and counterbalanced crossover study, participants answered the Groningen Sleep Quality Scale (GSQS) questionnaire before the measurement. All measurements were performed in an isolated meeting room with the dimensions of 7.2 m × 5.9 m (floor area) × 2.5 m (high), in which the temperature and humidity were regulated by a conventional air conditioner. They were asked to sit on a chair in an airtight chamber of a rectangular plastic flame (190 × 90 × 90 cm) covered with transparent plastic films, set at the center of the meeting room (Figure 1A). The measurement started 10 min before CO_2 exposure. Real-time monitoring of temperature, humidity, and environmental CO_2 concentration was recorded during the experiment (Tables S1 and S2). The information related to the device utilized is as follows; a sensor (Testo 174 H—Temperature and humidity mini data logger, Testo SE & Co. KGaA, Lenzkirch, Germany) with a measurement range from −30°C to +70°C (measurement accuracy ±0.5°C) for temperature and the measurement range from 0% to 100% (measurement accuracy ±3%) for humidity was used. Noise and illuminance were recorded before and after the measurement. A CO_2 sensor (SENSEAIR S8 ALARM 5%, Sense air Co., Ltd. Tokyo, Japan) was placed underneath the seat board of the chair (40.5 cm height). The measurement range of CO_2 was between 0.04% and 5% volume, and measurement accuracy was ±200 ppm or ±10% of reading, and a response time of 2 min. The CO_2 gas (99.99% purity) was injected from a liquid CO_2 cylinder manually into the airtight chamber until the CO_2 concentration monitored at the seat level reached the target levels. The constant CO_2 concentration was maintained by temporarily opening the chamber whenever the CO_2 level exceeds the designated level. The experiment room was ventilated with a rate of 0.3 L/s per m^2. The CO_2 levels at face height (115 cm) were also confirmed in CO_2 exposure conditions (Supplementary Table 25). The CO_2 concentration at face height (mean ± standard deviation [SD]: 3981 ± 30 ppm; 95% confidence interval [CI]: 3964–3999 ppm) was similar to that at measurement standard (mean ± SD: 4204 ± 61 ppm; 95% CI: 4167–4240 ppm) in the MH CO_2 condition. In H CO_2 condition, CO_2 concentration (mean ± SD:35 417 ± 2136 ppm; 95% CI: 34 155–36 679 ppm) was 11% lower than that of the seat level CO_2 concentration (mean ± SD: 39 725 ± 979 ppm; 95% CI: 39 147–40 304 ppm).

The Japanese version of the KSS (KSS-J) questionnaire was used to measure subjective sleepiness. The physiological data, including heart rate (*HR*, 3 CH), blood pressure (*BP*, pre and post), peripheral oxygen saturation (SpO_2, finger clip on the non-dominant hand), respiration rate (*RR*), and end-tidal CO_2 ($EtCO_2$, nasal tube), was recorded by a bedside monitor (CSM-1000 Series Lifescope G, Nippon Electric Co., Ltd., Tokyo, Japan) (Table S3). Participants were exposed to three experimental conditions on different days in a randomized order. C and MH of CO_2 conditions, for 60 min, while H CO_2 condition consisted of 6 min of sustained exposure due to ethical regulations.

2.3 | Electroencephalography

Electroencephalogram signals were recorded using a portable digital 8-channel data recorder (Polymate Mini AP108, Miyuki Giken Co., Ltd. Tokyo, Japan). EEG electrodes were placed on the scalp according to the International 10/20 system using the left earlobe as the reference. Participants were instructed to sit on a chair and focus their attention on the cross sign in front of them inside the chamber to minimize artifacts derived from body movements in the EEG signal. Although we did not assess participants' comfort level during the EEG measurement, based on the feedback from the participants in the pilot study, no obvious discomfort sign was observed in the participants. Because the transition to sleep led to changes in EEG activity in the central[32] and posterior regions[33] of the brain, data from both left and right hemispheres' central (C3 and C4, respectively) and occipital (O1 and O2, respectively) regions were used for further analyses. Before data acquisition, all contact impedance between electrodes and scalp was kept below 5 kΩ. Although we used a sampling rate of 500 Hz, the recordings were down-sampled to 250 Hz for the simplicity of data processing using the EEGLAB toolbox of MATLAB (Mathworks, Inc., Natick, MA, USA).

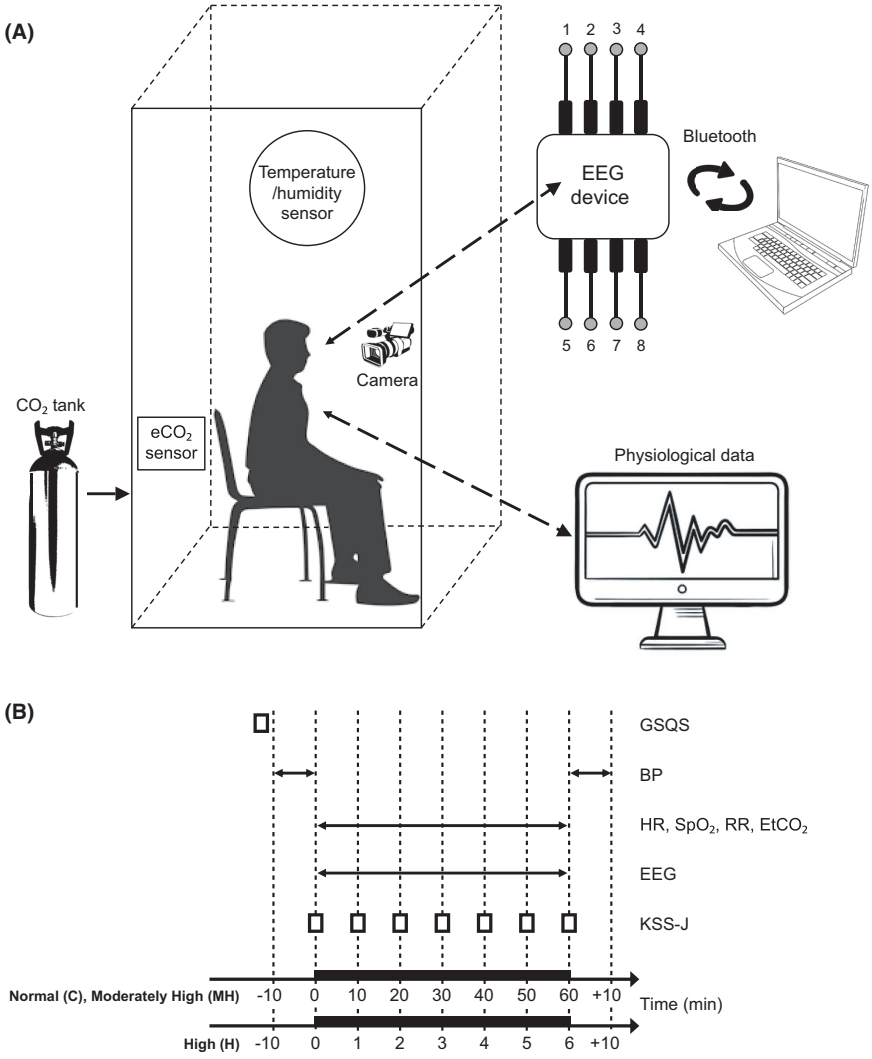

FIGURE 1 Schematic illustration of the experimental procedure. Panel A: Participants sat on a chair in an airtight chamber (190 × 90 × 90 cm). Physiological data were recorded during the experiment. Real-time temperature, humidity, environmental carbon dioxide concentration, illumination, and noise were also recorded. Panel B: Time scale for experimental procedures. GSQS, Groningen Sleep Quality Scale; HR, heart rate; BP, blood pressure; SpO_2, peripheral oxygen saturation; RR, respiratory rate; $EtCO_2$, end-tidal carbon dioxide; KSS-J, the Japanese version of the Karolinska sleepiness scale

After using a high-pass filter at 1 Hz, and a low-pass FIR filter at 45 Hz separately, powerline noise (50–100 Hz) was applied to attenuate electrical interference noise with a plugin (CleanLine, v.1.04). Finally, the Artifact Subspace Reconstruction toolbox[34] was used to remove artifacts from EEG data. To extract each frequency domain from the preprocessed EEG data for theta- (4–7 Hz) and alpha waves (8–13 Hz), the Darbeliai toolbox was used.

2.4 | Groningen sleep quality scale and Karolinska sleepiness scale

Because the previous night's sleep quality may affect daytime sleepiness, we needed to exclude the participant who had poor sleep quality the previous night and postpone the experiment. We assessed the previous night's sleep quality using the GSQS questionnaire. Since the results always indicated good sleep quality for each participant and condition, no experiment was rescheduled. Subjective sleepiness level was assessed using the KSS-J.[35] We used the original scale of KSS-J that included labels on every second step (1 = very alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy, but no effort to keep awake, and 9 = very sleepy, great effort keeping awake, fighting sleep). Participants reported their sleepiness level with gestures every 10 min during C and MH CO_2 conditions and each 1 min during H CO_2 conditions, minimizing the interruption of the participants' current state and motion artifacts in the EEG.

2.5 | Statistical analyses

The normality of all data was checked using the Shapiro-Wilk test. We considered two analysis approaches for this study. The JASP software (version 0.14.1) was used for both classical and Bayesian statistical analyses.[36] An essential part of Bayesian analysis is to define the prior distribution.[37] Therefore, in the present study, sample data from non-informative priors were assumed to control the posterior distribution. To investigate the change in alertness (KSS-J) over time during the exposure of the two CO_2 conditions, C and MH, a Bayesian repeated-measures ANOVA (BANOVA) were performed with a 95% credible interval estimated from the posterior distributions. The post-hoc tests were done with the time points (0–60 min) and conditions separately. Additionally, Bayesian paired t-test (Wilcoxon signed-rank) in a pre-exposure (C) x post-exposure (MH) was used to compare the means of KSS-J score following the main effect was determined. The

intensity of evidence (BF, Bayes' factor) in Bayesian's result is assessed via Jeffrey's criterion (see Figure S1), which allows us to quickly determine whether it supports or opposes the hypothesis.

To analyze the EEG signals (α, θ) in all four brain regions (C3, C4, O1, and O2) changes during different exposure conditions, the mixed-model analysis was performed using JMP Pro software (version 15.2.0, SAS Institute Inc., Cary, NC, USA). For comparison among three conditions, C, MH, and H, the EEG signals were analyzed every minute for 6 min. For comparison between C and MH CO_2 conditions, the EEG signals were analyzed every 10 min for 60 min. In the classical statistical results, we reported means and standard deviation (SD) for continuous variables with normal distribution, and the significance level was set at $p < 0.05$. Separated BANOVA was performed for the strength of evidence.

3 | RESULTS

Twelve healthy volunteers were recruited. One participant was excluded from the final analysis due to the high noise level of the EEG signals, and data from 11 participants (7 females; age = 26.6 ± 3.4; h eight = 161.3 ± 4.2; and weight = 52.5 ± 6.2) were analyzed.

3.1 | Physiological parameters

Table S3 summarizes the physiological parameters of participants in each condition group. We found no statistical differences between the groups in the scores of the questionnaires (GSQS and KSS-J) and physiological parameters before the experiment (all $p > 0.05$).

3.2 | CO_2 effect on subjective daytime sleepiness

Figure 2 shows the time course of daytime sleepiness development expressed as KSS-J scores under varying CO_2 conditions. It appears that the level of sleepiness developed earlier by CO_2 exposure (closed circle) from 0 to 20 min and became highest at 40 min. However, repeated measures ANOVA of KSS-J score showed a significant main effect of time ($F_{2.9,59} = 11.755$, $p = 0.001$, $\eta_p^2 = 0.37$) but no interaction between Times × Conditions ($F_{2.9,59} = 0.761$, $p = 0.52$, $\eta_p^2 = 0.04$). There was no significant difference in the KSS-J scores among CO_2 conditions ($F_{1,20} = 0.493$, $p = 0.491$, $\eta_p^2 = 0.02$). The post-hoc analysis revealed KSS-J score at 0 min was significantly different from those at 20- to 60-min time points. KSS-J score at 10 min was also significantly different from those at 30- to 60-min time points. There was no significant difference in the KSS-J scores among 20–60-min time points, suggesting that the level of daytime sleepiness developed after the start of the experiment and reached a plateau after 30-min independent of CO_2 conditions.

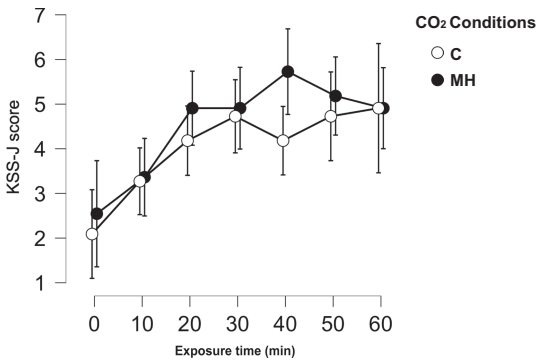

FIGURE 2 Time course of the KSS-J score in the different conditions. Black solid circle (●): Moderately High (MH) CO_2 condition, White hollow circle (○): Normal (C). Error bars indicate a 95% confidence interval

There was no significant difference in the KSS-J scores across CO_2 conditions when analyzed by the classical or conventional statistical analysis. Since sleepiness appeared to be developed and time-dependent, we applied the Bayesian approach to estimate the range of distribution probability. We also hypothesized that when the observed level exceeds or undermines the estimated range under varying CO_2 conditions, the CO_2 condition should impact the progression of daytime sleepiness. A BANOVA showed that time (duration of the experiment) was the primary factor related to daytime sleepiness development since the Bayes' factor for the time was the highest. The Bayes' factor for CO_2 condition was lower, suggesting that there is little evidence that the CO_2 exposure overall affected daytime sleepiness determined by KSS-J scores ($BF_{10} = 0.448$, Table S4). The effects analysis also revealed the higher contribution of time and a smaller effect of CO_2 condition, consistent with the result above ($BF_{inclsion} = 4.784 \times 10^7$, Table S5). The post-hoc comparison among different time points revealed that Bayes' factors at 0 and 10 min compared to the other time points were larger, suggesting the level of daytime sleepiness (KSS-J score) had shifted after 20 min (Table S6).

On the other hand, a post-hoc comparison of the CO_2 conditions only showed a small Bayes' factor value of less than 1, suggesting a weak contribution of CO_2 exposure to daytime sleepiness ($BF_{10,U} = 0.405$, Table 1). However, the probability distribution of normalized KSS-J score difference of control and CO_2 conditions showed a distinct difference with a slight overlap at the 40-min time point (Table 2 and Figure 3). Because the largest difference between conditions was observed at the 40 min in the BANOVA, the Bayesian paired *t*-test was applied to compare the mean KSS-J score at 40 min. In the Bayesian paired *t*-test, we used the alternative hypothesis with

TABLE 1 Post-hoc comparisons—CO_2 conditions

	Prior odds	Posterior odds	$BF_{10,U}$	Error%
MH/C	1.000	0.405	0.405	2.919e−6

Note: The posterior odds have been corrected for multiple testing by fixing to 0.5 the prior probability that the null hypothesis holds across all comparisons (Westfall, Johnson, & Utts, 1997). Individual comparisons are based on the default *t*-test with a Cauchy (0, $r = 1/\text{sqrt}(2)$) prior. The "U" in the Bayes factor denotes that it is uncorrected.
Abbreviations: C, Normal; MH, Moderately High.

TABLE 2 Model averaged posterior summary

Variable	Level	Mean	SD	95% credible interval	
				Lower	Upper
Intercept		4.256	0.364	3.508	4.982
Time points	0	−1.757	0.284	−2.328	−1.193
	10	−0.853	0.272	−1.403	−0.319
	20	0.257	0.267	−0.289	0.793
	30	0.507	0.268	−0.034	1.031
	40	0.629	0.271	0.084	1.171
	50	0.632	0.269	0.088	1.163
	60	0.585	0.270	0.043	1.124
CO_2 conditions	C	−0.160	0.289	−0.773	0.400
	MH	0.160	0.289	−0.416	0.765
Time points * CO_2 sonditions	0 & C	0.008	0.198	−0.388	0.411
	0 & MH	−0.008	0.198	−0.415	0.384
	10 & C	0.102	0.203	−0.302	0.526
	10 & MH	−0.102	0.203	−0.531	0.298
	20 & C	−0.059	0.202	−0.477	0.339
	20 & MH	0.059	0.202	−0.343	0.472
	30 & C	0.082	0.203	−0.321	0.492
	30 & MH	−0.082	0.203	−0.495	0.318
	40 & C	−0.274	0.217	−0.751	0.122
	40 & MH	0.274	0.217	−0.125	0.747
	50 & C	0.010	0.201	−0.401	0.415
	50 & MH	−0.010	0.201	−0.419	0.397
	60 & C	0.130	0.204	−0.266	0.561
	60 & MH	−0.130	0.204	−0.565	0.262

Abbreviations: C, Normal; MH, Moderately High.

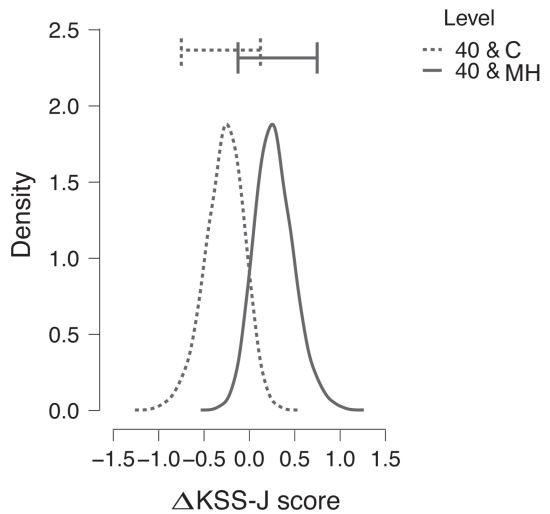

FIGURE 3 The model-averaged posterior distributions the interactions (40-min time point × 2 conditions). Distributions at 40-min time points showed a slight overlap. The horizontal error bars above each density represent 95% credible intervals around the median. Dotted line: Normal (C) and Solid line: Moderately High (MH) CO_2 condition

a default Cauchy prior for effect size δ that the mean KSS-J score in the MH CO_2 condition was larger than that of the C CO_2 condition at 40 min (one-sided Bayesian paired *t*-test). The alternative hypothesis (H_+) showed a larger BF (BF_{+0} = 2.884) than the null hypothesis (H_0), indicating that H_+ was 2.884 times more favorable than H_0 (Figure 4). The median of the effect size d in the posterior distribution was 0.558, with a 95% credible interval ranging from 0.065 to 1.245.

We also measured the KSS-J score as subjective daytime sleepiness at H CO_2 condition. Although a high KSS-J score was observed in the 6 min CO_2 exposure, we could not conclude the higher KSS-J score was caused by the CO_2 exposure because of no control condition. The result is shown in Figure S2.

3.3 | CO_2 effect on EEG signals

We analyzed the EEG in three conditions at different CO_2 concentrations. Although C and MH CO_2 conditions consisted of 60 min exposure, the first 6 min of each condition were used for further analysis to comprehensively represent the effect of different CO_2 levels on EEG signals (α, θ).

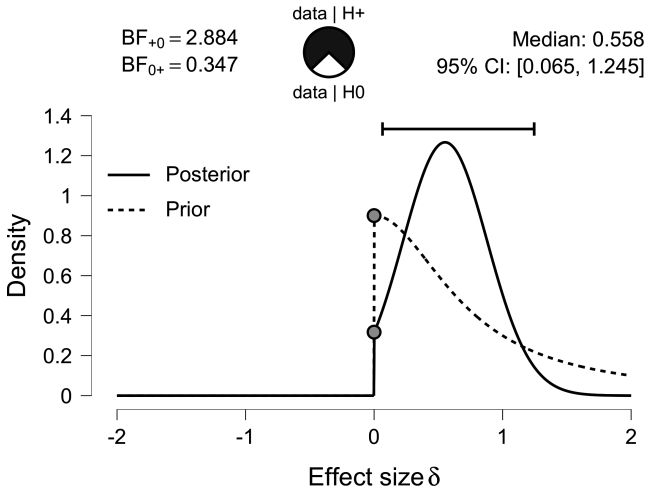

FIGURE 4 One-sided Bayesian paired t-test for analysis of two groups. The prior and posterior distribution plots for the analysis of group mean differences. The dashed line represents the prior distribution, and the solid line the posterior distribution. The posterior distribution was shifted to the right. Each of the distributions has a grey dot at the 0.0 effect size. If the dot on the prior distribution is higher than the one on the posterior distribution, the Bayes' factor supported the alternative hypothesis (MH CO_2 condition >C). The median effect size and 95% credible intervals are also shown. The pie chart represented the strength of evidence for the H_1 (alternative: MH CO_2 condition >C, red) and H_0 (null: MH CO_2 condition = C, white) hypotheses

3.4 | The analysis of EEG signals by mixed model

Figure 5 summarizes the alpha-band (α, 8–13 Hz) results in three conditions for each brain region and time point during the first 6 min. Mixed-model on condition, and time revealed a significant main effect of condition and time at C4 ($p = 0.0009$) and O2 ($p = 0.0021$) positions, while at C3 ($p = 0.0001$) and O1 ($p = 0.0125$) positions showed a significant main effect of condition only. However, there was no interaction between conditions × times in all four positions (all $p > 0.05$). The post-hoc comparison among different conditions revealed that all four brain regions (C3, C4, O1, and O2) showed a significant decrease in alpha power at the H CO_2 condition compared with MH CO_2 condition. In contrast, the C3, C4, and O1 regions also showed a significant decrease in H CO_2 condition compared with the C.

Figure 6 summarizes the theta-band (θ, 4–7 Hz) results in three conditions for each brain region during 6 min. Mixed-model on condition, and time revealed a significant main effect of condition and time at O1 ($p = 0.0029$) and O2 ($p = 0.0002$) positions, while at C3 ($p = 0.0001$) and C4 ($p = 0.0001$) positions showed a significant main effect of condition only. There was no interaction between conditions × times in all four positions (all $p > 0.05$). The post-hoc comparison among different conditions revealed that all four brain regions (C3, C4, O1, and O2) showed a significant increase in theta power at H CO_2 condition compared with the C, while the C3, C4, and O1 regions also showed a significant increase at the H CO_2 condition comparing with the MH CO_2 condition.

On the other hand, no significant differences were found in all four brain regions for alpha or theta power between the C and MH CO_2 conditions, suggesting that EEG activity might be affected by higher CO_2 exposure in a short duration of the first 6 min.

There was no significant difference between the C and MH CO_2 conditions in the EEG signals during the first 6 min exposure. For long-term exposure such as 60 min, however, a significant difference in a few regions in the alpha and theta power showed between the two conditions (Figures 7 and 8). A significant increase was observed in the alpha-band at O1 and O2 regions, while theta-band power was significantly decreased at C3, C4, and O1 regions in the MH CO_2 condition. In this two-condition analysis, the main effect was the CO_2 condition but not exposure time. This result contrasts with the result of daytime sleepiness, in which the exposure time was the sole effect on daytime sleepiness.

3.5 | BANOVA outcomes

To determine the strength of evidence for changes in EEG signals in each brain region in each condition, a BANOVA was performed. Overall, the results of the Bayesian analysis suggest greater strength of evidence that EEG signals were affected by conditions, but not time factors, which could support our results by the classical analysis (i.e., the main factor of condition).

The analysis of the alpha-band (α, 8–13 Hz) was summarized in Tables S7–S10. The Bayes' factor was significantly higher on C3 position ($BF_{10} = 772.347$) than on the other positions (C4, $BF_{10} = 9.23$; O1, $BF_{10} = 1.114$; and O2, $BF_{10} = 4.114$), suggesting there was stronger evidence that alpha power under the C3 position is more affected by exposure conditions. The post-hoc comparison revealed the strength of evidence that alpha power was affected across conditions. Specifically, At the C3 position, there was extreme evidence for the C vs. H CO_2 condition ($BF_{10, U} = 2709.495$). Strong evidence for MH vs H CO_2 condition ($BF_{10, U} = 17.21$) was found, suggesting greater alpha power differences between the C and H CO_2 conditions. At the C4 position, there was moderate evidence for the C vs. H CO_2 condition ($BF_{10, U} = 9.49$) and MH vs. H CO_2 condition ($BF_{10, U} = 8.097$) were found. At the O1 position, moreover, anecdotal evidence for the C vs. H CO_2 condition ($BF_{10, U} = 1.957$) was found, suggesting that the H CO_2 condition has little effect on alpha power at the O1 position. At the O2 position, there was moderate evidence for the MH vs. H CO_2 condition ($BF_{10, U} = 7.859$) was found (Tables S11–S14). In summary, extreme evidence for a large difference in alpha power was obtained at the C3 position between the C and H CO_2 conditions.

The analysis of theta-band (θ, 4–7 Hz) was summarized in Tables S15–S18. The Bayes' factor was extremely higher on C3 position ($BF_{10} = 79655.357$) than on the other positions (C4, $BF_{10} = 4953.74$; O1, $BF_{10} = 8.48$; O2, and $BF_{10} = 120.028$), suggesting there was extreme evidence that theta power under the C3 position is more affected by exposure conditions. The post-hoc comparison revealed the strength of evidence that theta power was affected across

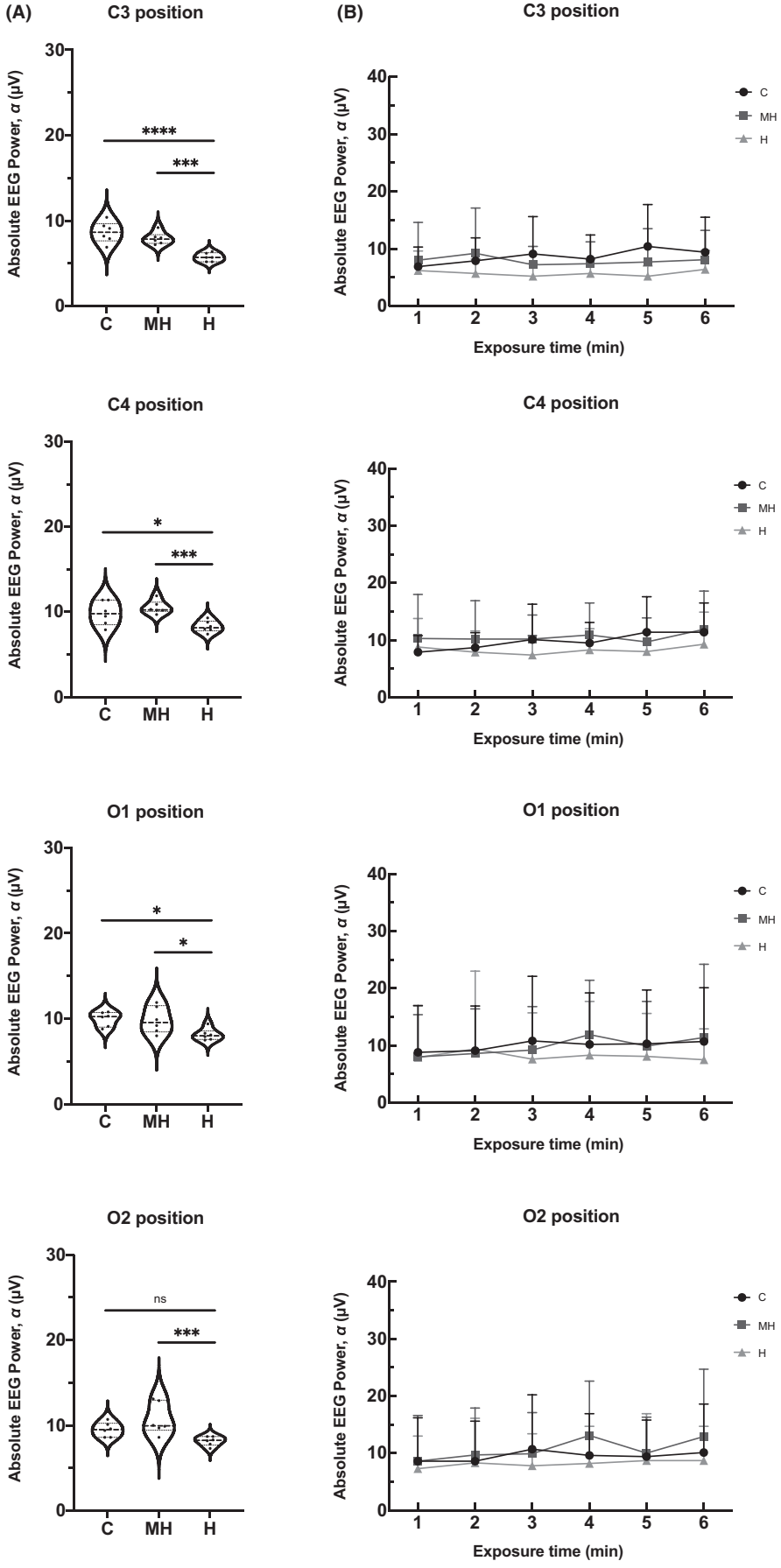

FIGURE 5 Effect of different levels of CO_2 exposure on the absolute power of alpha (α) at four positions (C3/4, Central; O1/2, Occipital). A. The violin plot with the median (Heavy dashed lines) with 25th and 75th (Light dashed lines) percentile. Each black dot represents the average EEG signal of all participants ($n = 11$) at each time point (6 min in total). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ and $^{****}p < 0.0001$. B. Time course of the average EEG signals in each condition. Error bars indicate standard deviation (SD)

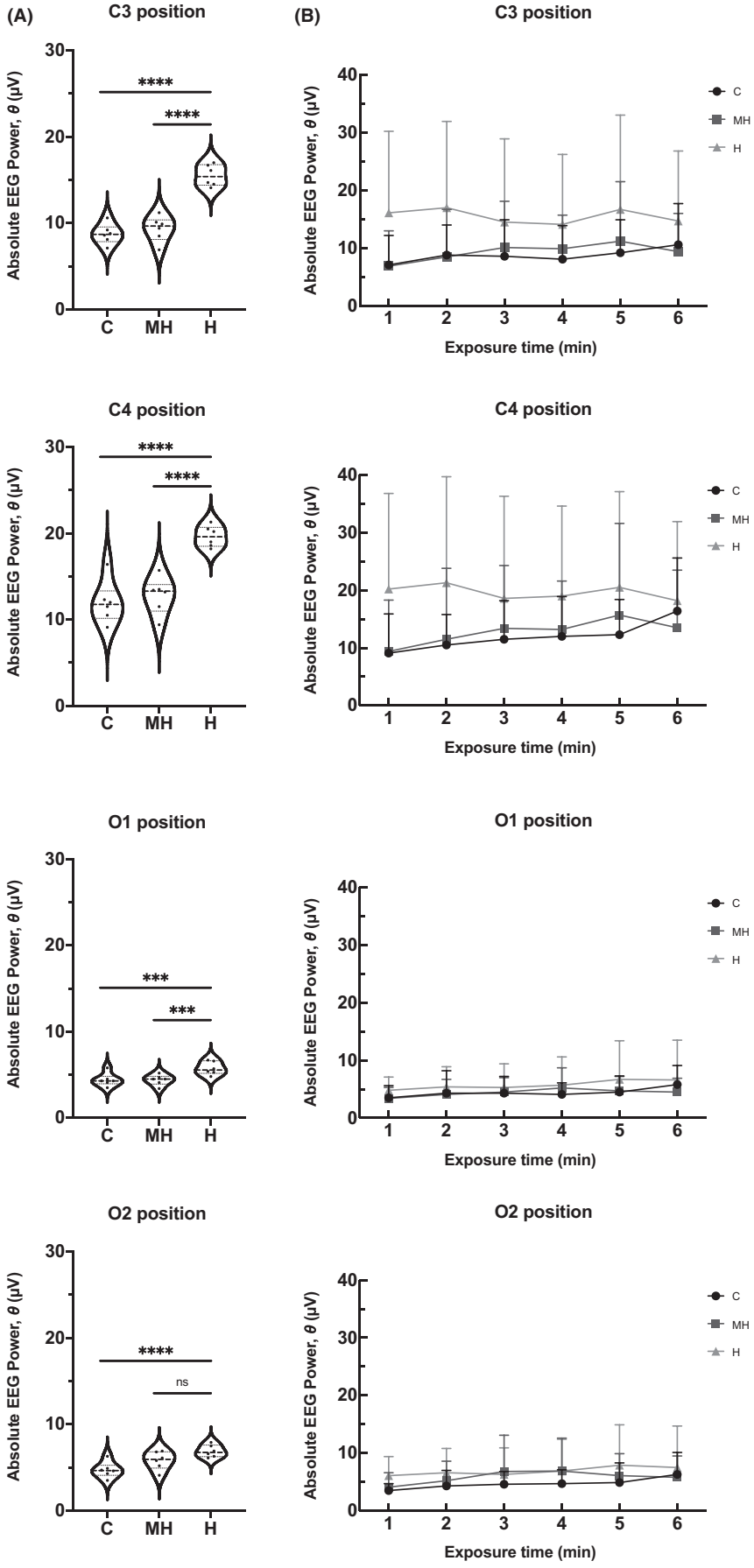

FIGURE 6 Effect of different levels of CO_2 exposure on the absolute power of theta (θ) at four positions (C3/4, Central; O1/2, Occipital). A. The violin plot with the median (Heavy dashed lines) with 25th and 75th (light dashed lines) percentile. Each black dot represents the average EEG signal of all participants ($n = 11$) at each time point (6 min in total). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$. B. Time course of the average EEG signals in each condition. Error bars indicate standard deviation (SD)

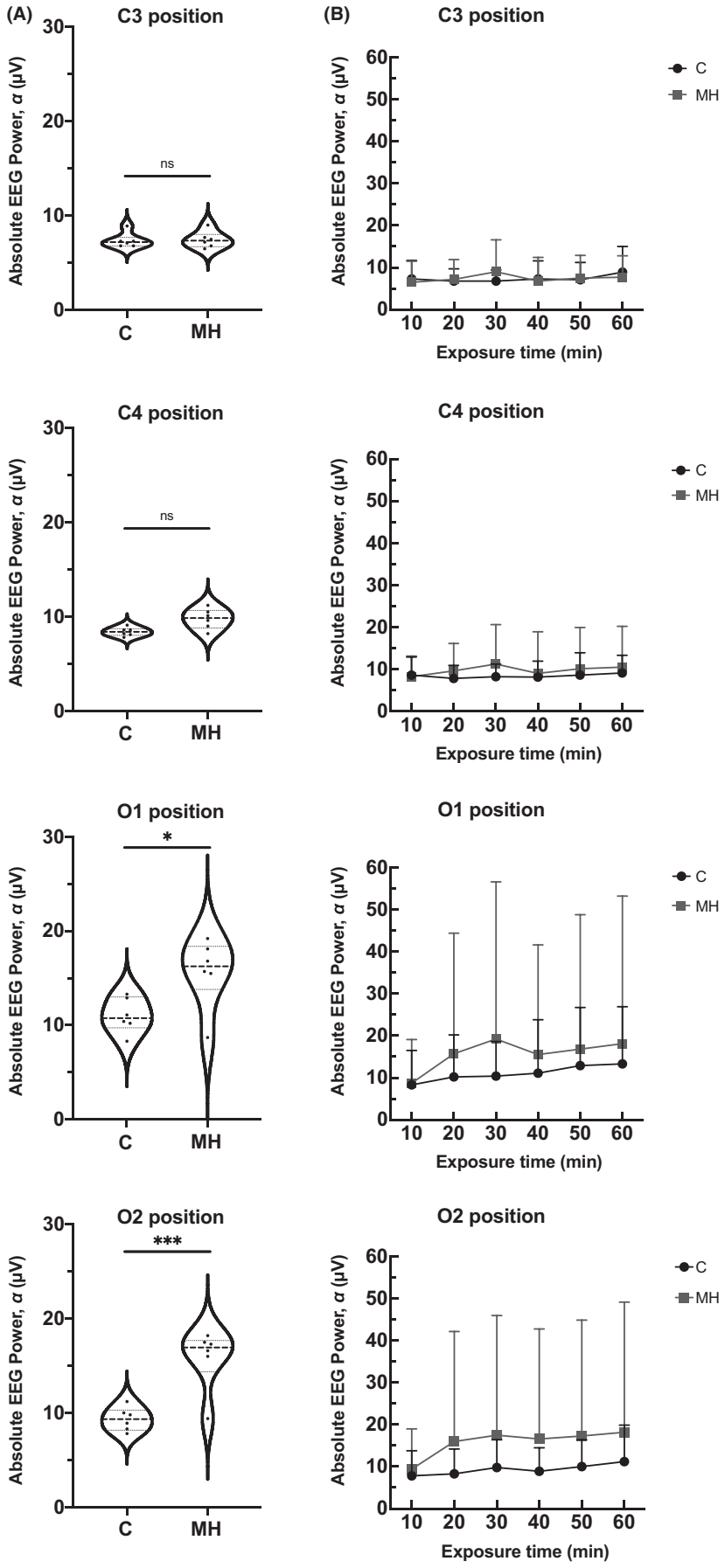

FIGURE 7 Effect of long CO_2 exposure on the absolute power of alpha (α) at four positions (C3/4, Central; O1/2, Occipital). The violin plot with the median (heavy dashed lines) with 25th and 75th (light dashed lines) percentile for the absolute power of alpha (A). Each black dot represents the average EEG signal of all subjects ($n = 11$). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ and $^{****}p < 0.0001$. Time course of the average EEG signals for the absolute power of alpha (B) in each condition. Error bars indicate standard deviation (SD)

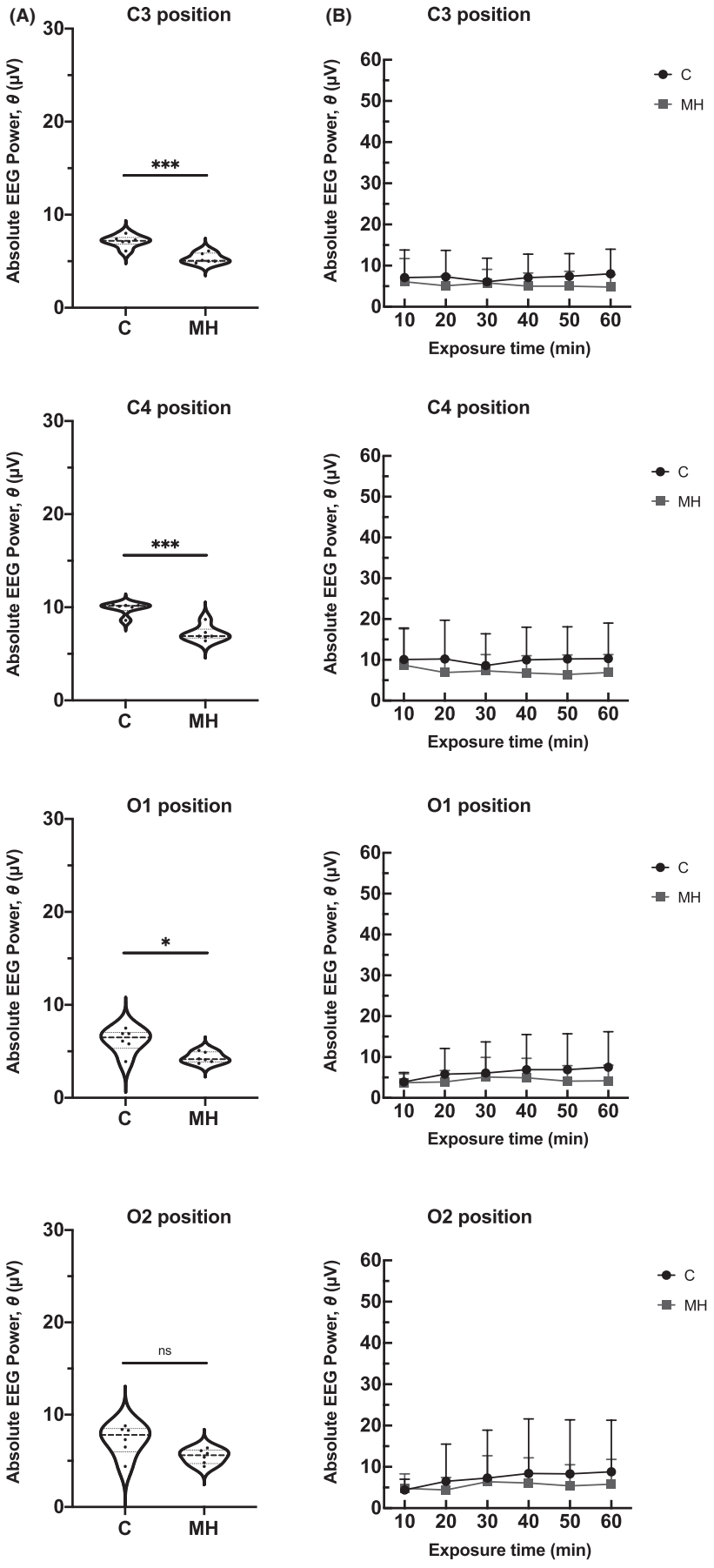

FIGURE 8 Effect of long CO_2 exposure on the absolute power of theta (θ) at four positions (C3/4, Central; O1/2, Occipital). The violin plot with the median (heavy dashed lines) with 25th and 75th (light dashed lines) percentile for the absolute power of theta (A). Each black dot represents the average EEG signal of all participants ($n = 11$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$. Time course of the average EEG signals for the absolute power of theta (B) in each condition. Error bars indicate standard deviation (SD)

conditions. Specifically, At the C3 position, there was extreme evidence for the C vs. H CO_2 condition ($BF_{10,U}$ = 279.654) and the MH vs. H CO_2 condition ($BF_{10,U}$ = 26728.333) were found, suggesting that greater differences in theta power between the MH and H CO_2 condition. At the C4 position, there was very strong evidence for the C vs. H CO_2 condition ($BF_{10,U}$ = 82.901), and extreme evidence for the MH vs. H CO_2 condition ($BF_{10,U}$ = 8956.561) were found. At the O1 position, moreover, there was moderate evidence for the C vs. H CO_2 condition ($BF_{10,U}$ = 3.356) and the MH vs. H CO_2 condition ($BF_{10,U}$ = 5.379) were found. At the O2 position, there was extreme evidence for the C and H CO_2 conditions ($BF_{10,U}$ = 507.283) found (Tables S19–S22). In summary, the greater differences in theta power at the C3 position between the MH and H CO_2 condition.

Intriguingly, the post-hoc comparison of the CO_2 conditions showed a small Bayes' factor ($BF_{10,U}$ = 2.933) in the O2 regions for theta power only between the C and MH CO_2 conditions, suggesting that EEG signal may be affected even at MH CO_2 condition (Table S22).

In the two-condition analysis, Bayesian analyses indicated anecdotal (alpha-band at O2) or moderate (theta-band at C3 and C4) evidence that CO_2 exposure affects EEG and strong ~very strong evidence that exposure time is not related to the EEG change (Table S23), which is consistent with the conclusion by the classical statistics.

4 | DISCUSSION

Our report here is the first study to apply a combinational approach to analyze the CO_2 effect on daytime sleepiness and EEG signals using classical and Bayesian statistics to compensate for each other. This novel approach combining the *p*-value and Bayes' factor will be more helpful to the characterization of the uncertainty in the data. Although we did not find statistical differences in participants' subjective sleepiness across CO_2 conditions by the repeated measures ANOVA, the results from the Bayesian statistics indicated anecdotal evidence that exposure to MH CO_2 condition of environmental CO_2 induced daytime sleepiness at 40 min, leading that further analysis will be required by focusing daytime sleepiness at 40 min in future studies.

Notably, EEG signals at some channels were affected by MH CO_2 conditions but not exposure time. Bayesian results were also consistent with results from classical statistics with different confidence levels. These findings suggest that the EEG signals may also be affected by a low concentration of CO_2 unrelated to sleepiness development during time. During CO_2 exposure thus, it is necessary to revisit the suitability of EEG-derived measures of objective sleepiness.

4.1 | CO_2 effect on daytime sleepiness

In the present study, a statistically significant difference was observed in the main effect of time but not CO_2 conditions in the classical repeated ANOVA consistent with two recent studies,[27,38] indicating that daytime sleepiness developed even under control normocapnic conditions. A previous study found that CO_2 at around 3000 ppm resulted in changes in heart rate variability with increased sleepiness.[16] In this previous study, however, it is worth noting that participants' maximum self-reported KSS score was 6, and the peak of sleepiness was observed about 2 h (10:00 am) and 5 h (1:00 pm) after the experiments had started (8–9 am). This may suggest that sleepiness might be influenced by the alertness rhythms (i.e., larger alertness fluctuations) and the circadian rhythms (i.e., "post-lunch dip").[39,40] Besides, unlike exposure to pure CO_2, participants' sleepiness in their experiments may have been affected by the confounding effects of bio effluents and other pollutants (e.g., volatile organic compounds) within the restricted ventilation room.[41]

On the other hand, the Bayesian paired *t*-test in our study revealed that exposure to MH CO_2 condition might induce daytime sleepiness at 40 min. This result suggests that CO_2 exposure may cause some degree of daytime sleepiness, but the time effect could mask the CO_2 impact. Tediousness or fatigue could be another reason to shade the sleepiness induction by CO_2 exposure since participants had to sit calmly on a chair with no allowance to do anything to avoid the artifact of EEG recordings, which possibly have led them into tediousness or fatigue even under the control condition. Therefore, it is expected that an improved experimental procedure excluding the effect of tediousness or fatigue factors may better demonstrate the effect of CO_2 exposure on the development of daytime sleepiness.

4.2 | CO_2 effect on EEG signals

The changes in EEG signals in specific frequency bands (e.g., theta- and alpha waves) are widely accepted as one of the valid indicators of objective sleepiness judgments.[42] However, whether the environmental CO_2 could affect the EEG signal as a "sleepiness indicator" during the CO_2 exposure remained unknown. We tested in this study the effects of two CO_2 conditions (MH and H) of CO_2 exposure on EEG signals by both classical and Bayesian statistics.

In our study, the EEG signals were significantly affected by CO_2 condition (C vs. MH) but not exposure time (Table S22), even though clear daytime sleepiness was induced depending on exposure time in the KSS-J score (Figure 2), suggesting that the significant change in EEG signals may not be related to daytime sleepiness. In the previous report, Snow et al.[43] attempted to use an EEG signal to measure objective sleepiness and suggested that "Individuals already lacking sleep may be more susceptible to the effects of CO_2 in enclosed spaces" at ~2700 ppm of CO_2 concentration. They have found no significant difference in EEG signals between normal and high CO_2 conditions by repeated measures ANOVA (4 EEG frequency × 4 electrode regions × 2 EEG recording sessions × 2 CO_2 conditions). By contrast, a recent study by Zhang et al. also reported that low levels of CO_2 exposure (approx. 3500 or 5000 ppm) lead to a significant

increase in EEG relative beta-power under 5000 ppm condition as well as physiological parameters such as breathing wave amplitude and heart rate variability during MATB (Multi-Attribute Task Battery) tasks.[44] Considering our results that exposure to MH CO_2 condition affected EEG signals without inducing subjective daytime sleepiness, the change of the relative beta-power might be related to CO_2 exposure but not arousal. In addition, the difference from Snow's report may be explained by the threshold in which CO_2 level affecting EEG signal could be above 4000 ppm. In conclusion, our study indicated that EEG measurement could not be a suitable way to estimate objective sleepiness during CO_2 exposure. EEG signal interpretation may result in unfavorable contamination unrelated to sleepiness.

A previous study has also indicated that the increased relative power of the beta band is associated with arousal and stress.[44] The mixed model analyzed the relative powers of all four frequency bands and found a significant main effect in both CO_2 concentration ($p = 0.0273$) and exposure time ($p = 0.0104$) on the relative delta power at position O2. Further analysis by mixed model, however, has found main significant effect of time ($p = 0.0051$) but neither condition ($p = 0.1404$) nor delta wave ($p = 0.1776$). The relative delta wave also did not correlate with the KKS-J score.

In the study, EEG responded in the opposite direction to the short exposure to H CO_2 condition and long exposure to MH CO_2 condition. Our results in the H CO_2 condition, decreased alpha power and increased theta power, were consistent with many previous studies. Exposure to over 50 000 ppm (5%) CO_2 caused significant EEG changes; reduced gamma, beta, and alpha powers[45–47] and increased power in the delta and theta powers.[25,48] These phenomena could reflect physiological effects of hypercapnia and hypoxia, respectively, or both.[48] It also needs to be noted that EEG changes might also be a result of elevated sympathetic nerve activity. Previous studies have demonstrated that exposure to elevated CO_2 caused an increase in heart rate and cardiac rhythm in humans and animals,[1,49,50] suggesting that CO_2 is associated with sympathetic activation.[51] This view was also consistent with the fact that the sympathetic nervous system contributes to the CO_2 response.[52] Indeed, heart rate was shown to be increased significantly by inhaling 5% CO_2.[53,54] We also observed that the heart rate increased significantly at the H CO_2 condition (71 ± 6 beats/min) compared to Normal (C, 68 ± 5 beats/min) and MH CO_2 condition (68 ± 5 beats/min) (Figure S3 and Table S26). On the contrary, there was no significant difference between C and MH CO_2 conditions during longer exposure (Figure S4 and Table S27). A human study by Shiraiwa et al, reported the theta power of EEG in the frontal area was positively linked ($r = 0.782$) with changes in sympathetic activity during craft activities[55] in a CO_2 non-adjusted condition. This finding is supported by previous research that the sympathetic activity depends on the strength of activation in the anterior cingulate cortex (ACC),[56] and ACC was also thought to play a critical role in theta wave generation and heart rate changes.[57,58] We assume the enhanced theta activation in H may be explained by transient sympathetic activation due to a physiological response to a short exposure to high CO_2 concentration, which was not relevant in a longer exposure to lower CO_2 concentration in MH. The number of EEG studies using moderately high CO_2 concentrations is limited.[27,44,59] Zhang et al. observed a trend of a global decrease in the relative theta power with no significance in the CO_2 exposure at 3500 or 5000 ppm,[44] which is also consistent with our results. Bullock et al. observed that spontaneous alpha activity was significantly affected by arterial CO_2: the alpha powers were elevated or declined during hypocapnia or hypercapnia conditions, respectively.[60] It has been reported that the CO_2 exposure at 5000 ppm significantly increased breathing wave amplitude.[44] In our study, we observed no significant increase in the respiratory rate by classical paired *t*-test ($p = 0.053$) but the Bayesian paired *t*-test indicated anecdotal evidence ($BF_{10} = 1.628$) of increase in the respiratory rate at MH CO_2 condition (Figures S5, S6 and Table S28). Considering above, MH CO_2 exposure might have caused mild hyperventilation, possibly avoiding the decrease in the alpha power. Altogether, the decrease in the alpha power at H may be as a general response of the brain to higher CO_2 exposure which was not present in our MH condition because of the suppressive effect of mild hyperventilation. Regarding the increase in theta power in H condition could be as result of sympathetic activation only present in H condition.

4.3 | Advantages of a combinational approach using classical and Bayesian analyses

Our combinational approach reported here would provide the following two advantages: (i) Although the classical statistical analysis didn't suggest any significance in the current data, Bayesian analysis could give us degrees of confidence as Bayes' factors, leading to a possible research target in the future study. (ii) Bayesian analysis can give confidence criteria to the *p*-values from the classical statistical analysis, solving *p*-threshold, multiple comparison, and *p*-hacking problems. Typically, $p < 0.05$ is used for a significant level in classical statistics, but there must be no clear reason. Multiple comparisons often require complicated statistical procedures, sometimes reducing detection power because of a compensated small *p*-value. The *p*-hacking is the unfavorable procedure to repeat statistical analysis until significant *p*-values are obtained. The Bayesian analysis could provide us with a second criterion, which avoids the problems mentioned above.

4.4 | Limitations and future recommendations

The present study has a few limitations. One of the most critical points is that daytime sleepiness could be influenced significantly even by slight sleep loss.[61] Although GSQS is considered a practical assessment for subjective sleep quality, the result does not always guarantee that participants had enough sleep time and quality due to incorrect self-assessment. Therefore, it would be strongly recommended that future studies consider using a clinical sleep quality testing device like polysomnography (PSG) to assess the objective

sleep quality of participants. The second point is that the subjective questionnaire was applied to the assessment of participants' sleepiness. For the current study, we used only the KSS-J to assess changes in subjective sleepiness during CO_2 exposure. However, subjective sleepiness perception may result from individual differences and misjudgments, for example, the KSS-J may not be valid for examination when local sleepiness is present in the brain.[46] In addition, although EEG is one of the effective methods to examine objective sleepiness, the CO_2 effect could contaminate the EEG signal, as indicated by our study; future studies should include the multiple sleep latency test, which is clinically used to measure daytime sleepiness in sleep disorder patients, to extend the readability of the results.

5 | CONCLUSIONS

Our study is the first report to apply the combinational approach using classical and Bayesian statistics to investigate the effect of CO_2 exposure on daytime sleepiness development and EEG signals to the best of our knowledge. Through comparison of classical and Bayesian statistical approaches, our results provided interesting insights into the understanding of how exposure time and CO_2 exposure induce daytime sleepiness. The Bayesian statistical analyses indicated anecdotal evidence that exposure to MH CO_2 condition induced daytime sleepiness at 40 min. We also showed that EEG signals could be affected by even a relatively low concentration of CO_2 (MH CO_2 condition).

Our combinational approach using classical and Bayesian statistics presented in this study would enable us to perform more flexible analyses of daytime sleepiness, which resulted in controversial conclusions due to large individual variations. Classical statistics frequently require an unfeasible sample size when the outcome variation is too large in the population, such as in the case of subjective daytime sleepiness. However, Bayesian statistics accepts a relatively small sample size and allows to include additional data as Bayesian updating, leading to gradual progress with a small sample number. Especially, our combinational approach would enable researchers more flexible and reasonable interpretation even if there is no statistically significant difference in the classical statistical analysis. We would recommend that future studies should consider using the Bayesian approach to further explore ambiguous data.

AUTHOR CONTRIBUTION

Ruinian Jin and Ryoichi Nagatomi conceptualized the study. Ruinian Jin, János Négyesi, and Daisuke Ito designed the experiments. Ruinian Jin collected data. Ruinian Jin and Hitoshi Inada curated and analyzed data. Ruinian Jin, Hitoshi Inada, and János Négyesi prepared the original draft. Ruinian Jin, Hitoshi Inada, János Négyesi, and Ryoichi Nagatomi reviewed and edited the manuscript. Ryoichi Nagatomi acquired funding and supervised the study. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

We greatly appreciate the rental and technical support of the CO_2 sensor from Asahi Kasei Microdevices Corporation.

CONFLICT OF INTEREST

All authors declare that they do not have any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ina.13055.

ETHICAL APPROVAL

No. 2018-1-862.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Jin RN, Inada H, Négyesi J, Ito D, Nagatomi R. Carbon dioxide effects on daytime sleepiness and EEG signal: A combinational approach using classical frequentist and Bayesian analyses. *Indoor Air*. 2022;32:e13055. doi:10.1111/ina.13055