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Effect of exposure to aldehyde C9 (nonanal) on the electroencephalographic activity of humans according to time series analysis

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ABSTRACT

Aldehyde C9 (nonanal) is naturally found in various essential oils and is mainly used for rose-like fragrances in perfumery products. This study aimed to evaluate the effect of exposure to aldehyde C9 odor on the electroencephalographic (EEG) activity of humans in relation to time series analysis. Healthy volunteers, 10 men and 10 women, were used for the EEG study. The EEG recording was done using eight-channel electrodes. The EEG measurement was conducted for a total of 30 seconds during the exposure to no odor and C9 odor, and recorded EEG data were examined for every second. In the results, only absolute mid-beta wave activity significantly changed at the left parietal region (8.8988–7.7534 μV^2) for a total of 30 seconds analysis time. However, exposure to C9 odor produced significant changes in absolute wave activity at specific times during time series analysis except for absolute gamma. Furthermore, C9 odor affects the prefrontal (Fp1 and Fp2) and frontal (F3 and F4) regions when compared with temporal (T3 and T4) and parietal (P3 and P4) regions. Based on the results, it could be concluded that C9 odor greatly alters the EEG activity of humans in terms of analysis time.

INTRODUCTION

In perfumery industries, aldehydes have been used for different fragrance notes. They are mainly derived from natural and anthropogenic sources. A number of aldehydes can also be synthesized chemically (O'Brien *et al*., 2005). In these, aldehydes C8–C13 are important bioactive fragrant compounds used in various perfumery products (Surburg and Panten, 2005). Aldehydes are important ingredients in the legendary perfume Chanel No. 5 and are mostly perceived as pleasant smells by humans. Among them, C9 aldehyde (nonanal) is widely used in perfumery products for its rose-like fragrance. In trace amounts, it adds floral notes to a broad range of fragrance types. Cinnamon, lemongrass, milkweed, citrus, and rose essential oils contain C9 (Omonov *et al*., 2014; Otienoburu *et al*., 2012; Park *et al*., 2020). Nonanal is an important signal volatile of tobacco plants which attracts oviposition in female moths, *Helicoverpa assulta* (Wang *et al*., 2020b). Moreover, nonanal is an important skin odorant of various animals such as birds and mammals in addition to humans (Haze *et al*., 2001). Recently, Kim *et al*. (2019a) found that aldehydes, nonanal (C9) and decanal (C10), exhibited markedly different electroencephalographic (EEG) activity according to nostril difference.

In aromatherapy, pleasant odors have been used to improve the psychophysiological functions of humans. Olfaction and emotion are highly interconnected (Hou *et al*., 2020). Odors are abundant in indoor air due to the release from room fresheners, cleaning solutions, insecticides, cosmetics, and scented candles (Bartsch *et al*., 2016; Wolkoff and Nielsen, 2017). In general, it is not easy to generalize that all pleasant odors produce positive psychophysiological effects on humans via inhalation. Functional changes in the brain induced by odor inhalation are highly linked

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to the alteration of electrical activity in neuronal cells through the olfactory system. Therefore, it is necessary to figure out the influence of fragrance inhalation on brain functions (Kutlu *et al*., 2008).

Brain waves, including delta, theta, alpha, beta, and gamma, are considered to have relationships with specific functions of the brain. Brain wave activities are measured using various electrophysiological techniques. Among them, EEG is a widely used technique to monitor changes in brain wave activity induced by odor inhalation (Iijima *et al*., 2009; Kim *et al*., 2018; Sowndhararajan and Kim, 2016). Previous studies have shown that the EEG activity of humans is greatly altered during exposure to odor molecules (Koomhin *et al*., 2020; MacDonald, 2015). The EEG technique is a noninvasive approach, and it does not require the active participation of subjects (Skoric *et al*., 2015).

In our previous study, aldehyde C9 odor exposure exhibited a significant change only for absolute mid-beta wave activity at the left parietal region (P3) via binasal inhalation when compared with no odor exposure (Kim *et al*., 2019a). However, previous studies have found that the EEG recording time for determining the influence of exposure to different odors can be varied at every second. In addition, EEG readings have been exhibited to reveal nonstationary behavior in various contexts. Hence, it is important to develop a method to analyze nonstationary data (Krystal *et al*., 1999; Sowndhararajan and Kim, 2016). Recently, Kim *et al*. (2019b) reported that aldehyde C10 (decanal) odor showed considerable variations in EEG power spectra values at a specific time interval and found that absolute waves significantly decreased during the first 13 seconds period. Time series analysis is an appropriate method to determine the nonstationary behavior of EEG data using evenly spaced time intervals to identify an exact pattern in EEG data (Gao *et al*., 2020; Wang *et al*., 2020). Therefore, this study aimed to evaluate the olfactory stimulation influence of aldehyde C9 fragrance on the EEG activity of humans with respect to analysis time.

MATERIALS AND METHODS

Materials

Nonanal [$CH_3(CH_2)_7CHO$] (CAS No. 124-19-6) was procured from Sigma (St. Louis, MO).

Subjects

This study was performed according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The Ethical Committee from Kangwon National University, Chuncheon, Republic of Korea (IRB No. KWNUIRB-2017-05-001-003), approved the EEG study protocol. A total of 20 healthy volunteers (10 men and 10 women) aged 20–30 years participated in this study. The participants were selected based on the protocol described by Kim *et al*. (2019b). The selection criteria for participants were being nonsmokers and right-handed. In this study, participants with olfactory diseases or abused drugs were not included. Furthermore, participants who were unable to distinguish the well-known aroma types were excluded from this study. The participants were not allowed to consume alcohol or any medications from 2 days prior to the experiment. Informed consent was received from all the participants before they participated in the EEG study.

Experimental design

A single-group pretest and posttest experimental design was used in the study (20 participants). The participants were told that the purpose of the study was to evaluate the effect of inhalation of an odor molecule on EEG activity. During EEG recordings, the participants were asked to sit quietly, keep their eyes closed, and breathe normally under awakening conditions.

EEG recordings and fragrance administration

A QEEG-8 system was used to record the EEG readings (LXE3208, LAXTHA Inc., Daejeon, Republic of Korea). The EEG data were recorded from eight-channel electrodes according to the International 10–20 System. The EEG recording conditions and administration of odor were followed according to the method described previously by Kim *et al*. (2019b).

Data analysis

The mean power spectra values were calculated for 25 EEG indicators, and the values were expressed as microvolts squared (μV^2) (Seo *et al*., 2016). We analyzed the EEG data for every second by splitting the total 30 seconds EEG data (from 5 to 35 seconds). SPSS 23 (SPSS, Inc., Chicago, IL) was used for statistical analysis (Kim *et al*., 2019b).

RESULTS

In this study, we investigated the olfactory stimulation effect of exposure to undiluted aldehyde C9 on the EEG activity of humans. The EEG power spectra changes between no odor exposure and C9 odor exposure were examined from eight electrode sites in the prefrontal, frontal, temporal, and parietal regions. Primarily, EEG power spectrum changes were analyzed between no odor exposure and C9 odor exposure for a total of 30 seconds, and then we split the EEG data into 30 separate seconds and analyzed changes during no odor and C9 odor for every second. In the results, we presented significant changes ($p < 0.05$) in absolute brain wave activity in relation to time series analysis. In a total of 30 seconds of EEG analysis time, a significant decrease in absolute mid beta (AMB) wave activity at the P3 site was observed due to the exposure to C9 odor (8.8988–7.7534 μV^2). The significant change in AMB wave activity due to the exposure to C9 odor is presented in Table 1. Figure 1 shows the topographical mapping of AMB power spectrum change during the exposure to C9 odor when compared to that of no odor exposure.

Table 2 shows the significant changes ($p < 0.05$) of absolute power spectra values between no odor exposure and C9 odor exposure based on different analysis times. In time series analysis, C9 odor exposure exhibited significant changes in all absolute waves with the exception of absolute gamma at a specific time interval when compared to that of no odor exposure. However, no significant change in absolute wave activity was observed during 6~8, 11~13, 15~16, 18~23, 28~30, and 33~35 seconds during the exposure to C9 odor. The absolute power spectra such as alpha, beta, slow alpha, low beta, and high beta activities markedly decreased in the first 6-second period. Significant differences in absolute alpha (AA), absolute slow alpha (ASA),

Table 1. Significant changes of EEG power spectrum values during no odor and C9 odor exposures in total 30 seconds.

EEG indices	Site	No odor exposure (μV^2)	C9 odor exposure (μV^2)	*t*-test	*p* value*
AMB	P3	8.8988 ± 1.360	7.7534 ± 1.387	2.119	0.047

beta; P3, left parietal.
Number of subjects – 20.
*Significant difference ($p < 0.05$).

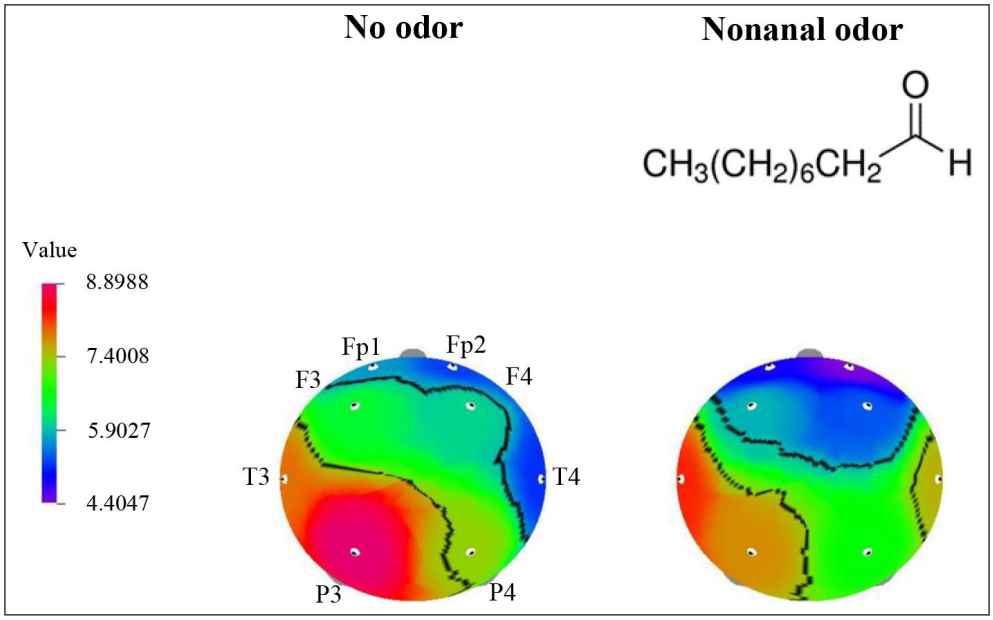


Figure 1. The topographical mapping of AMB activity due to no odor and C9 odor exposure in total 30 seconds recording time.

and AMB wave activities were observed during different analysis times (Figs. 2 and 3).

The EEG data analysis revealed that absolute theta (AT) wave activity significantly increased during 8~9 seconds (16.5963–26.6732 μV^2 at T3 and 16.0215–27.5788 μV^2 at Fp2) and 25~26 seconds (19.7777–31.4728 μV^2 at F3; 17.3160–28.1636 μV^2 at F4; and 9.3947–14.3709 μV^2 at T4) and decreased during 26~27 seconds (26.0982–16.7358 μV^2 at T3) and 32~33 seconds (17.3059–14.1615 μV^2 at T4) during the exposure to C9 odor (Fig. 4). Additionally, significant decreases in absolute beta (AB), low beta, mid beta, and high beta were observed at certain times due to the exposure of C9. AB wave activity significantly decreased during 5~6 seconds (P4), 16~17 seconds (Fp1), and 27~28 seconds (Fp1, Fp2, F3, P3, and P4), and absolute low beta (ALB) wave significantly decreased during 5~6, 14~15, 30~31, and 31~32 seconds (Figs. 5 and 6). Absolute high beta (AHB) also significantly decreased during 27~88 seconds during C9 odor inhalation when compared to that of no odor inhalation. Furthermore, AMB wave activity significantly decreased during 5~6, 9~10, 16~17, 27~28, and 30~31 seconds.

A significant decrease in AA and ASA activity was observed at similar analysis times during 5~6, 9~10, and 10~11 seconds and increased during 13~14 seconds. However, AA significantly increased during 17~18 seconds, while ASA significantly decreased at the same period during C9 odor inhalation. On the other hand, absolute fast alpha (AFA) significantly increased during 23~24 seconds and decreased during 24~26 seconds. In particular, AA wave significantly decreased at the Fp1, Fp2, F3, F4, and T4 regions during the period of 5~6 seconds. However, no significant change in AA and ASA activity was observed during the last 17 seconds of time series analysis (Table 2). Furthermore, C9 odor had no effect on absolute gamma wave activity. In the EEG time series analysis, significant changes were observed in more EEG indicators such as AA, AB, ASA, ALB, and AMB during the first second of analysis time (5~6 seconds) than in other periods. Furthermore, the F4 region was highly sensitive to C9 odor, followed by the Fp1, F3, T4, and P3 regions. According to time series analysis, exposure to C9 odor exhibited nonstationary EEG power spectra activity.

DISCUSSION

It is well known that odor molecules affect brain wave activities, thereby producing changes in the psychophysiological functions of humans. Brain wave modifications can be effectively measured by EEG (Angelucci *et al*., 2014; Ko *et al*., 2021). In the present study, only AMB wave activity significantly changed in the left parietal region during the exposure to C9 odor in a total of 30 seconds analysis time. On the other hand, all absolute wave activities significantly changed in different regions at different time points due to the exposure to C9 odor. However, no significant

Table 2. Significant changes of EEG power spectrum values at different time series during no odor and C9 odor exposures.

Time	EEG indices	Site	No odor exposure (μV^2)	C9 odor exposure (μV^2)	*t*-test	*p* value*
5~6	AMB	F4	6.8829 ± 0.816	4.6254 ± 0.810	3.047	0.007
	ALB	T4	6.9378 ± 1.194	3.7841 ± 0.559	2.987	0.008
		P3	18.0956 ± 3.907	8.7671 ± 1.078	2.957	0.008
		P4	12.1528 ± 2.530	6.1390 ± 0.685	2.828	0.011
		F3	10.5687 ± 1.895	7.0505 ± 1.553	2.719	0.014
		F4	9.0428 ± 1.694	6.0722 ± 1.393	2.577	0.018
	AA	T4	30.4753 ± 5.354	23.0236 ± 4.025	2.809	0.011
		F4	75.1153 ± 15.604	55.6016 ± 9.951	2.762	0.012
		F3	77.6444 ± 15.964	57.6285 ± 10.614	2.504	0.022
		Fp1	59.5069 ± 11.483	45.0147 ± 7.885	2.408	0.026
		Fp2	56.9187 ± 11.685	44.2258 ± 7.440	2.201	0.040
	ASA	T4	26.1319 ± 5.053	20.5602 ± 3.923	2.528	0.020
		F4	68.6475 ± 14.851	51.2244 ± 9.325	2.497	0.022
		F3	70.2707 ± 15.034	52.5769 ± 9.994	2.218	0.039
	AB	P4	20.7927 ± 2.211	16.2998 ± 2.450	2.142	0.045
8~9	AT	T3	16.5963 ± 2.546	26.6732 ± 6.321	−2.317	0.032
		Fp2	16.0215 ± 2.385	27.5788 ± 6.460	−2.207	0.040
9~10	AMB	P3	12.3057 ± 2.209	8.8152 ± 1.651	2.343	0.030
	ASA	Fp2	58.8280 ± 11.266	37.7272 ± 7.353	2.305	0.033
		F4	83.3203 ± 16.378	49.6211 ± 10.526	2.789	0.012
		T4	38.7050 ± 8.404	20.6957 ± 4.880	3.091	0.006
	AA	Fp2	62.7258 ± 11.499	41.5667 ± 7.729	2.303	0.033
		T4	41.0357 ± 8.492	24.3771 ± 5.393	2.914	0.009
		F4	88.1018 ± 16.713	54.1840 ± 10.967	2.811	0.011
10~11	AA	P3	83.3434 ± 16.086	61.8932 ± 14.391	2.641	0.016
	ASA	P3	76.1023 ± 15.431	55.8227 ± 13.968	2.478	0.023
13~14	AA	Fp1	39.4312 ± 7.289	59.3705 ± 12.356	−2.377	0.028
		Fp2	37.4491 ± 7.491	58.2389 ± 12.229	−2.492	0.022
		F3	46.1690 ± 8.679	71.9860 ± 15.827	−2.461	0.024
		F4	47.0134 ± 9.999	74.9361 ± 18.065	−2.356	0.029
	ASA	Fp1	35.5323 ± 6.903	54.2947 ± 12.201	−2.268	0.035
		Fp2	34.0981 ± 7.160	52.9446 ± 12.060	−2.323	0.031
		F3	41.9831 ± 8.387	65.3893 ± 15.413	−2.330	0.031
		F4	42.7714 ± 9.466	68.6313 ± 17.456	−2.316	0.032
14~15	ALB	T4	6.4774 ± 1.261	4.3465 ± 0.734	2.300	0.033
16~17	AMB	F4	8.3753 ± 1.068	6.7784 ± 1.074	3.007	0.007
		Fp1	8.3211 ± 0.847	6.0057 ± 0.927	2.878	0.010
	AB	Fp1	20.3180 ± 2.517	16.7795 ± 2.152	2.126	0.047
17~18	ASA	P3	61.4318 ± 12.270	45.3297 ± 11.424	2.406	0.026
	AA	P3	77.0064 ± 13.422	52.4709 ± 12.374	2.382	0.028
23~24	AFA	T4	4.8621 ± 0.784	7.9614 ± 1.831	−2.100	0.049
24~25	AFA	T3	10.7125 ± 1.681	6.9772 ± 1.235	2.504	0.022
25~26	AFA	F3	18.1766 ± 3.536	10.7904 ± 2.605	2.820	0.011
	AT	F3	19.7777 ± 2.752	31.4728 ± 5.645	−2.283	0.034
		F4	17.3160 ± 2.737	28.1636 ± 4.914	−2.287	0.034
		T4	9.3947 ± 1.361	14.3709 ± 3.120	−2.128	0.047

Continued

Time	EEG indices	Site	No odor exposure (μV²)	C9 odor exposure (μV²)	*t*-test	*p* value*
26~27	AT	T3	26.0892 ± 5.136	16.7358 ± 2.557	2.104	0.049
27-28	AB	Fp1	20.7079 ± 2.673	14.3626 ± 1.590	2.789	0.012
		Fp2	18.1651 ± 2.586	13.3344 ± 1.396	2.121	0.047
		F3	23.1439 ± 3.385	16.633 ± 2.330	2.558	0.019
		P3	31.1584 ± 5.199	20.0701 ± 3.562	4.006	0.001
		P4	23.8327 ± 3.266	16.7633 ± 2.477	3.014	0.007
	AMB	Fp1	8.5357 ± 1.078	5.8653 ± 0.889	2.769	0.012
		F3	9.4970 ± 1.665	6.7826 ± 1.501	2.225	0.038
		P3	14.8663 ± 3.439	9.1289 ± 2.317	3.319	0.004
		P4	11.2474 ± 2.016	7.4276 ± 1.807	2.809	0.011
	AHB	P3	12.2637 ± 1.744	7.4964 ± 1.075	3.384	0.003
30~31	ALB	T3	9.9809 ± 1.868	5.4615 ± 0.805	2.575	0.019
	AMB	Fp1	8.3108 ± 1.254	5.9703 ± 0.794	2.386	0.028
31~32	ALB	Fp1	9.2405 ± 2.176	6.4948 ± 1.883	3.362	0.003
		Fp2	9.1763 ± 2.301	6.4955 ± 1.740	2.661	0.015
		T3	9.1958 ± 1.921	6.1192 ± 1.782	2.575	0.019
32~33	AT	T4	17.3059 ± 3.564	14.1615 ± 2.910	2.193	0.041

AT, absolute theta; AA, absolute alpha; AB, absolute beta; ASA, absolute slow alpha; AFA, absolute fast alpha; ALB, absolute low beta; AMB, absolute mid beta; AHB, absolute high beta; Fp1, left prefrontal; Fp2, right prefrontal; F3, left frontal; F4, right frontal; T3, left temporal; T4, right temporal; P3, left parietal; P4, right parietal.
Number of subjects – 20.
*Significant difference ($p < 0.05$).

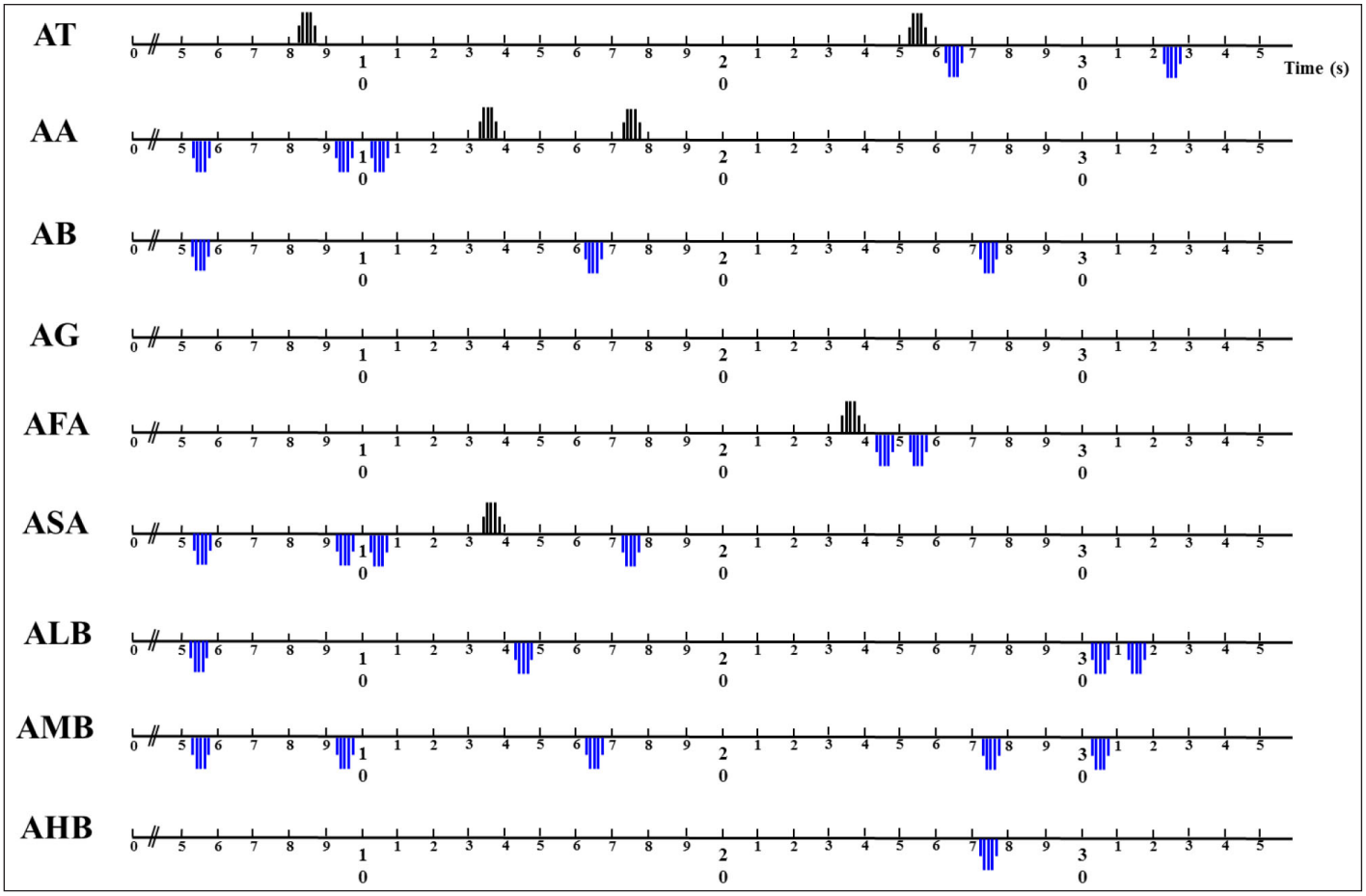


Figure 2. Significant increase and decrease in absolute brain waves due to the inhalation of C9 odor in relation to analysis time.

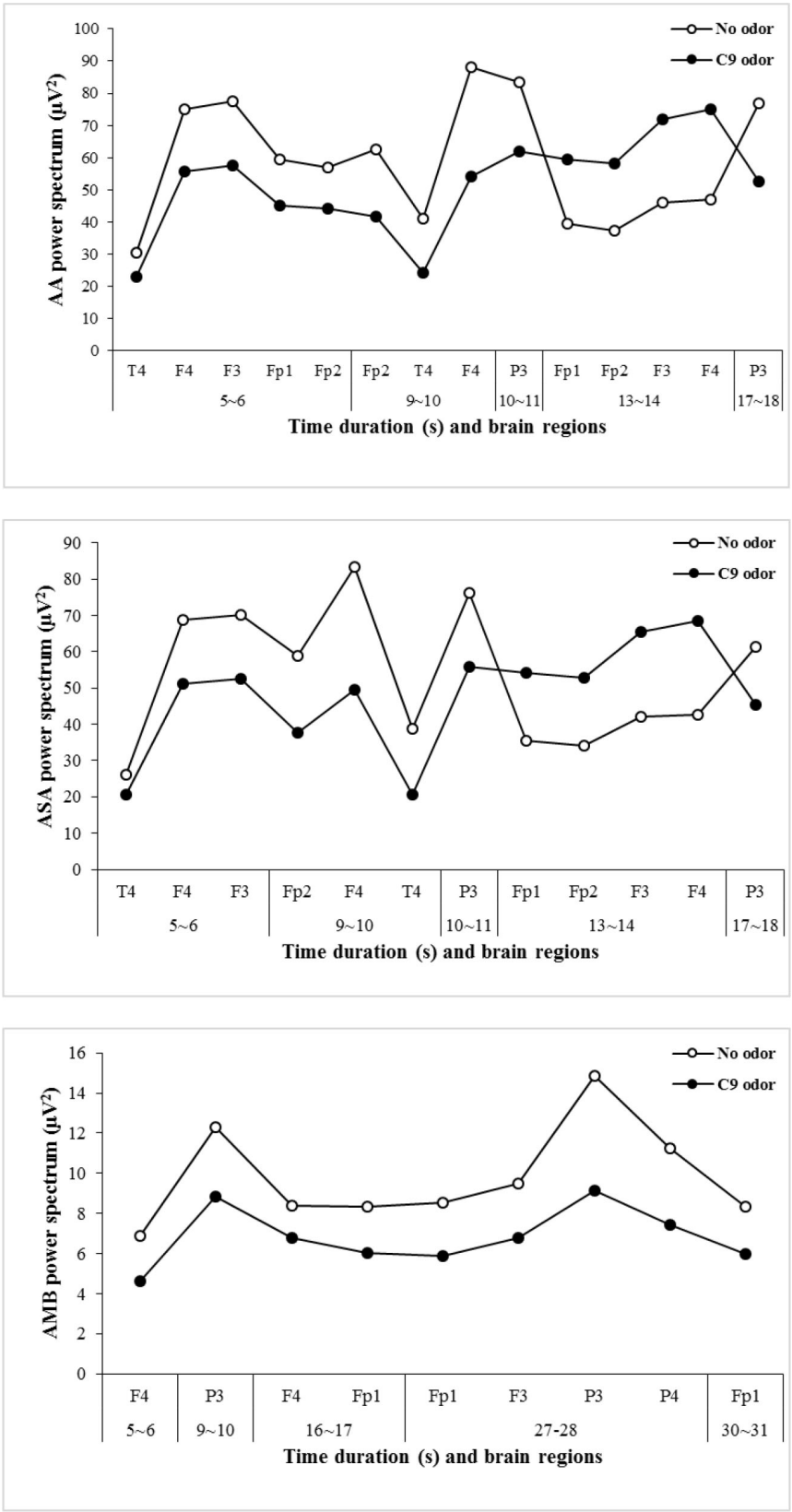


Figure 3. Significant changes in AA, AFA, and AMB waves due to the inhalation of C9 odor in relation to analysis time.

change in AG wave activity was observed during the exposure to C9 odor (Table 2).

The results revealed that the changes mainly occurred in AA, ASA, and AMB wave activities when compared with other brain waves (Fig. 3). In general, the neuronal electrical activity of the brain produces time-dependent potential alterations on the scalp. Masago *et al*. (2000) found that lavender, eugenol, and chamomile odors produced a significant decrease in alpha 1 wave

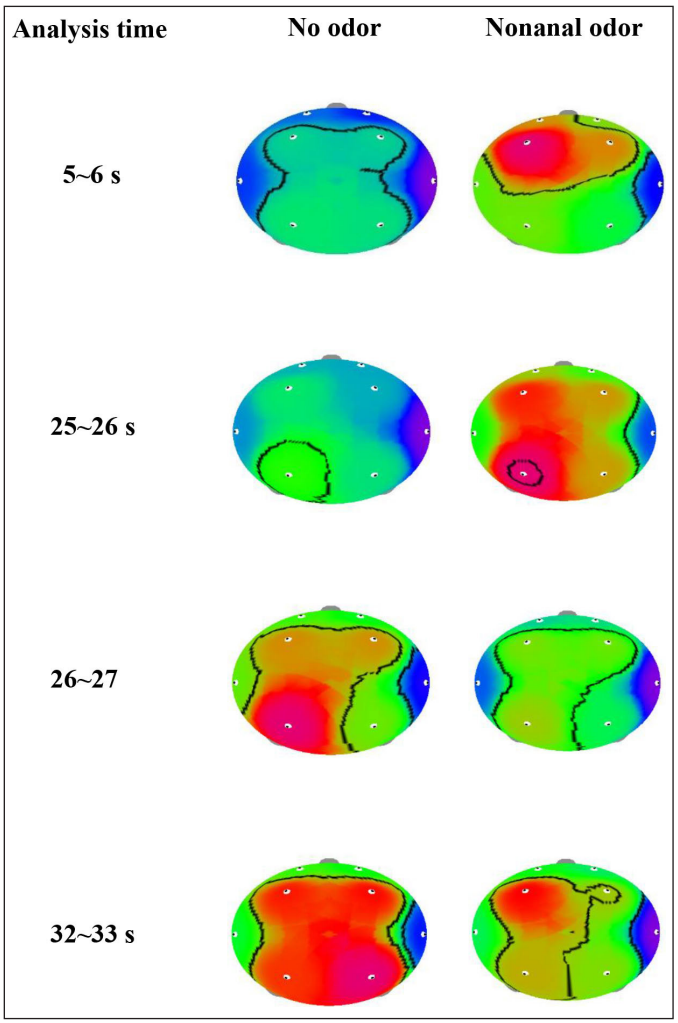


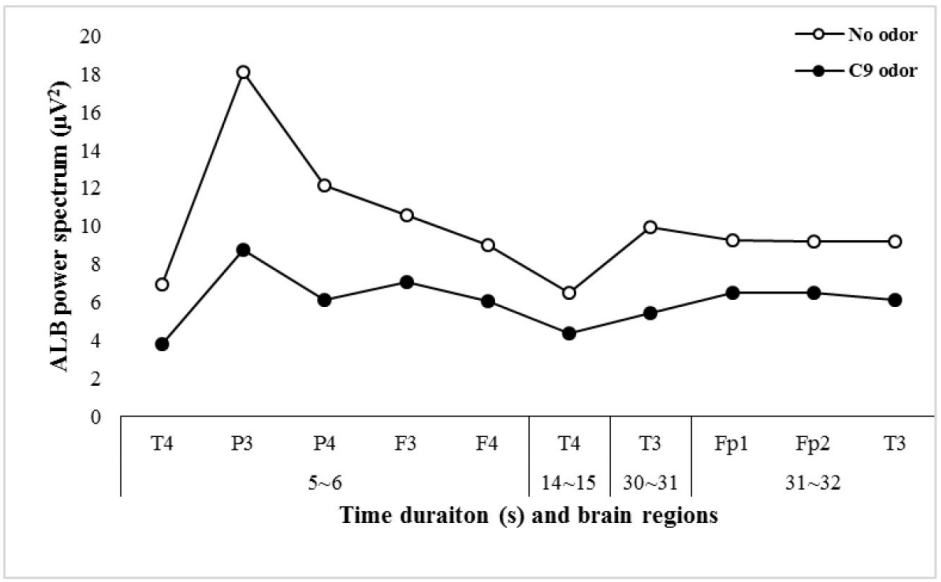
Figure 4. The topographical mapping of AT activity due to the inhalation of C9 odor in relation to analysis time.

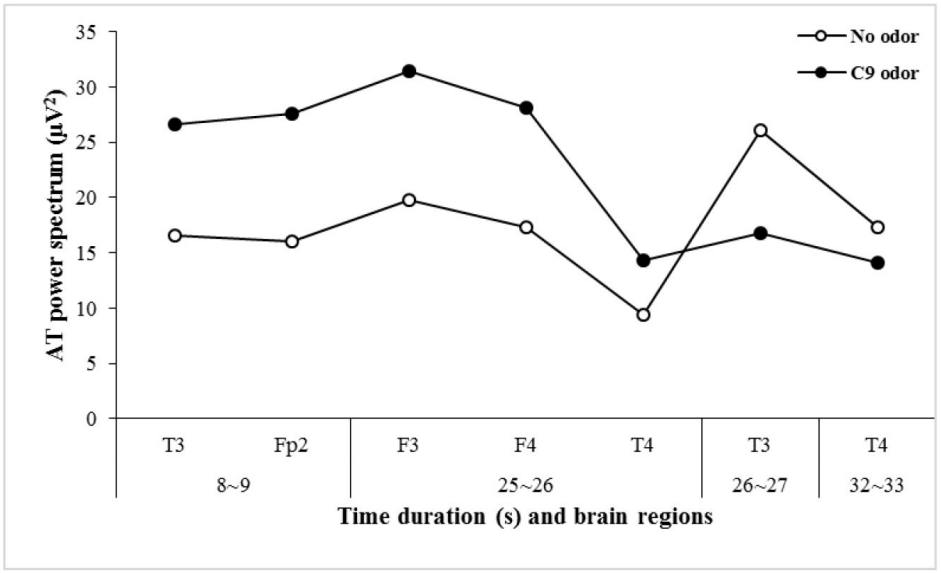
activity during the first 10-second period of odor inhalation. The authors found that the significant decrease in alpha 1 activity was observed during the exposure to lavender, eugenol, and chamomile aromas in which subjects felt comfortable. The significant decrease was stable only due to the inhalation of lavender odor, but the decrease was unstable during the inhalation of other kinds of odors. Previously, some researchers used the time-frequency analysis approach to evaluate EEG signals in regard to the time as well as frequency domains simultaneously. Huart *et al*. (2013) used time-frequency analysis of EEG signals to evaluate olfactory functions in patients. Time-frequency analysis was also used to study EEG power spectra change induced by olfactory stimuli, phenyl ethyl alcohol, and eucalyptol, and this approach reliably discriminates patients with olfactory impairments from healthy subjects (Schriever *et al*., 2017). A recent study showed that absolute waves markedly decreased in the first 13-second period due to the exposure to C10 odor. Later, AA, ASA, and AFA wave activities significantly increased. In addition, the odor inhalation of C10 mainly showed changes especially in the left frontal site (F3) when compared to that of other sites (Kim *et al*., 2019b). A functional magnetic resonance image study demonstrated that the time course to activate the human primary olfactory cortex induced by odor molecules is 30~40 seconds (Sobel *et al*., 2000). In addition, Boesveldt *et al*. (2009) used a time series approach for magnetoencephalography data to detect olfactory dysfunction in patients with Parkinson's disease and healthy individuals.

Among different brain waves, alpha and beta waves play a vital role in cognitive performance in humans. According to previous studies, a significant decrease in the alpha wave was observed during emotional tension and stress states and a significant increase was noticed during relaxation as well as calmness states of the brain (Iijima *et al*., 2009; Lorig and Schwartz, 1988; Sayorwan *et al*., 2012). The data of the present study indicated that AA waves (AA and ASA) decreased due to the exposure to C9 odor. However, the AA wave markedly increased during 13~14 and 17~18 seconds. However, the change in AA, ASA, and AFA waves was not persistent during time series analysis. Beta waves such as AB, ALB, AMB, and AHB significantly decreased at different time points during time series analysis. It is well known that beta wave activity is attenuated under the drowsiness state and increases under the awareness and concentration states of the brain (Lee *et al*., 2014). According to time series analysis results, reduction in beta wave activity due to C9 odor inhalation may connect with the drowsiness state of the brain.

In addition, absolute theta wave activity increased during 8~9 and 25~26 seconds and decreased during 26~27 and 32~33 seconds due to the exposure to C9 odor. Previous studies suggest that the decrease in theta wave activity is highly linked with memory formation (Greenberg *et al*., 2015; Razumnikova, 2007; Sowndhararajan and Kim, 2016). However, AT wave activity was not persistent during the exposure to C9 odor. The findings of this study suggest that C9 odor produced alterations in different brain waves at different brain sites based on time series analysis. From the results, we cannot predict the accurate action of C9 odor on brain function due to the unstable EEG signals during time series analysis.

Time series analysis of EEG signals also allows the measurement of durations and order of activation of each brain region (Jung *et al*., 2006). In this study, the results suggest that the inhalation of C9 odor highly affected the frontal and prefrontal regions when compared with the temporal and parietal regions. Particularly, C9 odor mainly affects the F4 region of the brain, followed by the F3, Fp1, T4, and P3 regions. The prefrontal and frontal sites are important functional areas in the cerebral cortex of the brain. The prefrontal and frontal regions are involved in various cognitive functions, such as decision-making skills, problem-solving, language, memory, attention, and movements (Collins and Koechlin, 2012; Sowndhararajan and Kim, 2016). Furthermore, Grabenhorst *et al*. (2007) stated that the medial orbitofrontal cortex region of the brain is mainly activated by odors with a pleasant smell. In olfaction, the odor molecules present in the air reach the primary olfactory cortex via olfactory receptor cells and the olfactory bulb (Simoes de Souza and Antunes, 2007). Primary olfactory regions, such as the piriform cortex, amygdala, and neighboring cortex, are mainly activated by the stimulation of odor molecules through the transmission between inhaling and odor molecules (Billot *et al*., 2011; Sobel *et al*., 2000).





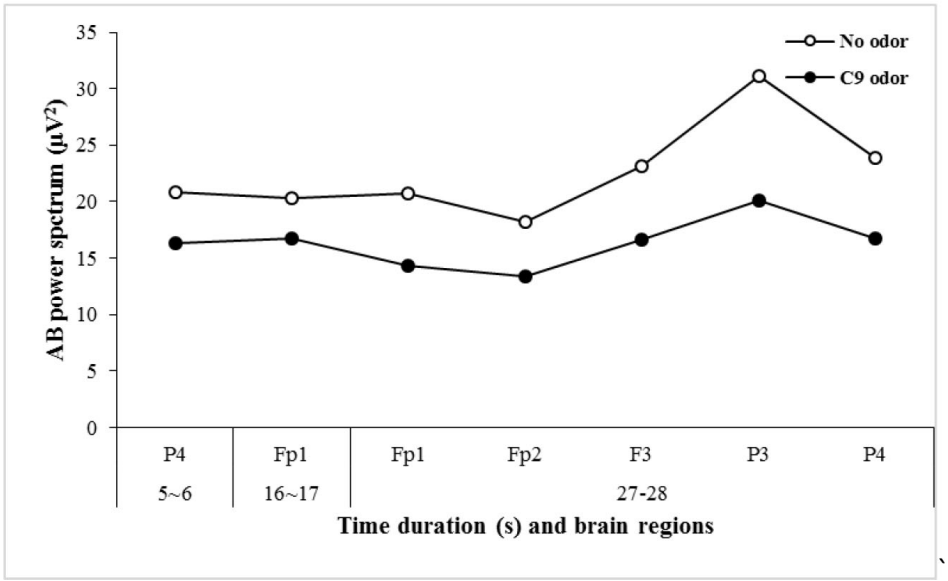


Figure 5. Significant changes in ALB, AT, and AB waves due to the inhalation of C9 odor in relation to analysis time.

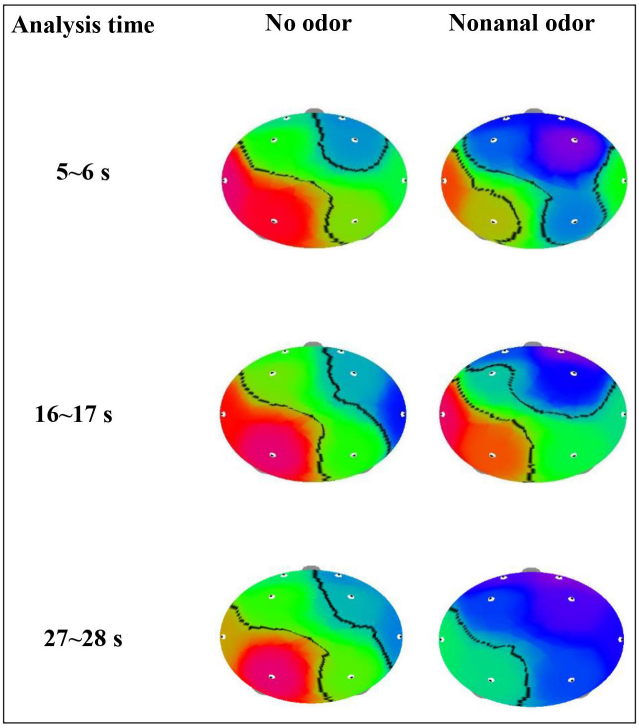


Figure 6. The topographical mapping of AB activity due to the inhalation of C9 odor in relation to analysis time.

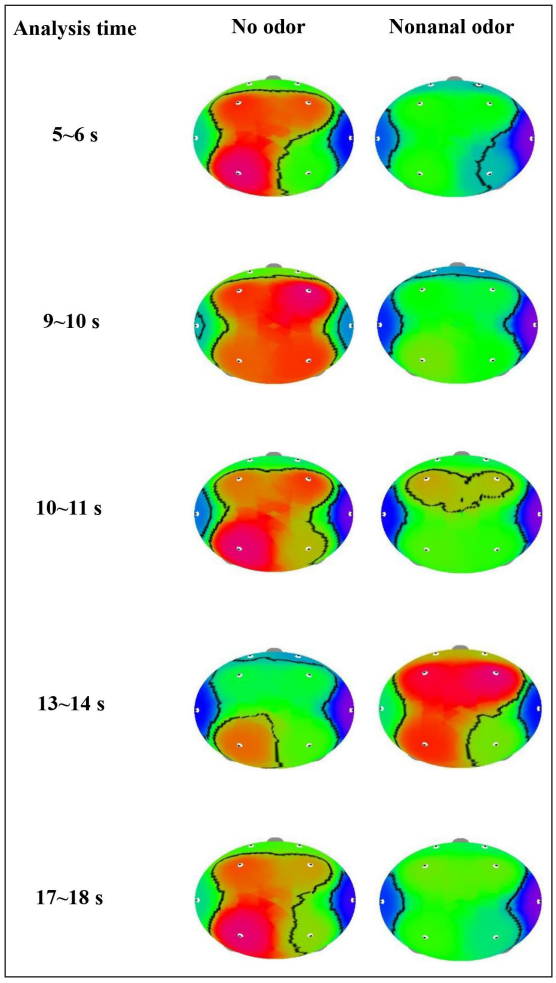


Figure 7. The topographical mapping of AA activity due to the inhalation of C9 odor in relation to analysis time.

CONCLUSION

The results revealed that the EEG activity of C9 odor exposure in a total of 30 seconds analysis time is completely different from time series analysis. In time series analysis, AB waves markedly decreased during C9 odor exposure, and these changes may reduce the alertness state of the brain. In aromatherapy, aldehyde C9 may be used for managing cognitive activities after fixing the appropriate dosage. In addition, this study demonstrates that there was no trend in the EEG activity of C9 odor during time series analysis. Hence, further investigations are needed in association with slightly longer EEG recording time along with time series analysis.

AUTHORS' CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or other conflicts of interest in this work.

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ETHICAL APPROVAL

The study protocol was approved by the Ethical Committee from Kangwon National University, Chuncheon, Republic of Korea (IRB No. KWNUIRB-2017-05-001-003).

DATA AVAILABILITY

The data presented in this study are available within the article.

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