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Effects of volatile sesquiterpenes from Japanese cedarwood on visual processing in the human brain: an event-related potential study

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Abstract

Odor environments in living spaces can influence human physiological and psychological states. To elucidate the effect of volatile organic compounds (VOCs) of wood in living spaces on the modulations of cognitive processing, we built two experimental huts to simulate wooden construction living spaces. One hut was made of cedarwood (*Cryptomeria japonica*), and the other was made of resin. We used cedarwood and resin, because they are often used as construction materials in Japan. In both huts, we measured the participants' first positivity in the early visual cortex (P1), the third positivity elicited by voluntary attention (P3b), and the automatic occipital negativity to infrequent visual stimuli in event-related potentials (ERPs), while they performed a visual discrimination task. The VOCs in both huts were measured by gas chromatography–mass spectrometry. The concentration of volatile sesquiterpenes was significantly increased in the cedarwood hut. Neither P1 nor P3b was affected by the cedarwood hut. Compared to the resin hut, we observed significantly larger occipital negativities to the infrequent stimuli in the cedarwood hut in the time windows of 280–300 ms at the mid-occipital region. These findings suggest that the increased concentration of volatile sesquiterpenes emitted from cedarwood facilitates the human brain's response to changes in visual stimuli.

Keywords *Cryptomeria japonica*, Event-related potential, GC–MS, Interior material, Odor, Infrequent visual stimulus, Sesquiterpene

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Introduction

The physiological and psychological states of humans can be influenced by their physical environments, and the use of wood as an interior material has been shown to affect buildings' indoor environments [1, 2]. In addition, the indoor environment quality (IEQ) values of wooden materials have recently been gaining attention. There are differences in humans' physiological responses to exposure to wood and the responses to other substances, and most of the studies of these responses have indicated that wood may provide a less stressful environment [3]. Several investigations have described the potential of IEQ to affect human health, comfort, productivity, cognitive function, and job performance [4]. For example, it has been demonstrated that Japanese cedar (*Cryptomeria japonica*) as an interior material induces physiological relaxation [5]. The latest research on the effects of cedar interiors on humans revealed that the scent of cedarwood can decrease an individual's blood pressure and salivary alpha-amylase level, regardless of personal preference [6]. The 2010 review by Nyrud and Bringslimars described the psychological effects of interior wood on humans, and the positive psychological effects of this interior material were acknowledged; however, Nyrud and Bringslimars pointed out the lack of clarity of psychological processes as a limitation of previous studies of wood interiors [7]. Advances in wood research could thus be achieved by clarifying which processes in the phasic processing of the human brain are affected by wood as building interior materials.

Several investigations obtained evidence that the use of wood in buildings can change humans' psychophysiological state. The effects of wood odors on brain function have been evaluated with the use of electrophysiological methods, which revealed changes in arousal levels. For example, in 2002 Hiruma et al. reported that the odor of hiba (the evergreen conifer *Thujopsis dolabrata*) generated high arousal levels [8]. Matsubara et al. later showed that low-dose bornyl acetate induced relaxation and low arousal levels in subjects after visual display terminal work [9]. Another study by those authors demonstrated that a low-concentration odor of laurel (*Laurus noblis* L.) tree leaves elicited high-level vigilance and a high hit rate to target stimuli in visual discrimination tasks [10], suggesting that wood odor can enhance humans' attentional function. Takahashi et al. observed in 2020 that the aroma compounds of cedar reduced behavioral and psychological symptoms of dementia in patients with Alzheimer's disease [11], and Ikei et al. demonstrated that the olfactory stimulation provided by air-dried wood decreased the oxy-Hb level in the prefrontal cortex compared to stimulation with high-temperature-dried wood [12]. These findings suggested that wood odor can alter the neural state in the human brain.

Electrophysiological methods for measuring perceptual/cognitive brain function processes in vision are well-established in the neurology and neuroscience fields. Investigations of the traditional evoked potential (EP), the visual evoked potential (VEP), and the event-related potential (ERP) revealed that the P100 (also called P1) component, the P300 (P3b) component, and slow components play distinct roles in the human brain. The P100 (M100) component is evoked by pattern stimulation in human vision and has been used to evaluate the conduction velocity to the primary visual cortex (V1) in the field of neurology [13–15]. Although the P300 component's function has been controversial, P3b has been elicited by at least voluntary attention in the human brain ([16, 17] for a review) as a biomarker of memory processing. In addition, brain activities related to selective attention and automatic sensory information processing were detected in the negative waveforms in middle latencies—such as mismatch negativity (MMN)—with the use of deviant stimuli during an oddball paradigm [18, 19]. MMN is thought to reflect the automatic sensory information processing or "primitive intelligence," which predicts changing patterns when the brain receives sensory input from various environments [20]. MMN was also suggested to be a prediction error signal [21]. MMN components can thus be used as a biomarker of cognitive function [22].

In fact, investigations using complex visual stimuli demonstrated that background chemical odors modulated components of the participants' ERP, such as N170, which is related to the recognition of faces and facial expressions [23, 24]. These results indicated that odor can alter not only the brain state but also higher cognitive brain function involving vision. We thus speculated that wood odor can affect perceptional and/or cognitive brain functions. A stepwise analysis of P1, P300, and MMN on ERPs is needed to determine whether wood volatile odor compounds cause changes in brain cognitive functions. In the present study, we predicted that volatile odor compounds from wood materials in living spaces can modulate early cognitive processing in the brain.

To the best of our knowledge, there have been no published multifaceted brain studies that focused on the effects of natural wood odors by evaluating subjects' ERPs. Here, we hypothesized that the natural scent of wood, which has been used as a building material in living spaces, facilitates some aspects of cognitive processing in the human brain. To test this hypothesis, we constructed a wooden hut from cedarwood (*Cryptomeria japonica*) and another typical hut from resin materials;

both of these materials are often used as construction materials in Japan. We first chemically quantified the concentrations of volatile organic compounds (VOCs) in the wooden hut and the resin hut before conducting the ERP experiments. The participants' subjective intensity and preference for cedar scents were measured. We then recorded three visual ERP components, i.e., the P1, the P3b, and the brain response to infrequent stimuli during a paradigm that is similar to that used in MMN studies to analyze the participants' brain responses regarding physical perception, voluntary attention, and infrequent stimulus detection processing in both the wooden and resin huts.

Methods

Experimental huts

We built two huts with the same structure: one was constructed with an interior made of only Japanese cedarwood (*Cryptomeria japonica*), which is traditionally used as a building material in Japan. The other was built in the same fashion but with only resin materials for the interior (Fig. 1, Additional file 1: Table S1, Fig. S1). The experiment was conducted in November 2017. To avoid contamination by low-frequency EEG artifacts due to perspiration, we set the temperature to 24 °C and the humidity to 50% in each hut, as these settings are in the comfortable range described by the World Health Organization (WHO) standard for a healthy indoor setting [25]; these settings were maintained by an air conditioner, a humidifier, and a ventilating fan. The temperature and humidity values were confirmed just before the participants entered either hut. The concentration of CO_2 in each room was kept below 1000 ppm, while the participants were in either hut, for their safety. The interior design of the two huts was almost the same in appearance, with wood-grain wallpaper made of vinyl cloth on the resin-based construction materials (medium-density fiberboard and particle board) used in the resin hut. The wallpapers in the two huts were placed as closely as possible to the same wood grain pattern to avoid having the wallpaper grain a psychophysiological factor in the visual ERP. However, it was not possible to make the wood grains exactly the same. We, therefore, assessed whether the



Fig. 1 Exterior and interior of the experimental huts. The interiors of both huts had a similar wood-grain appearance, but the interior of the resin-material hut was covered with wood-grain vinyl cloth to avoid visual effects. During the experiments, the window in each hut was covered with blackout curtains to prevent the effects of sunlight on the participants' vision (see Additional file 1: Fig. S1)

wood grain pattern influenced the visual ERPs by comparing the participants' P1 component, which reflects the processing of the physical traits of visual stimuli.

VOC analysis and statistical analyses

Before the visual ERP experiments were conducted, three pumps with sorbent tubes (Tenax TA, Gerstel, Linthicum, MD) were set in each hut, and the VOCs were collected (flow rate, 0.15 L/min; amount, 9 L; duration, 60 min). To prepare for the collection of VOCs, we opened the windows and doors of each hut 25 h before the start of the VOC collection and ventilated the rooms for 1 h with the fan running. We then turned off the ventilation fans and kept closed the windows and doors for 24 h until the start of the VOC collection.

The collected VOCs were analyzed by gas chromatography–mass spectrometry (GC–MS) system (model 7890 GC/5975C MS, Agilent Technologies, Santa Clara, CA) using thermal desorption units (TDUs; Gerstel) and cooled via a cooled injection system (CIS; Gerstel). The initial temperature for desorption was 40 °C; it was held for 0.1 min and then raised to 220 °C at 720 °C/min and held for 3 min. Desorbed compounds were then cryofocused on the CIS cooled at − 100 °C and held for 0.1 min with liquid N_2. At the end of the desorption, the CIS temperature was raised to 220 °C at 12 °C/min and held for 10 min for the injection of the compounds into the column.

The GC–MS system was equipped with a DB-5MS column (30 m × 0.25 mm; film thickness, 0.25 μm, Agilent Technologies). The oven temperature program was 60 °C for 3 min, and the temperature then increased to 230 °C at 3 °C/min and held at this level for 30 min. Helium was used as a carrier gas at a flow rate of 1 mL/min. The samples were injected in splitless injection mode.

For the quantification of the VOCs in each hut, 1 μL of benzaldehyde diluted with acetone (standard quantity, 200 μL/L) was added to the absorption tubes, and their calibration curve was calculated. To determine the calibration curve, we used β-caryophyllene as the sesquiterpene. Benzaldehyde was used as an internal standard. We calculated the VOC concentration in the air (μg/m^3) as a β-caryophyllene equivalent in the total amount of detected VOCs. The VOC measurements were conducted three times before the human experiments in each hut. The VOC concentrations were compared between the cedarwood and resin huts using a two-tailed Student's *t* test ($df = 2$).

Participants

The study participants were 18 young adults who reported no history of neurological disorders and had normal or corrected-normal vision (nine males and nine females; mean age 21.3 ± 1.67 years, range 19–25 years). The participants were paid for their participation and gave their written informed consent. The local Ethics Committee of the Faculty of Agriculture of Kyushu University approved the study (approval no. 52). This experiment was carried out in accord with the Declaration of Helsinki.

Procedures

Upon his or her entry to either the wood or resin hut, the participant was asked to rate the intensity of the smell of the hut and his/her preference for the smell. The intensity of the smell in each hut was evaluated by the participants on our custom 7-point scale based on semantic differential methods [26]: 0 = none, 1 = very weak, 2 = slightly weak, 3 = moderate, 4 = slightly strong, 5 = strong, and 6 = very strong. The participant's preference for the huts' smells was evaluated as: − 3 = dislike very much, − 2 = moderately dislike, − 1 = slightly dislike, 0 = neither like nor dislike, 1 = slightly like, 2 = moderately like, and 3 = like very much.

After the participant completed these two evaluations in either hut, he or she immediately underwent an EEG examination in the hut as follows (Additional file 1: Fig. S1). The participant was seated in a chair covered by an electromagnetic shield sheet of polyester cloth, including a nickel plate connected to the ground (Noi-cut sheets 44552, GE Healthcare Japan, Tokyo) that was used to reduce the alternate current noises of the air conditioner from the floor of the hut. The participant then viewed three types of stimuli presented on a 17-inch CRT monitor (refresh rate, 85 Hz; 1024 × 768 pixels; Image Quest Q770, Hyundai, Korea). The orders of exposure to each hut were counterbalanced across the participants. To avoid carryover effects, the participants' second hut exposures were conducted at the same time of day > 7 days from the first exposures.

Each stimulus was presented at random for 200 ms with a randomized inter-stimulus interval (ISI) between 850 and 1100 ms at the right or left side (visual angle, 3.9° each side) of the computer screen to make the discrimination task more difficult, under the control of the software program Presentation ver. 16.4 (Neurobehavioral Systems, Berkeley, CA). The viewing distance was 114 cm (visual angle, 3.6° × 3.25°) (Additional file 1: Fig. S1).

Task

In both huts, we administered a random sequence oddball paradigm in which frequent (F) stimuli and infrequent (I) stimuli with a detection (target, T) stimulus were presented in the same sequence to the participant to assess the participant's physical perception, infrequent visual detection, and visual target detection (Fig. 2). All

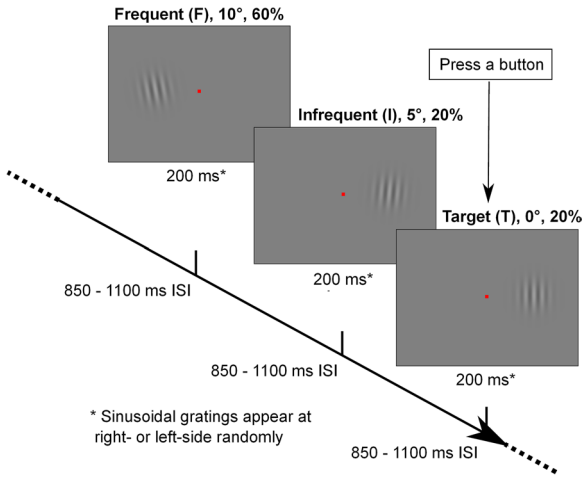


Fig. 2 Representative examples of the sinusoidal grating stimuli and the time sequence of the task. A 10° angular sinusoidal grating was presented as the frequent stimulus (F) at a 60% probability. A 5° angular infrequent (I) stimulus and a 0° angular target (T) stimulus were each presented at 20% probability

visual stimuli were presented to elicit P1. We subtracted the ERPs that occurred in response to the frequent stimuli from the ERPs in response to the infrequent stimuli, which elicited the occipital negativity in the middle latencies.

The P3b component was elicited by button pressing; the participant was instructed to fixate on a point in the center of the CRT monitor and push a button on the mouse of a personal computer when a target stimulus (0° angle, 20% probability) appeared when compared to a frequent stimulus (10° angle, 60% probability), but to ignore the infrequent stimuli (5° angle, 20% probability). The target stimulus was also used to control voluntary attention and further maintain the participant's persistent vigilance. The visual stimuli were replaced by a background image (1024 × 768 pixels) with a gray value of 128 (mean luminance, 18.71 cd/m^2) during the ISI.

The participants' reaction time (RT) and accuracy for responding to the target stimulus were also measured for the assessment of the participant's performance, while the participant's visual ERPs were simultaneously recorded. To determine whether all of the participants' α-activities were normal, we administered an eye-opening and -closing test to each participant to observe the α-attenuations when the participants opened their eyes after closing them, both before and after the oddball task.

Visual stimuli

As the visual stimuli, 256-level grayscale images of sinusoidal gratings (2.22 cycles/degree) were used. We defined three different orientations for the sinusoidal gratings with the physically same luminance and contrast values as the frequent, infrequent, and target stimuli (10°, 5°, and 0° angular, respectively). The minimum and maximum luminance values were 13.72 and 28.54 cd/m^2, respectively, and the contrast was 35.07% in both; we used the same CRT monitor for all of the visual stimuli.

ERP recordings

For the ERP recordings of each participant, active gold plate electrodes with internal amplifiers (AP-C151(A)-015, Miyuki Giken Co., Tokyo) were applied to 21 scalp sites based on the International 10–20 system [27] (Fpz, Fz, Cz, Pz, Oz, Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, and O2) with electrode paste (10–20, Miyuki Giken). An EEG device, the Polymate V (Miyuki Giken), was used for all of the recordings. All of the recording electrodes were referred to an electrode at the tip of the participant's nose, and the impedance was kept below 50 kΩ. Active gold plate electrodes with internal amplifiers can record EEGs that are sufficient to extract ERPs even with high impedance (> 5 kΩ).

Vertical and horizontal electrooculograms (VEOGs and HEOGs) were also recorded to reject artifacts caused by the participants' blinking and eye movements during the sessions. The VEOGs and HEOGs were recorded using bipolar deviations. The electrodes for each VEOG were placed below the left eye and above the left eyebrow, and those for each HEOG were placed on the left corner of the left eye and the right corner of the right eye. A trigger pulse (10 ms, 5 V rectangular wave) was generated from a parallel port of a personal computer that generated the visual stimuli to an EEG recording apparatus at the onset (0 ms) of each stimulus via the Presentation software cited above.

A total of 120 trials were averaged for each session with a bandpass filter between 0.05 and 200 Hz (second-order Butterworth filters for low-cut filtering; first-order Butterworth filters for high-cut filtering). A 40-Hz high-cut filter (first-order Butterworth filter) and a 60-Hz notch filter were applied for smoothing and reducing alternate current noise before the segmentation and averaging in the offline analyses. A total of 1440 trials for 12 sessions was obtained to compensate for the loss of a number of trials. The sampling rate was 1000 Hz.

ERP analysis

All components, i.e., P1, P3b, and occipital negativities, were separately analyzed as a within-participant factor. The P1 components were measured from the baseline to the first positive peak around 100–200 ms at the occipital-midline and left–right regions (Oz, O1, and O2

electrodes). The P3b components were defined as the largest positive peaks to the target stimuli after 300 ms at the parietal-midline region (Pz electrode). To determine the infrequent visual detection components, we calculated the negativities by subtracting the ERPs for the frequent stimuli from those of the infrequent stimuli.

All of the ERP components were corrected using a −100-ms to 0-ms baseline and were measured as absolute amplitudes. The recording time for each trial was 1000 ms. Artifacts caused by blinks, eye movements, perspiration, the electromyogram, and the electrocardiogram were rejected based on deflections above 70 μV from the baseline. The ERP waveforms were then created by averaging the accepted waveforms. The above process was computed using MATLAB ver. 9.1 (Mathworks, Sherborn, MA).

Statistical analyses for the subjective evaluation, behavioral performance, and ERPs

The Kolmogorov–Smirnov test confirmed the normalities of the ERP amplitudes and latencies. Before a paired *t* test and analyses of variance (ANOVAs) were conducted, the variance's homogeneities between the variables were also clarified by an *F* test and Bartlett test. Gender was tested as a between-participant factor; all other factors were tested as within-participant factors. A two-way repeated-measures ANOVA was used to compare the participants' evaluations of the intensity and preference for the environments' smells and for their behavioral performance between the participant's gender under the cedarwood and resin conditions. The amplitudes and latencies of the occipital P1 were analyzed by a four-way repeated-measures ANOVA: (Environment (cedarwood or resin) × Electrode (Oz, O1, or O2) × Stimulus (frequent, infrequent, or target) × Gender (male or female).

We compared the amplitudes and latencies of the P3b components at Pz to the target between gender and the cedarwood hut and the resin hut using a two-way repeated-measures ANOVA. The amplitudes of negative shifts to the infrequent stimuli at the medial and occipitotemporal sites were compared by a four-way repeated-measures ANOVA (Environment [cedarwood or resin] × Electrode [Fz, Cz, Pz, Oz, T5 and T6] × Time [sequential 10-ms time-window in 0–900 ms] × Gender [male or female]). Post hoc paired comparisons were conducted using the Holm correction. All statistical analyses were conducted using a two-tailed test and performed using R ver. 4.0.5 [28] and JASP ver. 0.16.4 [29]. The post hoc power analyses were conducted using G*Power 3.1 [30]. Statistical significance was defined as a probability (p) value < 0.05.

Results

Comparison of the VOC concentrations in the cedarwood and resin huts

Figure 3 shows the odor compounds that were detected in both huts, and Table 1 provides the concentrations of the VOCs in each hut. Thirteen compounds were identified in both huts. The peaks of γ-cadinene and γ-muurolene in the chromatogram were superimposed; we thus combined them to calculate the concentration. The concentrations of α-cubebene, α-copaene, β-elemene, caryophyllene, *cis*-muurola-3,5-diene, α-humulene, (+)-*epi*-bicyclosesquiphellandrene, α-muurolene, δ-cadinene, and the total compounds in the cedarwood hut were significantly higher than those in the resin hut ($p < 0.05$ each). None of the volatile compounds detected in this study has been labeled a harmful VOC by Japan's Ministry of Health, Labor, and Welfare (MHLW). We also observed no harmful compounds from the resin materials that were above the detection thresholds in GC–MS in either hut (Fig. 3, Table 1).

Subjective evaluation of odor intensity and preference

The subjectively evaluated intensity for cedarwood, 3.56 ± 0.232, was higher than that for the resin materials, 3.28 ± 0.240, but the difference was not significant (F (1, 16) = 0.96, $p = 0.341$). Similarly, there was no significant difference in the participants' preference between the cedarwood and resin huts (1.11 ± 0.212 vs. 1.22 ± 0.191, respectively; F (1, 16) = 0.327, $p = 0.576$). We observed no interaction between gender and the material condition for the intensity and preference (F (1, 16) = 0.346, $p = 0.565$; F (1, 16) = 1.306, $p = 0.270$).

The participants' accuracy and RTs in the oddball tasks

We observed no significant differences in the participants' accuracy or RTs between the two huts' conditions. The mean accuracies ± SE (standard error) in the oddball task were 95.1 ± 1.0% under the cedarwood condition and 95.3 ± 1.0% under the resin condition (F (1, 16) = 0.116, $p = 0.738$). The mean RTs ± SE were 540.8 ± 13.0 ms and 546.0 ± 12.2 ms under the cedarwood and resin conditions, respectively (F (1, 16) = 0.572, $p = 0.460$). We observed no interaction between gender and the material condition for the accuracy or RTs (F (1, 16) = 0.823, $p = 0.378$; F (1, 16) = 0.366, $p = 0.554$).

The P1 and P3b components in each environment

P1 was evoked by all three types of stimuli, and P3b was elicited only for the target (T), which suggests that our oddball task functioned well. However, there were no significant main effects or interactions in the P1 amplitude,

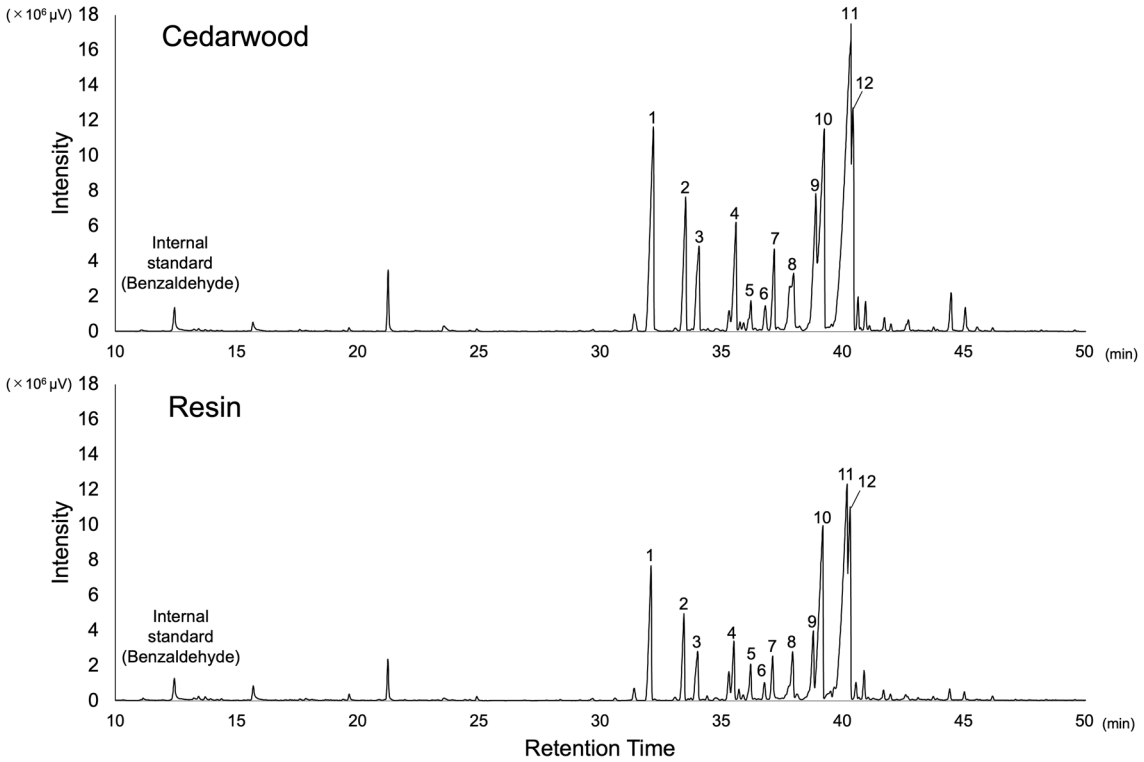


Fig. 3 Representative examples of the volatile organic compounds (VOCs) identified on chromatograms in the GC–MS analysis. Thirteen volatile organic compounds were identified in both the cedarwood and resin huts. The peaks of γ-cadinene and γ-muurolene were superimposed. Each peak area of the 13 identified main sesquiterpene compounds per peak area of the internal standard was approx. twice as large in the cedarwood hut compared to the resin hut

Table 1 Volatile organic compounds (VOCs) and their concentrations identified in this study

No.	Compound	RT	Cedarwood		Resin		*p*	*d*	$1-\beta$
			Mean μg/m^3	SD	Mean μg/m^3	SD			
1	α-Cubebene	32.11	233.08	9.82	95.47	7.34	0.000041**	15.87	1.0000
2	α-Copaene	33.46	114.87	2.07	53.32	4.71	0.000032**	16.92	1.0000
3	β-Elemene	34.03	86.98	2.89	36.38	2.96	0.000029**	17.30	1.0000
4	Caryophyllene	35.52	94.42	1.40	33.59	2.54	0.000003**	29.66	1.0000
5	*cis*-Thujopsene	36.21	24.05	0.87	21.31	1.79	0.075536†	1.95	0.4439
6	*cis*-Muurola-3,5-diene	36.78	27.94	7.83	9.35	0.36	0.014731*	3.35	0.8606
7	α-Humulene	37.12	57.83	1.53	25.42	2.37	0.000038**	16.25	1.0000
8	γ-Cadinene + γ-Muurolene	37.95	87.19	21.41	41.27	4.13	0.021810*	2.98	0.7770
9	(+)-*epi*-bicyclosesquiphellandrene	38.80	153.03	2.77	48.80	6.39	0.000013**	21.16	1.0000
10	α-Muurolene	39.20	266.24	4.85	188.99	29.16	0.010608*	3.70	0.9148
11	δ-Cadinene	40.20	624.89	3.76	281.92	53.54	0.000379**	9.04	1.0000
12	Calamenene	40.33	140.33	5.61	120.79	16.05	0.117315	1.63	0.3334
	Total		1955.26	51.84	959.75	119.49	0.000188**	10.81	1.0000

RT retention time

**$p < 0.01$, *$p < 0.05$, $^{\dagger}p < 0.10$

Table 2 P1 latencies and amplitudes in response to each stimulus under each condition at the Oz electrode (occipital) site

	Cedarwood			Resin		
	Frequent	Infrequent	Target	Frequent	Infrequent	Target
Latencies, ms	165.3 ± 8.9	165.9 ± 8.1	159.8 ± 12.0	165.1 ± 6.7	165.2 ± 8.8	167.7 ± 7.2
Amplitude, μV	1.82 ± 0.38	2.25 ± 0.46	1.87 ± 0.39	1.56 ± 0.38	2.25 ± 0.56	2.42 ± 0.49

The data are mean ± SE

Table 3 P3b latencies and amplitudes in response to the target stimulus under each condition at the Pz electrode (parietal site)

	Cedarwood	Resin
Latency, ms	534.6 ± 15.0	526.8 ± 12.6
Amplitude, μV	13.70 ± 1.05	13.52 ± 1.07

The data are mean ± SE

P1 latency (Table 2), P3b amplitude, or P3b latency (Table 3) between the cedarwood and resin conditions (F (1, 16) = 0.124, p = 0.729; F (1, 16) = 0.002, p = 0.967; F (1, 16) = 0.096, p = 0.761; F (1, 16) = 0.222, p = 0.644). We also observed no interaction between gender and the material condition for the P1 amplitude, P1 latency, P3b amplitude, or P3b latency (F (1, 16) = 1.322, p = 0.267; F (1, 16) = 0.034, p = 0.855; F (1, 16) = 0.837, p = 0.374; F (1, 16) = 0.014, p = 0.907).

Distribution of elicited visual ERP waveforms at each scalp site

Figure 4A, B illustrates the distributions of ERPs for the three types of stimuli in the cedarwood and resin huts. The first positive component (P1) was predominantly evoked over the occipital region under both hut

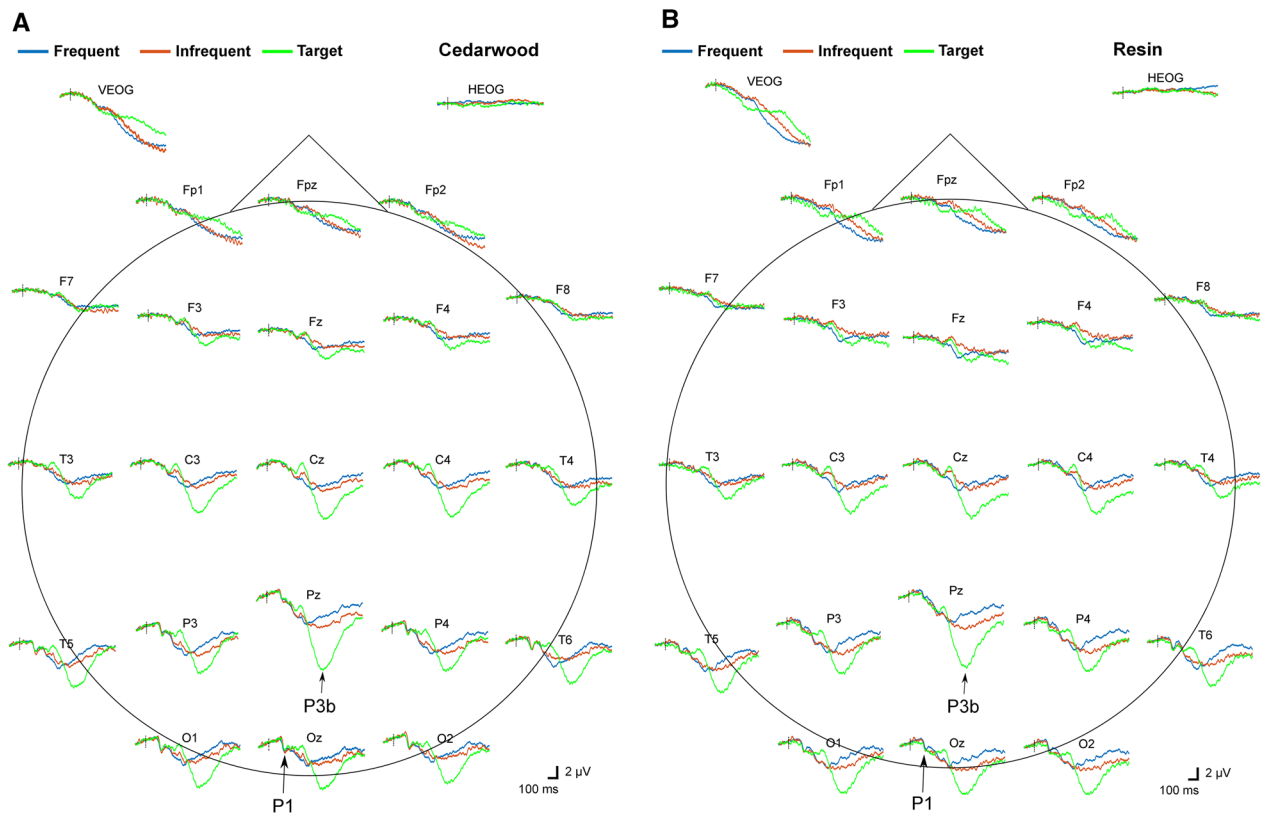


Fig. 4 Topographical mapping of grand-averaged ERPs under the cedarwood and resin conditions. The P1 components were elicited at the occipital region (Oz). P3b was predominantly recorded for the target stimuli at the parietal site (Pz) in both the cedarwood (**A**) and resin (**B**) huts. The latencies of the P1 and P3b components were almost the same regardless of the hut condition. Note that P1 was evoked at Oz, and P3b was recorded only for the target stimuli predominantly at Pz regardless of the hut condition

conditions. P3b showed the largest positivity at the parietal region (the Pz electrode). P3b was recorded only for the target stimuli regardless of the hut, indicating that the participants' intentional attention was equally controlled in both the wood and resin huts.

Occipital negative shifts to infrequent stimuli were elicited in the occipital region in the cedarwood hut but not in the resin hut. Figure 5 shows that occipital negativity to the infrequent stimuli was detected at the mid-occipital region (Oz) under the cedarwood condition, whereas it was not elicited in any time window at Oz under the resin condition. In addition, lateralized occipital negativity was observed at the right occipitotemporal region (T6) under the resin condition.

Occipital negativities to infrequent stimuli in the cedarwood and resin huts

The three-way repeated-measures ANOVA revealed a significant interaction for environment × electrode × time (F (267, 4272) = 1.543, $\eta^2_p = 0.088$, $p < 0.0001$). Moreover, the two-way repeated-measures ANOVA revealed significant quadratic interactions for environment × electrode (F (3, 48) = 3.070, $\eta^2_p = 0.161$, $p = 0.037$), electrode × time (F (267, 4539) = 3.176, $\eta^2_p = 0.185$, $p < 0.0001$), and environment × time at Oz (F (89, 1424) = 1.284, $\eta^2_p = 0.074$, $p = 0.043$). Regarding gender differences, the four-way interaction for environment × electrode × time × gender was not significant (F (267, 4272) = 0.647, $p = 1.00$). The three-way interaction for environment × electrode × gender was also not significant (F (3, 48) = 0.349, $p = 0.790$). The two-way interaction for environment × time × gender at Oz was not significant (F (89, 1424) = 0.644, $p = 0.996$).

The post hoc multiple comparisons with Holm correction for each time window revealed that the amplitude of the occipital negativity to infrequent stimuli at the Oz electrode at 250–260 ms was augmented compared to that at Fz under only the cedarwood condition (t (17) = 3.0318, $d = 0.7353$, $1-\beta = 0.8363$, $p < 0.05$). In addition, the amplitudes of the occipital negativity to infrequent stimuli at Oz in the cedarwood hut were significantly greater than those in the resin hut at 280–300 ms (280–290 ms, t (17) = 5.9470, $d = 0.5915$, $1-\beta = 0.6576$, $p < 0.05$; 290–300 ms, t (17) = 9.2313, $d = 0.7369$, $1-\beta = 0.8379$, $p < 0.05$) (Figs. 5, 6).

In addition, the amplitude of the right-lateralized occipitotemporal negativity to infrequent stimuli between 270 and 280 ms at the occipitotemporal region (T6) under the resin condition tended to be significantly larger than that under the cedarwood condition (F (1, 16) = 3.219, $d = 0.4359$, $1-\beta = 0.4347$, $p = 0.092$) (Fig. 6). In contrast, no significant interaction for environment × gender at T6 was observed (F (1, 16) = 0.003, $p = 0.956$).

Discussion

We presented 60% frequent stimuli, 20% target stimuli, and 20% infrequent stimuli to the participants during an oddball task in huts built with cedar and resin interior materials. The results of the subsequent analyses

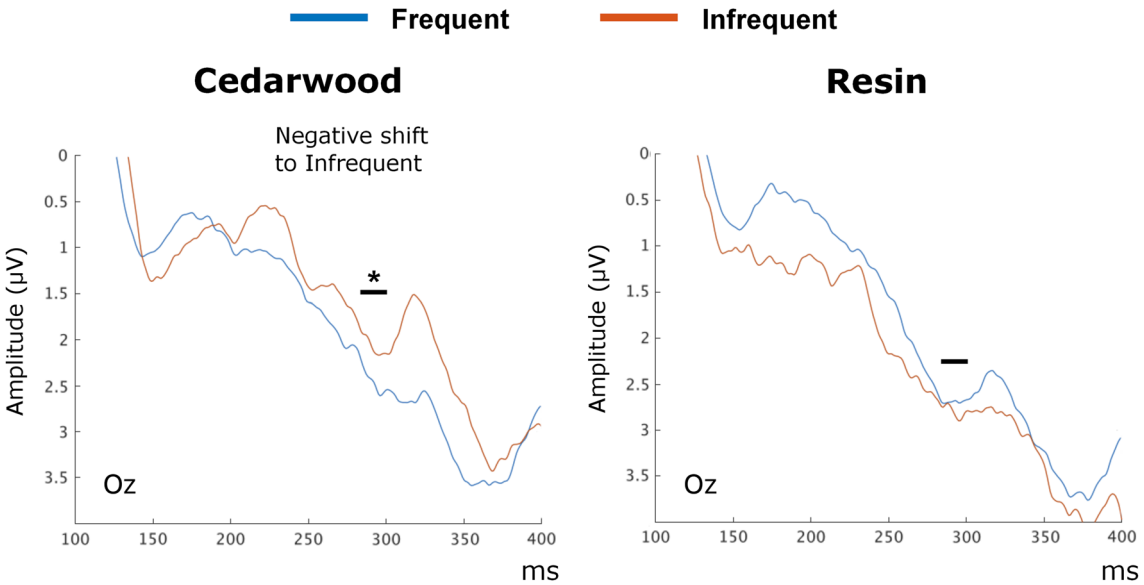


Fig. 5 Waveforms of the occipital negativities at the mid-occipital site (Oz) in the middle latencies. The occipital negativities to infrequent stimuli were observed under the cedarwood condition, especially at 280–300 ms ($p < 0.05$) (left column), whereas they were not elicited in any time window at Oz under the resin condition (right column)

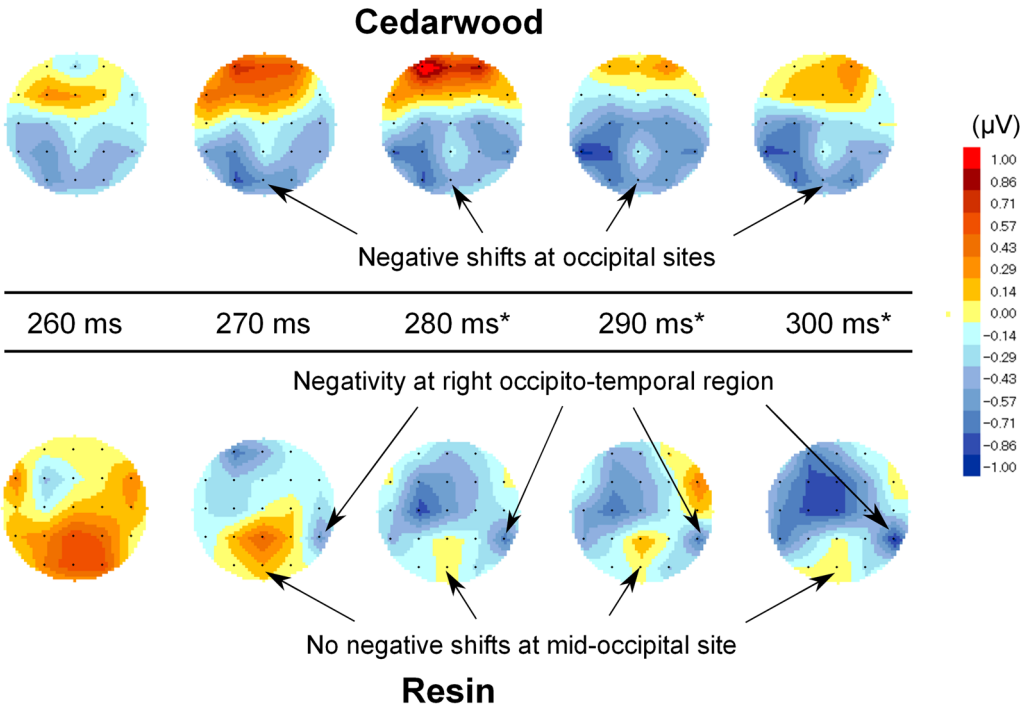


Fig. 6 Topographical maps of the grand-averaged occipital negativity in the middle latencies (260–300 ms) in response to the infrequent stimuli in the cedarwood and resin huts. ERPs to frequent stimuli were subtracted from the ERPs to infrequent stimuli for the topographic mapping. In the topography, blue indicates negativities. Note that the negative component was observed at the occipital region under the cedarwood condition, whereas in the resin condition, the negativity was not obvious at the mid-occipital electrode but was observed at the right occipitotemporal region

revealed significant negative shifts at mid-occipital sites to the infrequent stimuli in the cedar-interior hut, which suggests that the cedarwood interior enhanced the participants' detection of the infrequent stimulus. We instructed the participants to discriminate between the frequent and target stimuli and to ignore the infrequent stimuli. Each participant retained the stimulus angle of the frequent and target stimuli in his/her memory. The appearance of the infrequent stimuli could interfere with the participants' prediction of the expected stimulus pattern. The negative shift to infrequent stimuli could, therefore, reflect a prediction error signal during the visual change detection.

Although the concentration of volatile sesquiterpenes in the cedarwood hut was significantly higher than that in the resin hut, there was no significant difference in the subjective intensity and preference for the odor in the two huts. Our findings thus suggest that cedar interior wood, which has higher concentrations of volatile sesquiterpenes, could enhance the sensitivity to visual change detection in the human brain, even if the participants could not discriminate the difference in odor intensity. There is a contradiction in that sesquiterpene concentrations differ if people's subjective evaluation does not differ. However, there is not necessarily a contradiction in that sesquiterpene concentrations differ without people's subjective evaluations differing. The experimental huts were built in accord with traditional Japanese wood construction methods. Volatile components from the structural materials contributed to the inconclusive difference in sesquiterpene concentrations between the cedar and resin huts. In the present study, P3b, which reflects conscious processing, was not affected by the cedar odor, whereas negative occipital potentials, which reflect unconscious automatic processing, were affected by the cedar odor. Therefore, the behavior of the occipital negative component in response to the cedar odor is consistent with our finding that there was no difference in the participants' subjective evaluations of odor. These results are consistent with a report that the scent of cedarwood has physiological effects regardless of personal preference [6]. Our present results thus demonstrate that the difference in the concentration of volatile sesquiterpenes can affect humans' cognitive brain response in living environments regardless of the subjective intensity and preference.

We observed stable P3b components in the oddball task regardless of the hut environment, whereas the

occipital negativities to infrequent stimuli behaved differently depending on the environmental condition, i.e., the hut interior material. These results suggest that the characteristic change occurred in response to infrequent visual stimuli in the brain in the cedarwood environment. On the other hand, the activities of an early visual area (P1) and target detection (P3b) were not modulated by the cedarwood condition. The unique change in the occipital negativity to infrequent stimuli was elicited in the early visual area. Specifically, the P1 amplitudes and latencies were not affected by the difference between the similar wood-grain wallpaper and the wood grain of the cedarwood. If this slight difference in the wood-grain affects visual processing in the brain, the P1 amplitudes or latencies can be altered by the environment.

However, we observed no difference in P1 components under the two hut-material conditions. It thus appears that the cedarwood scent (and not the difference between the wood grains) could enhance the brain response to infrequent visual stimuli in the brain. Cortical negativity to deviant stimuli in MMN experiments has been considered to reflect pre-perceptual change detection or unintentional prediction [19, 31]. We thus conclude that cedarwood scents or their VOCs could enhance the sensitivity of prediction error to visual changes as the response to infrequent stimuli in the early visual cortex.

Regarding the ERP latencies, the occipital negativity to infrequent stimuli occurred after 200 ms, which is outside the range of the first exogenous component, P1, at the posterior region, indicating that the occipital negativity to the infrequent stimuli used in this study could not be elicited as perceptual ERP components of the first V1 activities modulated by physical traits of the visual stimuli. The P1, P300, and occipital negativity to infrequent stimuli in the present study were relatively delayed and smaller than those in earlier studies and reviews [32–36]. The small amplitude of negative shifts could have been due to our use of a side-to-side stimulus presentation method to make the task more difficult. However, the stimulus pattern, stimulus timing, and stimulus train likely did not in themselves cause the small amplitudes [37]. In addition, our stimuli showed relatively low spatial frequency and low contrast; this could have affected the latencies and amplitudes in the P1 component.

A 2018 study demonstrated that top-down modulation from olfactory to visual systems resulted in attentional ERPs that were large in amplitude at 400–900 ms [38]. In the present study, the occipital negativity to the infrequent stimuli ranged from about 250 to 300 ms, which is faster than 400–900 ms. Andersson et al. presented intensity-matched olfactory stimuli (amyl-acetate) with a 10–20-s ISI before a visual detection task [38]. In contrast, our cedarwood olfactory stimuli were presented as background stimuli throughout the time during which the participant performed the oddball task. We thus speculate that sustained odors of cedarwood facilitate the latencies of ERP components.

In macaques, attention-biased electrophysiological responses after 150–200 ms [39] and attention caused top-down projection to the amygdala into visual cortices [40]. Direct cedrol odors into the lower airway increased the cerebral blood flow in the bilateral hippocampus [41]. We thus speculate that when humans are exposed to cedarwood odors in a cedarwood interior, volatile sesquiterpenes in the cedarwood can enhance the occipital negativity to infrequent stimuli by a direct neural projection from the frontal olfactory area, amygdala, or hippocampus into the early visual cortices.

Considering the ERP distribution of occipital negativity to infrequent stimuli, we presume that the VOCs of cedarwood could have activated the striate or extrastriate cortex. This activation may be caused by top-down projection from the frontal olfactory area in the cedarwood hut and could have affected the distribution difference. Otherwise, the dipole orientation of occipital negativity to infrequent stimuli would differ in the cedarwood hut with odorant influence. We observed the occipitotemporal negativity to infrequent stimuli under the resin condition, and this lateralization was apparently similar to that reported in visual MMN studies [42]. It was also suggested that the neural generator of the brain activities to infrequent stimuli could be the middle occipital gyrus (MOG) [43].

In our present study, the distribution of occipital negativity was similar to that of MMN during the visual task: the occipital negativity to infrequent stimuli under the resin condition was observed in the right occipitotemporal region. In contrast, the occipital negativity to infrequent stimuli under the cedar condition was augmented at the mid-occipital site (Oz). The source of occipitotemporal negativity to infrequent stimuli could thus be shifted to the MOG by the scent of cedar. This shift of the neural generator of the occipital negativity modulated by cedarwood odors should be further investigated with simultaneous recordings using high-density EEG, magnetoencephalography, and/or functional magnetic resonance imaging.

With regard to odorants, an electrophysiological study reported that the odor of hiba (a conifer) did not affect the amplitudes of MMN for auditory stimuli [8]. A wood odor could, therefore, affect the brain response to infrequent visual stimuli but not to auditory stimuli. Tsunetsugu and Miyazaki and Park et al. reported that participants' total hemoglobin at the frontal cortices decreased during forest (including cedarwood) baths [44, 45] Their results are consistent with our present

findings: the negativities to infrequent stimuli at the frontal areas were decreased, but those of occipital sites were increased (see Fig. 6). A study focusing on how visual attention is affected by environmental odors using a line-bisection task revealed that odor pleasantness in the surrounding spaces shifted the participants' visuospatial attention [46]. We thus conclude that the natural cedarwood-specific VOCs' characteristics could have enhanced our participants' visuospatial sensitivity in the occipital cortex in vision, producing occipital negativity to infrequent visual stimuli.

Our chemical analyses revealed that the concentration of volatile sesquiterpenes in the cedarwood hut was high, although no difference in its profile was observed between the cedarwood and resin huts. This suggests that the concentration of sesquiterpenes could be essential for the modulation of brain function. A study using EEG showed that a low concentration of (−)-bornyl acetate, which is a monoterpene, induced a low arousal level after a visual display terminal task [9]. In contrast, our present results indicate that a high concentration of volatile sesquiterpenes can affect cognitive functions in the brain. It is worthwhile to focus on α-cubebene, α-copaene, β-elemene, caryophyllene, α-humulene, (+)-*epi*-bicyclosesquiphellandrene, α-muurolene, δ-cadinene, and the total amount of the compounds, as these are significant components of the volatile sesquiterpenes that were present in significantly large amounts and effect sizes in the cedarwood hut. However, we cannot conclude whether the brain's modulation was affected by each specific compound or by the total amount of volatile sesquiterpenes. The effects of each compound on ERP modulations should be examined in future studies.

Our study has limitations to address. First, at the individual-participant level, we could not obtain evidence of the action mechanisms of sesquiterpenes in occipital negativity to infrequent stimuli, as we did not measure the concentrations of volatile sesquiterpenes in each participant. Notably, brain responses to wood odors differ substantially among individuals and age groups [45, 47]. Future studies should examine individual and age-group cognitive modulations in the brain by cedarwood and other odors. Second, the wood-grain patterns in the two rooms differed slightly. However, the hut materials did not affect the P1 amplitude or latency, which can be affected by luminance and contrast. This result suggests that the slight visual difference in the wood grain did not alter the early cortical activity of visual processing; higher concentrations of volatile sesquiterpenes could increase occipital negativity to infrequent stimuli under the cedarwood condition.

Third, we constructed the experimental huts as Japanese traditional wooden structures that generally use cedarwood. The sesquiterpenes were detected even in the resin hut affected by the structural materials, and brain responses in a sesquiterpene-free environment could not be recorded. Therefore, the changes in brain responses that we observed reflect the effect of the increased concentration rather than the presence or absence of sesquiterpenes. Notably, it has been demonstrated that compared to a room with Japanese cedar odor, a room without Japanese cedar odor increased cortisol levels in females [48]. Gender differences in the brain's cognitive processing in the absence of sesquiterpenes should thus be clarified in further studies.

Taken together, our findings indicate that an increased concentration of volatile sesquiterpenes diffused from natural-wood interior materials (unlike resin materials) can enhance the infrequent visual change detection in the early visual area, regardless of participants' impression or evaluation of odors. We thus propose that a specific type of terpenoid, sesquiterpenes, from natural wood products used as interior materials can modulate cognitive functions in the human brain.

Conclusions

Increased concentrations of sesquiterpenes released by cedarwood interior materials altered cognitive brain responses in healthy adults. Our findings indicate that increased odors derived from natural cedarwood used as the interior material in a wooden living space modulate the sensitivity of infrequent visual detection in the early visual areas in the human brain. Occipital negativities related to infrequent visual detection were modulated based on the frequency with which the stimuli appeared in this study; the negativities were also affected by the changes in odor concentration. One of the characteristics of cedarwood that impacts the modulation of visual change detection in the human brain is an increased concentration of volatile sesquiterpenes regardless of the subjective intensity and preference for the odor. Further studies are necessary to focus on the extent to which each sesquiterpene and its concentration derived from cedarwood contributes to the facilitation of the modulation based on early visual detection. Such investigations should identify the neural generators of the occipital negativity. The modulation of infrequent stimulus detection in individuals' brains by sesquiterpenes from cedarwood should be further investigated in detail with a focus on behavioral traits using more sophisticated cognitive paradigms compared to zero concentration conditions.

Controversial ideas about the brain functionality of odorants from various natural materials and the odors of living spaces should be examined. The enhancement effect of brain function by volatile sesquiterpenes in social contexts in various environments also merits further study.

Abbreviations

ANOVA	Analysis of variance
C (in scalp sites)	Central
CIS	Cooled injection system
CRT	Cathode ray tube
EEG	Electroencephalogram
EP	Evoked potential
ERP	Event-related potential
F (stimuli)	Frequent
F (in scalp sites)	Frontal
GC–MS	Gas chromatography–mass spectrometry
HEOG	Horizontal electrooculogram
I (stimuli)	Infrequent
IEQ	Indoor environmental quality
ISI	Inter-stimulus interval
MHLW	Ministry of Health, Labour and Welfare
MMN	Mismatch negativity
MOG	Mid-occipital gyrus
N (in ERP components)	Negativity
O (in scalp sites)	Occipital
P (in ERP components)	Positivity
P (in scalp sites)	Parietal
RT (in GC–MS)	Retention time
RT (in behavior analysis)	Reaction time
T (stimuli)	Target
T (in scalp sites)	Temporal
TDU	Thermal desorption unit
V1	Primary visual cortex
VEOG	Vertical electrooculogram
VEP	Visual evoked potential
VOC	Volatile organic compound
WHO	World Health Organizaion

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10086-023-02083-4.

Additional file 1: Table S1. Materials of each hut. **Figure S1.** Floor plan of the experimental huts. The layouts of the two huts were the same. The participant was instructed to fixate on a point in the center of the CRT monitor and push a button on the mouse of a personal computer when a target stimulus (0° angle, 20% probability) appeared at the viewing distance of 114 cm.

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Author contributions
TNakashima supervised the EEG experiments, analyzed the visual ERPs and behavioral performance, wrote all of the main manuscript text, and prepared Figs. 1, 2, 4, 5, and 6; Tables 2 and 3, and prepared the revised manuscript. MS and AH conducted all of the visual ERP and behavioral experiments. YYoshimura and TNakagawa analyzed the VOCs and prepared Table 1 and Fig. 3. YYoshimura wrote the legend of Fig. 3, and prepared the revised manuscript. HI and KS supervised the VOC analysis. JN provided emergency responses to all of the participants' medical conditions. TNakashima, MS, AH, TO, and YYamada designed the task. YW prepared the natural cedarwood for the hut construction. SY built the experimental huts. NF gave advice about the wood materials. KO and KS managed this project. All authors read and approved the final manuscript.

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Availability of data and materials
The data sets used and/or analyzed in this study are available from the first author or the corresponding author upon reasonable request.

Declarations

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

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