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Enhanced brain images in the limbic system by functional magnetic resonance imaging (fMRI) during chemical exposures to patients with multiple chemical sensitivities

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Objectives: To elucidate the pathophysiology of multiple chemical sensitivities (MCS) and to explore the possible objective diagnosis approach, we used functional magnetic resonance imaging (fMRI) to examine the reaction of MCS patients' brains at the exposure to chemical substances.
Materials and Methods: Fourteen patients diagnosed as having MCS (average age, 40.6 ± 10.6 years) and 17 normal control participants (average age, 36.9 ± 13.4 years) were examined by a single blind test. They were exposed to nasal inhalation of 5 ppb, 10 ppb, 25 ppb of toluene, and 10 ppm of phenylethyl alcohol (PEA) as the control fragrant substance. Compared to when they inhaled pure air, increased signal-intensity regions at exposures to chemicals in their brains were determined by fMRI.
Results: The percentages of participants who had at least one increased signal-intensity region at the exposure to 25 ppb toluene or PEA in the MCS group was significantly higher than those in the control. The number of increased signal-intensity regions in the MCS group exposed to PEA was also significantly higher than that in the control. Looking at respective brain regions, the limbic systems of the MSC patients showed more frequent signal enhancements when the participants were exposed to PEA compared with that of the control group.
Conclusions: When exposed to 25 ppb of toluene and the fragrant substance, PEA, more patients in the MCS group showed increased signal-intensity regions determined by the fMRI. In addition, MCS patients showed a stronger signal-intensity reaction in the limbic system when exposed to PEA. These findings suggest that the central nervous system is involved in the clinical state of MCS patients and fMRI analysis may contribute to the diagnosis of MCS.

Key words: multiple chemical sensitivities, functional MRI, limbic system, fragrant substance

Introduction

During the late 1950's and early 1960's, a new etiology of a clinical state induced by chemical substances was proposed. According to the etiology, the clinical state, which had been once considered as one of allergy-associated diseases, was a development of new hypersensitive condition in individuals as a result of failure of adaptation to chemical substances in the environment.[1,2] Subsequently, the clinical state, which could not be categorized as either allergy or toxicosis, was termed multiple chemical sensitivities (MCS) by Cullen in the United States in 1987.[3] Since then, a number of disease names were proposed; however, the state is generally known as MCS. It has been reported that some MCS patients have nonspecific neural symptoms or dysautonomia and express a high sensitivity to odor when they are exposed to small amounts of multiple chemical substances.[4] However, it has not been reported that their olfactory threshold is lower than that of normal people.[5,6] Therefore, it is hypothesized that the nasal trigeminal nerve instead of the olfactory nerve may be stimulated,[6] or the information processing system for odor in their brains may not work properly.[5] It is possible that such reactions occur unconsciously in the brains of MCS patients when they are exposed to chemical substances.

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These reactions may induce increases in blood flow in some regions in their brain, and the increases in blood flow could be detected by functional magnetic resonance imaging (fMRI) as increased signal intensities.

To examine this hypothesis, it is useful to compare the occurrence of increased signal intensity detected by fMRI between MCS patients and the control exposed to a chemical substance which has been reported as a cause of MCS. Toluene is a good candidate chemical for this examination, because it is a known cause of MCS[7,8] at low concentrations close to the olfactory threshold. Formaldehyde is also a known cause of MCS[7,8] at low concentrations; however, formaldehyde is a carcinogen[9] and, thus, not suitable as a substance inhaled by the participants of a study.

It should be noted that MCS patients generally feel more unpleasant with the smell of chemical substances compared with controls in odor tests.[10] To examine the involvement of olfaction in MCS patients, the effects of inhalation of a fragrant substance on the brain signal intensity detected by an fMRI may also be useful. Phenylethyl alcohol (PEA), which is usually called "the scent of roses" and not unpleasant for most people, is a suitable fragrant substance in an olfactory exposure experiment.

The objective of this study was to examine whether or not MCS patients show increased brain-signal intensity detected by fMRI when they were exposed to small amounts of toluene at concentrations lower than the olfactory threshold. In the event that an increase in the signal intensity occurred, we also examined which specific regions such as the corpus amygdaloideum, the part of the brain that processes emotions and may be involved with the development of symptoms, showed increased brain-signal intensity. In addition, the effects of PEA were also examined. Such information would contribute to the clarification of the pathophysiology of MCS and to establish an objective diagnostic approach for MCS.

Materials and Methods

Subjects

The participants were 14 patients who were diagnosed as having MCS at the Clinical Environmental Medical Center of Kitasato Institute Hospital between September 2005 and August 2008 and agreed to participate in the experiment (9 men and 5 women; median age, 38 years; average age, 40.6 $\pm$ 10.6 years) and 17, roughly, age-sex matched people selected from the public for controls (9 men and 8 women; median age, 39 years; average age, 36.9 $\pm$ 13.7 years).

The diagnostic criterion created by a study group of allergies supported by the Japanese Ministry of Health and Welfare was used for the diagnosis of MCS in the present study.[7] No MCS patients had a history of brain surgery or impairment of their olfactory senses. The controls were healthy and nonsmokers, and they did not have any problems performing daily activities, and no history of MCS, toxicosis, fibromyalgia, chronic fatigue syndrome, allergic diseases, central neurological diseases, or brain surgery.

fMRI

A conventional clinical MRI instrument (Signa CV/I 1.5 T Ver 9.1, Q/D Head Coil, General Electric, Milwaukee, WI, USA) was used. The configurations of the fMRI in the pulse sequence were: single shot gradient echo planar imaging, repetition time (TR), 3,000 msec; echo time (TE), 50 msec; flip angle (FA), 90 °; number of excitations (NEX), 1; field of view (FOV), 240 $\times$ 240 mm^2; matrix, 128 $\times$ 128; slice thickness, 5 mm; slice gap, 1.5 mm; and slice number, 4 $\times$ 110.

Exposures

The participants were exposed to 5 ppb, 10 ppb, and 25 ppb of toluene and 10 ppm of PEA by inhalation as illustrated in Figure 1. To adjust 5 ppb, 10 ppb, and 25 ppb of toluene in an air bag, we developed a generator system in collaboration with Shigematsu Works Co., Ltd., (Tokyo). The concentration of 10 ppm of PEA was also adjusted by using the same system. In addition, pure air was used as air supplying gas. At the MRI room, respective gases in a 100 L fluorine contained resin bag (Tokyo Deodorant, Tokyo) were exposed to the noses of the participants through the Teflon coated air-supplying pipe and glass pipe. All the participants wore blinders and earplugs to reduce effects of stimulations other than olfaction on the brain image. Figure 2 illustrates the scheme of the exposure to each gas that was conducted for 30 seconds, followed by a 30-second interval while breathing pure air. This was repeated 5 times. The participants were not informed of the order of the exposures of the gases. And between each type of gaseous exposure, there were 5-minute intervals. At the beginning and end of each exposure, pure air was supplied to remove the exposure gas inside the tube. Additionally, during the intervals after the exposure of each gas, the participants were asked whether they smelled any lingering odors or not.

Image analyses and statistics

Advantage Workstation Ver. 4.0 (General Electric Medical Systems, Milwaukee, WI, USA) was used for brain image analysis. We divided the brain regions into 110 parts according to the brain map. Each visualized signal-intensity region was confirmed by a radiologist. The enhancements in the signal were confirmed when the pattern of enhancement was synchronized with the pattern of exposure of the gas schemed in Figure 2. The percentages of the participants that had at least one increased signal-intensity region were calculated for the MCS and the control groups, respectively, and compared by the chi-square test using Microsoft Office Excel 2003. For comparison of the number of increased signal-intensity regions per participant, the Mann-Whitney U test was performed. In addition the brain was divided into the following 9 areas: the limbic system (cingulate gyrus, amygdala, hippocampus, septula, fornix, corporis mamillaris, and gyrus parahippocampalis), frontal lobe, basal ganglion, temporal lobe excluding hippocampus and gyrus parahippocampalis, diencephalon, cerebellum, midbrain, occipital lobe, and pons to compare the

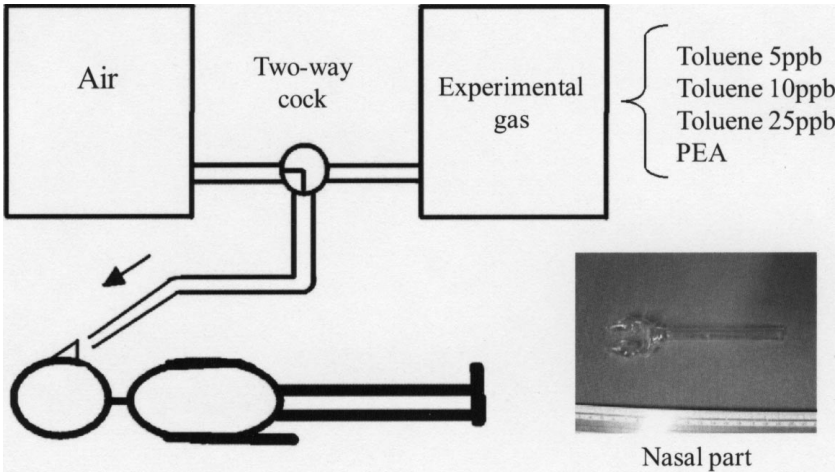

Figure 1. Inhalation of vapors for the participants with MCS and the controls

The experimental gases (toluene 5 ppb, 10 ppb, 25 ppb, and PEA 10 ppm) and pure air, which was prepared in the fluorine contained resin bag, were given to participants lying down on an fMRI bed alternatively, through a two-way cock.

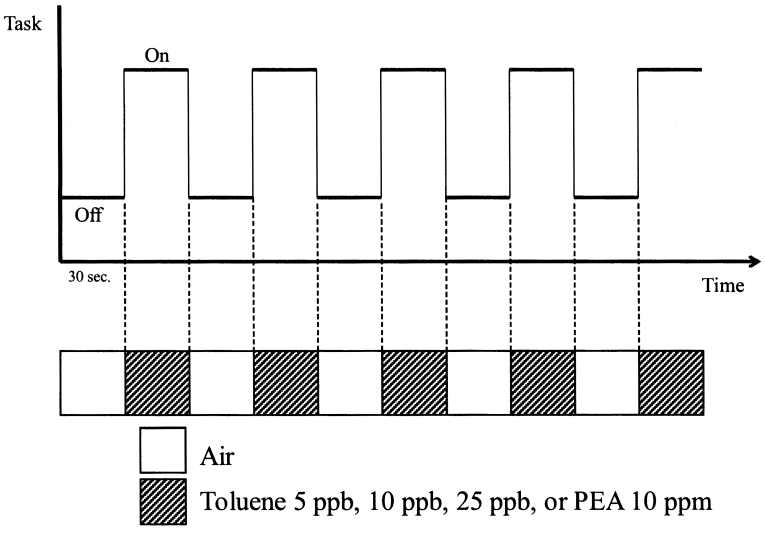

Figure 2. Time scheme of inhalation vapors to participants

According to the ON or OFF of a task, the participants were exposed to the gases or air for 30 seconds.

numbers of increased signal-intensity regions in their respective brain regions to each gaseous exposure between the two groups.

The percentages of the participants who could smell each gas were calculated for the MCS and the control groups respectively, and compared by the chi-square test. In addition, the percentages of the participants who had at least one increased signal-intensity region stratified by sensing smell or not between the MCS and the control groups were also compared by the chi-square test.

Ethical considerations

This study was approved by the Ethical Committee of Kitasato University School of Medicine. We gave appropriate consideration to the protection of health, safety, and personal information of each individual participant who fully understood and agreed to the risk and meaning of this experiment as we explained it to them.

Results

Increased signal-intensity regions in the whole brain

The percentages of the participants who had at least one increased signal-intensity region in their brains in the MCS and the control groups exposed to each gas are shown in Table 1. The percentages of the participants who had at least one increased signal-intensity region at the exposure to 25 ppb toluene or 10 ppm PEA in the MCS group was significantly higher than those in the control. There were no significant differences with 5 ppb and 10 ppb toluene exposures between the MCS and the control groups.

The typical images of sum of the number of increased signal-intensity regions among 110 regions in the brain in the MCS and the control groups are shown in Figure 3. The median and mean value of the number of increased signal-intensity regions among 110 regions in the brains of the MCS patients and the controls exposed to each

Table 1. Percentages of participants who had at least one intesified region in the brain in the MCS and the control groups detected by the fMRI

Substance	Concentration	MCS n = 14	Control n = 17	x^2	P
		%	%		
Toluene	5 ppb	64.3	58.8	0.096	0.756
	10 ppb	71.4	41.2	2.837	0.092
	25 ppb	78.6	35.3	5.806	0.015*
PEA	10 ppm	85.7	41.2	6.418	0.011*

*Significant difference

MCS, multiple chemical sensitivities; fMRI, functional magnetic resonance imaging; PEA, phenylethyl alcohol

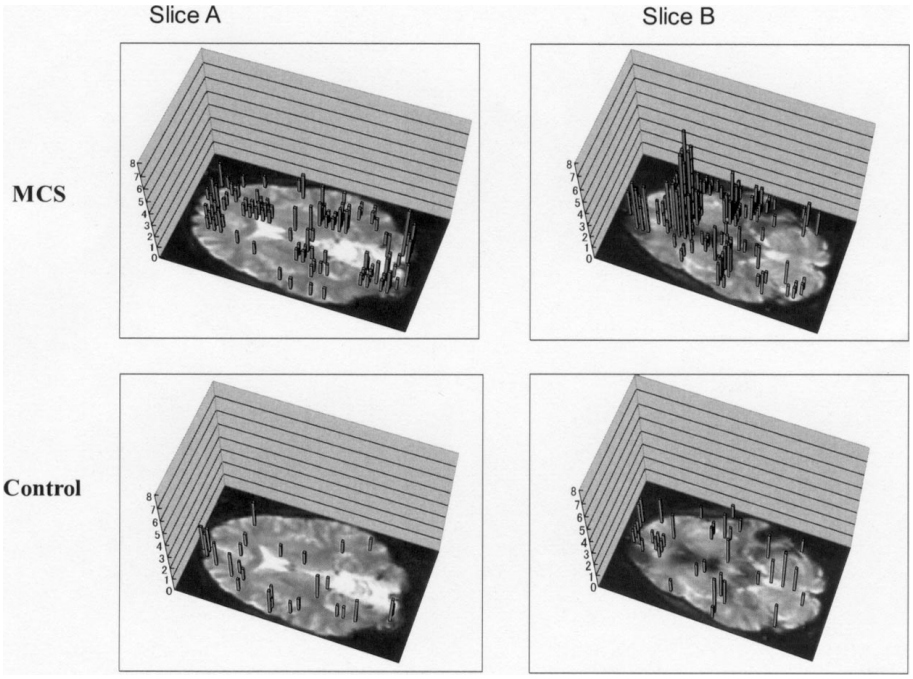

Figure 3. The sums of increased signal-intensity regions of two slices indicated as vertical bars in 110 brain areas of an fMRI at the upper two levels (Slice A) and the lower two levels (Slice B) in the MCS and the control groups exposed to PEA.

Table 2. The numbers of increased signal-intensity region on the fMRI brain image in 110 regions according to the brain map in the MCS and the control groups exposed to toluene and PEA

Substance	Concentration	MCS n = 14		Control n = 17	
		Median	Mean ± SD	Median	Mean ± SD
Toluene	5 ppb	4.5	(5.8 ± 5.26)	5.0	(7.5 ± 6.39)
	10 ppb	5.0	(5.7 ± 4.60)	3.0	(4.1 ± 3.75)
	25 ppb	4.5	(7.1 ± 8.05)	3.0	(4.4 ± 6.03)
PEA	10 ppm	8.5	(9.6 ± 6.14)*	2.0	(3.9 ± 4.35)

*P < 0.05

fMRI, functional magnetic resonance imaging; MCS, multiple chemical sensitivities; PEA, phenylethyl alcohol

Table 3. The median, mean, standard deviation of numbers of signal-intensity sites in nine brain areas of fMRI in the MCS and control groups exposed to toluene and PEA

Group	LS	FL	BN	TL	DC	CB	MB	OL	Pons
MCS (n = 14)									
5 ppb	0.0 (0.6 ± 0.93)	0.0 (0.6 ± 0.93)	0.0 (0.5 ± 0.65)	0.0 (0.3 ± 0.47)	0.0 (0.2 ± 0.58)	0.5 (0.8 ± 1.12)	0.0 (0.1 ± 0.27)	0.0 (0.1 ± 0.6)	0.0 (0.0 ± 0.00)
10 ppb	0.0 (0.6 ± 0.76)	0.5 (0.7 ± 0.83)	0.0 (0.3 ± 0.47)	1.0 (0.6 ± 0.51)	0.0 (0.0 ± 0.00)	0.0 (0.9 ± 1.17)	0.0 (0.0 ± 0.00)	0.0 (0.3 ± 0.61)	0.0 (0.0 ± 0.00)
25 ppb	0.5 (1.0 ± 1.57)	0.0 (0.6 ± 1.01)	0.0 (0.3 ± 0.47)	0.0 (0.7 ± 0.99)	0.0 (0.2 ± 0.43)	1.0 (0.7 ± 0.83)	0.0 (0.1 ± 0.27)	0.0 (0.2 ± 0.43)	0.0 (0.1 ± 0.27)
PEA	1.0* (1.1 ± 1.03)	1.0 (1.4 ± 1.08)	0.0 (0.4 ± 0.51)	1.0 (0.7 ± 0.61)	0.0 (0.4 ± 0.63)	0.0 (0.7 ± 1.14)	0.0 (0.2 ± 0.43)	0.0 (0.2 ± 0.43)	0.0 (0.0 ± 0.00)
Control (n = 17)									
5 ppb	0.0 (0.4 ± 0.62)	1.0 (0.9 ± 0.99)	0.0 (0.6 ± 0.79)	0.0 (0.7 ± 0.99)	0.0 (0.6 ± 0.72)	1.0 (0.9 ± 0.93)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)
10 ppb	0.0 (0.2 ± 0.44)	0.0 (0.4 ± 0.49)	0.0 (0.4 ± 0.49)	0.0 (0.5 ± 0.72)	0.0 (0.2 ± 0.39)	0.0 (0.6 ± 0.94)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)
25 ppb	0.0 (0.5 ± 0.94)	0.0 (0.5 ± 1.01)	0.0 (0.1 ± 0.33)	0.0 (0.4 ± 0.80)	0.0 (0.2 ± 0.53)	0.0 (0.6 ± 0.86)	0.0 (0.0 ± 0.00)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)
PEA	0.0 (0.2 ± 0.39)	0.0 (0.8 ± 0.95)	0.0 (0.1 ± 0.33)	0.0 (0.3 ± 0.59)	0.0 (0.2 ± 0.39)	0.0 (0.5 ± 0.94)	0.0 (0.1 ± 0.24)	0.0 (0.1 ± 0.24)	0.0 (0.0 ± 0.00)

Median (Mean ± SD)

*Significant difference contrasted MCS versus Controls

fMRI, functional magnetic resonance imaging; MCS, multiple chemical sensitivities; PEA, phenylethyl alcohol; LS, limbic system; FL, frontal lobe; BN, basal nucleus; TL, temporal lobe; DC, diencephalon; CB, cerebellum; MB, midbrain; OL, occipital lobe, PEA, phenylethyl alcohol

gas are shown in Table 2. The number of increased signal-intensity regions in the MCS group exposed to PEA was also significantly higher than that in the controls.

Specific increased signal-intensity regions

As shown in Figure 3, the increased signal-intensity regions were distributed around the frontal lobe. The medians and mean values of the number of the increased signal-intensity regions in 9 brain areas are shown in Table 3. The number of the increased signal-intensity regions in the limbic system of the MCS group exposed to PEA 10 ppm was significantly higher than that of the control group.

Relationship to presence or absence of odor

When conducting exposure experiments of each gas, the participants were asked if they could smell any odor or not. There was no difference of odor perception between the MCS patients and the controls for any gases (Table 4).

Table 4. Percentages of the participants who smelled each experimental gas in the MCS and control groups

Substance	Concentration	MCS n = 14	Control n = 17	x^2	P
		%	%		
Toluene	5 ppb	42.6	47.1	0.055	0.815
	10 ppb	35.7	64.7	2.584	0.108
	25 ppb	35.7	47.1	0.406	0.524
PEA	10 ppm	92.7	88.2	0.188	0.665

Table 5 shows percentages of the participants who had at least one increased signal-intensity region detected by fMRI in the MCS and the control groups classified by sensing the odor of each experimental gas. With toluene and PEA exposure, there was no significant difference in fMRI reaction caused by the perception of odor.

Discussion

Although pathophysiological mechanisms are uncertain, MCS etiology has been discussed in both the physiological and psychogenic categories.[11] Studies have been carried out from various angles, but no abnormalities in the defined parameters have yet to be found to be sufficient as scientific evidence. The kindling which originally indicates the induced convulsion following repeated low-level electric stimulation was proposed for the mechanism of chemical sensitivity following repeated exposures to chemical substances.[12] Time-dependent sensitization is another hypothesis of the development of chemical sensitivities.[13]

In the present study, a provocation test followed by fMRI analysis was performed on the patients diagnosed with MCS in order to find its mechanism and a possible objective diagnostic method. There are several studies of provocation tests using blood pressure, heart rate, and clinical condition[4,14,15] with olfaction and trigeminal stimulation[5] as parameters for MCS. In addition, imaging tests have been performed using positron emission tomography (PET) and single photon emission computed

Table 5. Percentages of the participants who had at least one increased signal-intensity region detected by fMRI in the MCS and control groups classified by sensing smell of each experimental gas

Group	Substance	Concentration	Odor + %	Odor – %	x^2	P
MCS (n = 14)						
	Toluene	5 ppb	100.0	88.9	0.944	0.529
		10 ppb	81.8	66.7	0.495	0.445
		25 ppb	87.5	55.6	0.443	0.706
	PEA	10 ppm	60.0	100.0	1.236	0.404
Control (n = 17)						
	Toluene	5 ppb	85.7	85.6	1.077	0.500
		10 ppb	80.0	77.8	0.009	0.725
		25 ppb	80.0	88.9	0.207	0.604
	PEA	10 ppm	92.3	100.0	0.082	0.929

Note: Odor + indicates the participants who sensed odor at the exposure of each gas. Odor – indicates the participants who did not sense odor at the exposure to each gas.

tomography (SPECT) as an objective diagnostic method for MCS, but they are insufficient as diagnostic methods for MCS.[16-19] The relationship between olfactory irritation and the limbic system may be related to neuronal irritation or kindling.[20,21] Therefore, we performed this provocation test followed by fMRI analysis to detect the increase in blood flow in brain regions in areas of the limbic system.

The increases in the brain blood flow between the time of air exposure and the gaseous exposure was expressed as increased signal-intensity regions. In the present study, more patients in the MCS group were found to exhibit signal enhancement compared to the control when exposed to toluene at the concentration of 25 ppb, which is generally a lower concentration than the olfactory threshold. The percentages of the participants that detected the smell of toluene at 25 ppb were not different between the MCS and the control groups. The olfactory threshold seems to be the same in both groups. Doty et al.[4] reported that MCS patients had more nasal resistances and respiratory rates at the olfactory tests including PEA. However, the olfactory thresholds for all types of fragrant substances in the MCS group were not lower than those in normal control participants.[4,6] Since there were no differences in the percentages of the participants who had at least one increased signal-intensity region between the participants who sensed the smell of toluene and those who did not, the increase in blood flow may not be related to the perception of the smell. It is possible to hypothesize that toluene at a concentration 1/20th of the olfactory threshold is perceived by other sensory nerves such as the trigeminal nerve[5] or by transporting molecules of toluene into the brain via the blood. However, this hypothesis was not relatively supportive because no differences were observed in the number of increased signal-intensity regions in specific regions of the brain between the MCS and the control groups at the exposure to 25 ppb of toluene.

Following the exposure to PEA, the percentage of participants who had at least one increased signal-intensity region and the number of increased signal-intensity regions detected by fMRI in the MCS group were significantly higher than those in the control. The exposure to PEA, perceived as a smell by both groups, created a stronger brain response in the MCS group than it did in the control group. Therefore, although it may not have enough sensitivity and specificity for the diagnosis, fMRI analysis after the exposure to PEA could contribute to the diagnosis of MCS.

The MCS and the control groups had a high rate of perception for the smell of PEA; however, no significant differences in the perception of smell were observed between the two groups. In addition, there were no differences in the signal-intensity between the presence or absence of perception. Chemical substances that were perceived by smell induced an extreme brain response in the MCS patients. From the observation of signal-intensity enhancement for each brain region, the MCS group showed a stronger signal-intensity reaction in the limbic system at the exposure to PEA in comparison to the control, suggesting emotional brain involvement. An emotional response may have been induced by the exposures to various chemical agents including fragrance in the MCS group, and this reaction may be a pathophysiological characteristic of MCS. It was reported that the MCS group thought PEA more unpleasant than did the control group, and they seemed to have had extreme trigeminal stimulation.[6] This reaction may have been caused by limbic kindling, resulting in the disorders of the autonomic nerve system or other mental symptoms.

The limitations of the present study were as follows. The number of participants was insufficient due to difficulties in obtaining those who were willing. Many MCS patients were sensitive to odors, and hesitated to be exposed to chemical substances. Considering the safety of the patients, it was not possible to employ a concentration of toluene that could be detected by smell. The 25 ppm of toluene may not be a sufficient provocation concentration. In addition, although fMRI is effective in detecting the increase in blood flow with an associated rise in reduced hemoglobin, it is incapable of detecting the decrease in blood flow, which indicates the possible inhibition of brain functions. It may be useful for brain analysis to combine fMRI with other methods such as brain SPECT.

In conclusion, the exposures to toluene at 25 ppm or the fragrant substance, PEA, induced increased signal-intensity regions in the fMRIs among the MCS patients. The MCS patients showed a stronger signal-intensity reaction in the limbic system when exposed to a fragrant substance. These results indicate the possibility of dysfunction of the limbic system due to kindling by the stimulation of olfactory neurons. These results indicate that fMRI analyses could contribute to the diagnosis of MCS.

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