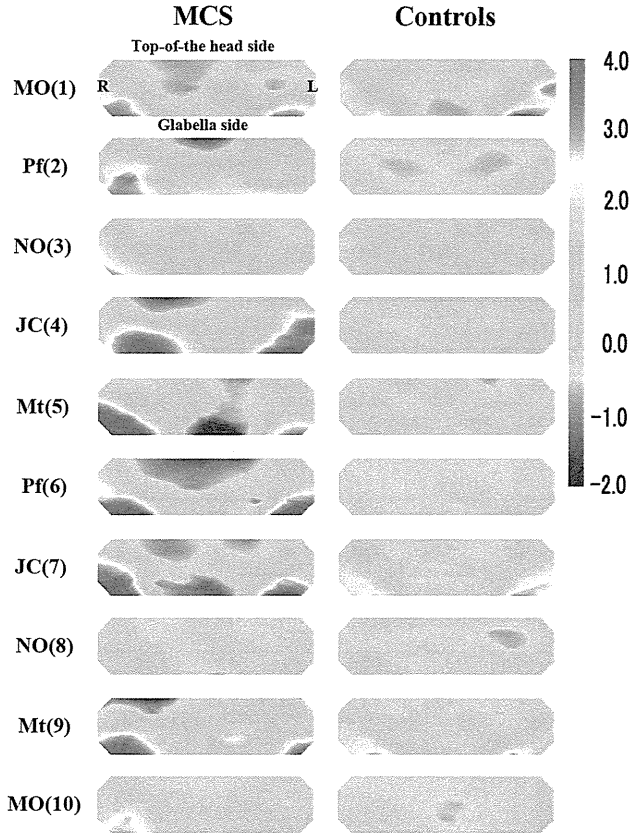

Fig. 4 Topographical maps of average *z*-scores for oxyHb between patients with MCS ($n = 6$) and controls ($n = 6$). *MO* mandarin orange, *Pf* perfume, *NO* non-odorant, *JC* Japanese cypress, *Mt* menthol. *Numbers in parentheses* indicate the order of the 10 repetitions (1–10)

olfactory stimulation test. And then, the NIRS imaging revealed that the CNS of patients with MCS may have been confused in the late stage of the olfactory stimulation test [14]. The results of the present study support this hypothesis.

Physical and psychological measurements

Table 3 shows the results of the *t* test for the physical and psychological scales. CSS-SHR scores were significantly higher of patients with MCS than of controls ($p < 0.001$). Thus, chemical sensitivity in patients with MCS was demonstrated not only by the results of QEESI but also by those of the CSS-SHR scale. In the psychological evaluations, the APQ ($p < 0.1$) and TAS-20 DIF ($p < 0.1$) scores showed a higher tendency only for patients with MCS compared with controls, probably because of the small sample size, but these differences were significant in our previous study [14]. No significant differences were observed in the SSAS, TAS, MCSD, TMAS, TAS-20 total, TAS-20 DDF, and TAS-20 EOT scores, similar to our previous study [14].

Discussion

As shown in Fig. 2, strong activation was observed during olfactory stimulation with several different odorants in patients with MCS compared with controls. All patients with MCS participating in this study had participated in our previous study [14]. Although the previous study had been conducted 1–2 years before this study, similar responses were observed in both.

The first olfactory stimulation with MO (1) lead to increased rCBF levels in the PFC, which was not significantly different between patients with MCS and controls. Because MO (1) was the first test, the patients may not have had the chance to get used to the olfactory stimuli and the response may have been caused by affective tension. After the first test, rCBF levels in controls remained almost stable until the end of the test involving MO (10). Thus, we did not superimpose the data of first and second block but showed all the data as the results.

In the subjective measurement by irritating and hedonic scales and physical and psychological measurements, the overall results were similar to our previous study [14] and were reproducible. In the present study, even after olfactory stimulation, significant activations were observed in the PFC of patients with MCS than in that of controls. The activations were especially strong on both right and left sides of OFC in the PFC. Further, the activations in both patients with MCS and controls were suppressed after the olfactory stimulation involving NO, and the differences were not significant. These results indicate that the olfactory system in patients with MCS adequately distinguishes the non-odorant. Comparing the rCBF between the first and second exposures revealed significant correlations in both patients with MCS and controls for all stimuli, with the exception of MO and NO in patients with MCS. The lack of correlation in the MO and NO test in patients with MCS may be due to the small sample size.

An odorant-related increase in activation in the ACC has been observed in patients with MCS [18]. The ACC is involved in adequate control of top–down or bottom–up modulation of stimuli and is connected to the PFC. Past exposures to hazardous chemicals are stored as memories in the PFC through olfactory nerve circuits, causing various physical or psychological responses such as emotional, visceral, or autonomic responses during the processing of top–down stimuli when exposed to odorants later in life [14]. In the present study, we found that recovery from activation in the PFC after an olfactory stimulation is delayed in patients with MCS compared with controls. These findings support the current understanding of the pathology of this disorder: compared to healthy subjects, patients with MCS strongly respond to odorants that they encounter in daily life, the repeated daily exposure to the odorants keeps

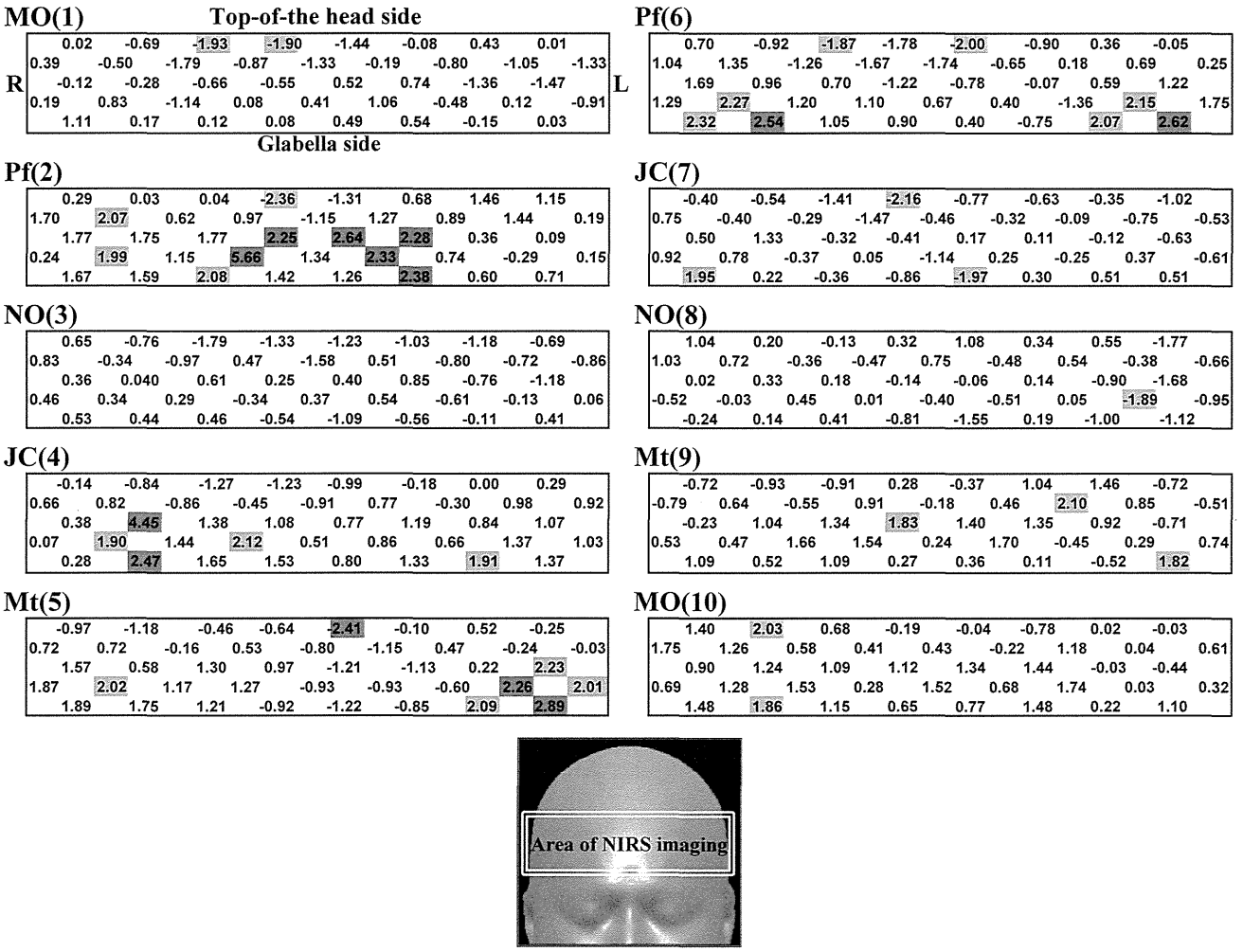

Fig. 5 Average t value of each channel comparing z-scores for oxyHb between patients with MCS ($n = 6$) and controls ($n = 6$). *Red rectangles* denote statistically significant positive correlations ($p < 0.05$), and *blue rectangles* denote statistically significant negative correlations ($p < 0.05$). *Yellow rectangles* denote positive correlations ($p < 0.10$), and *green rectangles* denote negative correlations ($p < 0.10$). The channels are located in the position shown by the *white double line rectangle* below

them in a reactive state. Due to their physical and psychological intolerance to odorants, the patients try to avoid exposure to the odorants. In this study, 4 patients with MCS had episodes of initial exposure to chemicals that triggered the first symptoms. These included organic solvents or incense at the workplace, exhaust gas from diesel machines in the neighborhood, odors from pesticides, or fragrance from a neighbor. Two patients had episodes of repeated exposure to solvents emitted from a neighboring industrial plant or a neighboring paint store, respectively. Patients with MCS complained about a chemical-sensitive condition thereafter. The psychological evaluations in our study support the theory of a strong response in patients with MCS.

In the recovery stage after the stimulation, the activation was especially strong in the OFC. The olfactory neuroanatomy is intertwined, via extensive reciprocal axonal connections, with primary emotion areas including the amygdala, hippocampus, and OFC [39, 40]. Olfactory stimulation directly activates amygdala neurons, innervating a region in the OFC. The olfactory sense has a unique intimacy with the emotion system, and the perception of smell is known to be dominated by emotion [41]. Strong activation in the OFC might remain as potent affective experiences following olfactory stimuli in patients with MCS compared with controls. In this study, lateral orbitofrontal regions were specifically activated in the patients with MCS. The valence of odors is represented in particular in the OFC [42]. Nearly all odors were evaluated as unpleasant by the MCS patients in the subjective evaluation after the stimulation. Pleasant odors preferentially activate medial orbitofrontal regions, whereas unpleasant odors activate more lateral regions [43–46]. The strong activations of the lateral OFC in the patients with

Table 3 Results of the *t* test for the physical and psychological scales

Scales	MCS ($n = 6$)	Controls ($n = 6$)	p value
QEESI (CI)	75.0 (19.2)	4.2 (5.3)	<0.001*
QEESI (OI)	33.2 (24.1)	6.7 (15.8)	0.048*
QEESI (SS)	72.7 (13.5)	5.2 (11.3)	<0.001*
CSS-SHR	51.7 (2.2)	32.5 (3.8)	<0.001*
SSAS	34.3 (8.7)	28.0 (5.2)	0.156
APQ	178.3 (39.4)	131.2 (42.6)	0.075
TAS	13.3 (7.7)	12.8 (10.4)	0.927
MCSD	16.0 (4.7)	20.5 (5.1)	0.141
TMAS	11.0 (4.1)	8.2 (1.5)	0.156
NAS	37.0 (17.0)	27.5 (8.6)	0.250
TAS-20 total	48.7 (16.2)	38.0 (4.0)	0.172
TAS-20 DIF	14.5 (5.4)	9.5 (3.0)	0.076
TAS-20 DDF	12.8 (4.8)	10.3 (1.2)	0.264
TAS-20 EOT	21.3 (7.2)	18.2 (4.0)	0.375

Values are expressed as means (±standard deviations)

CI chemical intolerance, *OI* other intolerance, *SS* symptom severity

* Significant at $p < 0.05$

MCS suggest that these odors were extremely unpleasant for the MCS patients.

Both the ACC and OFC are implicated in decision-making, emotion, and social behavior. Recent evidence suggests that the ACC and OFC make distinct contributions to each of these aspects of decision-making [47]. The OFC is involved in the cognitive processing of stimuli and the representation of preferences. The ACC may mediate the relationship between a past experience and the choice of the next action. Thus, our results suggest that a past strong exposure to hazardous chemicals activates the ACC (and the connected PFC) during olfactory stimuli in the patients with MCS, and a strong activation in the OFC remains after the stimuli. In particular, the lateral OFC is specifically activated when the odor is unpleasant for the patients with MCS. However, the OFC and ACC are anatomically interconnected, and their interaction stimulates decision-making. Their individual function independent of each other remains unclear. Further research is required to understand the recovery process in MCS and the pathology of this disorder.

The present study has some limitations. First, the very small sample size makes the results vulnerable to selection bias. This could be alleviated by including a larger study population. However, despite the small sample size of this study, differences between the patients with MCS and the controls in the NIRS imaging were evident. The results indicate that the evaluation combining NIRS imaging with olfactory stimulation tests is a valuable method for the objective evaluation of MCS. Second, to the best of our knowledge, this is the first case–control study evaluating changes in rCBF in the PFC using NIRS imaging after olfactory stimulation in patients with MCS. Further long-time evaluation after olfactory stimulation would provide valuable information for understanding the pathology of MCS. A third limitation of this study is the lack of standardized objective measures to identify and define MCS. Therefore, most definitions of MCS are entirely qualitative, relying on subjective reports of distressing symptoms and environmental exposure from patients and clinicians. Several individuals with self-reported MCS symptoms were excluded, at the discretion of the clinic physician, because of mental disorders or allergic symptoms.

In conclusion, despite the small sample size, this experimental study detected an activation that remained even after olfactory stimulation, specifically in the PFC of patients with MCS. We propose that recovery from such activation is delayed in patients with MCS and that their chemical-sensitive state remains due to the repeated daily exposure, leading them eventually to develop intolerance to these odorants. Our study demonstrates that NIRS imaging objectively reflects the status of patients with MCS.

Acknowledgments This study was financially supported by a Grant-in-Aid for Scientific Research (ID: 22590568) provided by the Japan Ministry of Education, Culture, Sports, Science and Technology. This study was also financially supported by a health science research grant (H25-5962) from the Japan Ministry of the Environment and a Grant-in-Aid for Health and Labour Sciences Research Grant (H25-008) provided by the Japan Ministry of Health, Labour and Welfare. We express our sincere appreciation to the staff members of the Hyakumanben Clinic for their assistance in data collection.

Conflict of interest The authors declare that no conflict of interests exists.

Ethical standard This study was approved by the ethical committee for human research at the Hyakumanben Clinic (99642-61) and the Louis Pasteur Center for Medical Research (LPC.11).

Informed consent This manuscript does not contain the personal medical information about an identifiable living individual. All patients provided written informed consent.

References

1. Cullen MR. The worker with multiple chemical sensitivities: an overview. Occup Med. 1987;2:655–61.
2. Graveling RA, Pilkington A, George JP, Butler MP, Tannahill SN. A review of multiple chemical sensitivity. Occup Environ Med. 1999;56:73–85.
3. Winder C. Mechanisms of multiple chemical sensitivity. Toxicol Lett. 2002;128:85–97.
4. Berg ND, Linneberg A, Dirksen A, Elberling J. Prevalence of self-reported symptoms and consequences related to inhalation of airborne chemicals in a Danish general population. Int Arch Occup Environ Health. 2008;81:881–7.

5. Caress SM, Steinemann AC. Prevalence of multiple chemical sensitivities: a population-based study in the southeastern United States. Am J Public Health. 2004;94:746–7.
6. Hausteiner C, Bornschein S, Hansen J, Zilker T, Förstl H. Self-reported chemical sensitivity in Germany: a population-based survey. Int J Hyg Environ Health. 2005;208:271–8.
7. Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol. 1999;150:1–12.
8. Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population. Arch Environ Health. 1996;51:275–82.
9. Azuma K, Uchiyama I, Katoh T, Ogata H, Arashidani K, Kunugita N. Prevalence and characteristics of chemical intolerance: a Japanese population-based study. Arch Environ Occup Health. 2014;. doi:10.1080/19338244.2014.926855 [Epub ahead of print].
10. Sorg BA. Multiple chemical sensitivity: potential role for neural sensitization. Crit Rev Neurobiol. 1999;13:283–316.
11. Berg ND, Linneberg A, Dirksen A, Elberling J. Phenotypes of individuals affected by airborne chemicals in the general population. Int Arch Occup Environ Health. 2009;82:509–17.
12. Lacour M, Zunder T, Schmidtke K, Vaith P, Scheidt C. Multiple chemical sensitivity syndrome (MCS)—suggestions for an extension of the US MCS-case definition. Int J Hyg Environ Health. 2005;208:141–51.
13. McKeown-Eyssen GE, Baines CJ, Marshall LM, Jazmaji V, Sokoloff ER. Multiple chemical sensitivity: discriminant validity of case definitions. Arch Environ Health. 2001;56:406–12.
14. Azuma K, Uchiyama I, Takano H, Tanigawa M, Azuma M, Bamba I, et al. Changes in cerebral blood flow during olfactory stimulation in patients with multiple chemical sensitivity: a multichannel near-infrared spectroscopic study. PLoS One. 2013;8(11):e80567. doi:10.1371/journal.pone.0080567.
15. Hock C, Müller-Spahn F, Schuh-Hofer S, Hofmann M, Dirnagl U, Villringer A. Age dependency of changes in cerebral hemoglobin oxygenation during brain activation: a near-infrared spectroscopy study. J Cereb Blood Flow Metab. 1995;15:1103–8.
16. Obrig H, Villringer A. Beyond the visible–imaging the human brain with light. J Cereb Blood Flow Metab. 2003;23:1–18.
17. Okamoto M, Matsunami M, Dan H, Kohata T, Kohyama K, Dan I. Prefrontal activity during taste encoding: an fNIRS study. Neuroimage. 2006;31:796–806.
18. Hillert L, Musabasic V, Berglund H, Ciumas C, Savic I. Odor processing in multiple chemical sensitivity. Hum Brain Mapp. 2007;28:172–82.
19. Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity. J Neurol Sci. 2009;287:72–8.
20. Dalton P. Psychophysical and behavioral characteristics of olfactory adaptation. Chem Senses. 2000;25:487–92.
21. Elsberg CA, Spotnitz H. Relation of stimulation time of receptors to recovery time in the nervous system: visual, olfactory and auditory senses. J Neurophysiol. 1939;2:227–33.
22. Zufall F, Leinders-Zufall T. The cellular and molecular basis of odor adaptation. Chem Senses. 2000;25:473–81.
23. Anonymous. Multiple chemical sensitivity: a 1999 Consensus. Arch Environ Health. 1999;54:147–49.
24. Kameyama M, Fukuda M, Yamagishi Y, Sato T, Uehara T, Ito M, et al. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. Neuroimage. 2006;29:172–84.
25. Tanida M, Sakatani K, Takano R, Tagai K. Relation between asymmetry of prefrontal cortex activities and the autonomic nervous system during a mental arithmetic task: near infrared spectroscopy study. Neurosci Lett. 2004;369:69–74.
26. Hoshi Y, Kobayashi N, Tamura M. Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. J Appl Physiol. 2001;90:1657–62.
27. Strangman G, Culver JP, Thompson JH, Boas DA. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage. 2002;17:719–31.
28. Nordin S, Millqvist E, Lowhagen O, Bende M. A short Chemical Sensitivity Scale for assessment of airway sensory hyperreactivity. Int Arch Occup Environ Health. 2004;77:249–54.
29. Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. Psychosom Med. 1988;50:510–9.
30. Mandler G, Mandler JM, Uviller ET. Autonomic feedback: the perception of autonomic activity. J Abnorm Psychol. 1958;56:367–73.
31. Tellegen A, Atkinson G. Openness to absorbing and self-altering experiences (''absorption''), a trait related to hypnotic susceptibility. J Abnorm Psychol. 1974;83:268–77.
32. Crowne DP, Marlowe D. A new scale of social desirability independent of psychopathology. J Consult Psychol. 1960;24:349–54.
33. Bendig AW. The development of a short form of the manifest anxiety scale. J Consult Psychol. 1956;20:384.
34. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988;54:1063–70.
35. Taylor GJ, Bagby RM, Parker JD. The 20-Item Toronto Alexithymia Scale. IV. Reliability and factorial validity in different languages and cultures. J Psychosom Res. 2003;55:277–83.
36. Schroeter ML, Zysset S, Kruggel F, von Cramon DY. Age dependency of the hemodynamic response as measured by functional near-infrared spectroscopy. Neuroimage. 2003;19:555–64.
37. Matsuda G, Hiraki K. Sustained decrease in oxygenated hemoglobin during video games in the dorsal prefrontal cortex: a NIRS study of children. Neuroimage. 2006;29:706–11.
38. Horaguchi T, Ogata Y, Watanabe N, Yamamoto M. Behavioral and near-infrared spectroscopy study of the effects of distance and choice in a number comparison task. Neurosci Res. 2008;61:294–301.
39. Haberly LB. Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. Chem Senses. 2001;26:551–76.
40. Gottfried JA. Central mechanisms of odour object perception. Nat Rev Neurosci. 2010;11:628–41.
41. Krusemark EA, Novak LR, Gitelman DR, Li W. When the sense of smell meets emotion: anxiety-state-dependent olfactory processing and neural circuitry adaptation. J Neurosci. 2013;33:15324–32.
42. de Araujo IE, Rolls ET, Velazco MI, Margot C, Cayeux I. Cognitive modulation of olfactory processing. Neuron. 2005;46:671–9.
43. Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, et al. Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci. 2003;6:196–202.
44. Gottfried JA, Dolan RJ. The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. Neuron. 2003;39:375–86.
45. Rolls ET, Kringelbach ML, de Araujo IE. Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci. 2003;18:695–703.
46. Zald DH, Pardo JV. Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. Proc Natl Acad Sci USA. 1997;94:4119–24.
47. Rushworth MF, Behrens TE, Rudebeck PH, Walton ME. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. Trends Cogn Sci. 2007;11:168–76.

厚生労働科学研究費補助金　健康安全・危機管理対策総合研究事業

シックハウス症候群の診断基準の検証に関する研究
平成27年度　総括・分担研究報告書

平成28年（2016）5月発行

編　　者　坂部　貢
発 行 所　東海大学医学部基礎医学系生体構造機能学領域
〒259-1193　神奈川県伊勢原市下糟屋143
E-mail：sakabek@tokai-u.jp
印刷・製本　株式会社栄文舎印刷所
〒252-0157 神奈川県相模原市緑区中野545
TEL：042-784-1185　FAX：042-784-6637