Neuromagnetic Changes of Brain Rhythm Evoked by Intravenous Olfactory Stimulation in Humans


Summary: To identify the changes in the respective frequency band and brain areas related to olfactory perception, we measured magnetoencephalographic (MEG) signals before and after instilling intravenously thiamine propyl disulfide (TPD) and thiamine tetrahydrofurfuryl disulfide monohydrochloride (TTFD), which evoked a strong and weak sensation of odor, respectively. For the frequency analysis of MEG, a beamformer program, synthetic aperture magnetometry (SAM), was employed and event-related desynchronization (ERD) or synchronization (ERS) was statistically determined. Both strong and weak odors induced ERD in (1) beta band (13-30 Hz) in the right precentral gyrus, and the superior and middle frontal gyri in both hemispheres, (2) low gamma band (30-60 Hz) in the left superior frontal gyrus and superior parietal lobule, and the middle frontal gyrus in both hemispheres, and (3) high gamma band 2 (100-200 Hz) in the right inferior frontal gyrus. TPD induced ERD in the left temporal, parietal and occipital lobes, while TTFD induced ERD in the right temporal, parietal and occipital lobes. The results indicate that physiological functions in several regions in the frontal lobe may change and the strength of the odor may play a different role in each hemisphere during olfactory perception in humans.

Key words: Magnetoencephalography; Synchronization; Desynchronization; Odor; Gamma band; SAM; MEG.

Introduction

In the study of the olfactory system in animals, changes in activity, mainly in the frequency band around 40 Hz, have been recorded from the olfactory bulb (Adrian 1942; Otto son 1959; Yamamoto and Yamamoto 1962; Freeman 1974; Breseseler and Freeman 1980). The orbitofrontal cortex was identified as the olfactory area cortex in rhesus monkeys (Tanabe et al. 1975). However, for studies in humans, the number of reports is still small and the findings are not consistent, so there is little agreement on what activity occurs and where the processing center for odor lies in the human brain. Various methods and devices have been used to present odor stimuli, for example, odor papers or bottles, the spraying of odors into the nasal cavity, (blast method), and the apparatus designed by Kobal (Kobal and Hummel 1988). However, it is difficult to separate the response of the olfactory nerve from that of the trigeminal nerve caused by direct chemical or mechanical stimuli. When the olfactory nerve was stimulated with TPD (Alamin®, Takeda Pharmaceutical Company Ltd, Osaka, Japan) and TTFD (Alamin P®, Takeda Pharmaceutical Company Ltd, Osaka, Japan), subjects smelled a drastic and distinct odor like garlic in their expired air after the injection. Since the odor is not sprayed directly, this method is expected to reduce the effect caused by directly stimulating the trigeminal nerve. In addition, TPD and TTFD induce a stronger and weaker sensation of odor, respectively, so we may be able to compare brain activation caused by each stimulus.

Since neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) cannot record physiological cortical oscillation, electrophysiological methods such as magnetoencephalography (MEG) and electroencepha-
lography (EEG) should be used. MEG was used for its theoretical advantage in terms of spatial resolution over EEG. To analyze frequency, we employed synthetic aperture magnetometry (SAM) using the adaptive beamformer technique with a nonlinear constrained minimum-variance. With this technique, one can calculate event-related desynchronization (ERD) or event-related synchronization (ERS) statistically with a high signal-to-noise ratio. The duration of odor perception lasts no less than 70 seconds, so it is suited to frequency analysis using SAM. Though there have been several reports recording evoked magnetic fields following odor stimulation (Kettenmann et al. 1996, 1997; Sakuma et al. 1997; Tonoike et al. 1998; Walla et al. 2001 2003), to our knowledge, this is the first report of a frequency analysis of MEG using SAM in the study of human olfaction. We speculated that cortical activity, especially in the beta or gamma frequency band, should be detectable in multiple cortical areas when one perceives odors.

**Methods**

**Subjects**

Nine healthy right-handed subjects (six males and three females; mean ± SD age 33.8 ± 9.3 years, range 25-53 years) with normal olfaction participated in this study. The subjects understood the experimental procedures and gave their informed consent to participate in this experiment, which had been approved by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan.

**Odor Stimuli**

We used intravenous infusions of TPD and TTFD as the odor stimuli. TTFD evoked a weaker sensation than TPD owing to the substitution of the side chain of odor components in it, but its medicinal action is the same as that of TPD. We dissolved TPD and TTFD (2 ml) in physiological saline (50 ml) and instilled them slowly into the left median cubital vein. The subjects were instructed to raise the forefinger when the smell started and ceased. By this procedure, each subject felt the same odor sensation, though the amount administered was different in each subject. Physiological saline was instilled the same as TPD and TTFD as the state in which no odor was perceived.

**MRI**

MRI data were acquired with a 1.0T MRI system (Magneton Impact, Siemens, Germany). Individual MRI data consisted of T1-weighted sequences in 130 sagittal slices (1.5 mm thickness), and three markers affixed to the nasion and bilateral pre-auricular points of each subject. Because the head’s location was recorded by these three markers, MEG data could be superimposed on individual MRI data with an accuracy of a few millimeters.

**MEG**

MEG recordings were made using a whole head 64-channel MEG system equipped with third-order SQUID gradiometers (Omega 64, CTF Systems Inc., Canada) in a magnetically shielded room in Osaka University, Japan. The localization of each subject’s head relative to the sensor array was measured with three coils affixed to the nasion and bilateral pre-auricular points. The magnetic field signals were low-pass filtered at 200 Hz and notch filtered at 60 Hz to eliminate the AC line noise. Then the data were digitized with a sampling rate of 625 Hz.

Figure 1 shows the experimental time course. Each subject sat comfortably in a chair in a magnetically shielded room. The subjects kept their eyes closed so as to avoid noticing the time of instillation. Also, they heard pink noise of 70dB SPL through headphones to mask any auditory cues. They wore masks with a tube for ventilation to keep the air clean in the shielded room. The order in which TPD and TTFD were administered was randomized across the subjects. Four trials were measured in