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

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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; Ottoson, 1959; Yamamoto and Yamamoto, 1962; Freeman, 1974; Breesseler 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. When the olfactory nerve was stimulated with TPD (Alinamin ®, Takeda Pharmaceutical Company Ltd, Osaka, Japan) and TTFD (Alinamin F ®, 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

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weaker sensation of odor, respectively, so we may be able to compare brain activation caused by each stimulus.

We speculated that cortical activity, especially in the beta or gamma frequency band, should be detectable in multiple cortical areas when one perceives odors.

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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 Ethical Committee of the National Institute for Physiological Sciences, Okazaki, Japan.

Odor Stimuli

We used intravenous infusion 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 (2ml) in physiological saline (50ml) and instilled them slowly into the left median cubital vein. The subjects were instructed to raise the forefinger when the smell started and ceased.

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MEG Acquisition

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.

Figure 1 shows the experimental time courses. The order in which TPD and TTFD were administered was randomized across the subjects. Four trials were measured in each subject.

SAM Analysis

The procedure for SAM analysis was as follows. First, the recorded MEG data were filtered into seven frequency bands using fast Fourier transformation (FFT): 1-4 Hz (delta), 4-8 Hz (theta), 8-13 Hz (alpha), 13-30 Hz (beta), 30-60 Hz (low gamma), 60-100 Hz (high gamma 1) and 100-200 Hz (high gamma 2) band. Second, the region of interest (ROI), which covered the entire cerebrum, was set. The resolution of the SAM voxels was 5mm. Third, the earliest 20 seconds after subjects felt a

smell were picked for the analysis from the active recording of 115 seconds while the subjects perceived the odor of TPD and TTFD, because it was considered as the duration in which odor intensity was the strongest. Similarly, the earliest 20 seconds were picked from each trial before the TPD and TTFD were instilled. Fourth, the covariance of the MEG data in each band was calculated using 20 seconds of data sectioned into 10 epochs of 2 seconds each. Fifth, the source power in each band was calculated with multiple covariance matrices. Sixth, the change of the source power in a state of olfactory sensation was compared with that in a state of non-olfactory sensation voxel-by-voxel using the jack knife t-test. Seventh, the statistical SAM data were superimposed on individual MRI data in each subject. Finally, statistical parametric maps representing the significant voxels as color voxels were generated in each subject. Uncorrected p values of less than 0.001 were regarded as significant.

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Results

Overall, ERD was observed but ERS was not. Figures 2 and 3 show representative SAM statistical parametric maps in the beta (13-30 Hz), low gamma (30-60 Hz), high gamma (60-100 Hz) and high gamma 2 (100-200 Hz) bands, respectively. Delta, theta and alpha bands showed no significant ERD or ERS. Both strong and weak odors induced ERD in (1) beta band (13-30 Hz) in the right precentral gyrus, and superior and middle frontal gyrus 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.

Discussion

We mainly focused on the changes of each frequency band in the present study, since it is well known that 40 Hz activity is induced from the olfactory bulb (Adrian, 1942; Ottoson, 1959; Yamamoto and Yamamoto, 1962; Freeman, 1974; Breesseler and Freeman, 1980).

The ERD was observed in response to both strong and weak odor stimuli, which were considered to be the locations related to olfactory processing. These results indicate that several regions including the frontal and parietal lobes play some role in olfactory perception.

Concerning the beta band (13-30 Hz), the cortical activity can be seen on auditory (Makinen et al., 2004) and somatosensory stimulation (Neuper et al., 2001), the performance of a movement (Paradiso et al., 2004) and working memory (Serrien et al., 2004). The ERD and ERS of the beta band might reflect the thalamo-cortical networks to enhance focal cortical activation by simultaneous inhibition of other cortical areas (Neuper et al., 2001; Paradiso et al., 2004). Taking their theory into consideration, the

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physiological cortical oscillation in the superior and middle frontal gyri in both hemispheres might reflect the enhancement of activities in those regions by simultaneous inhibition of other cortical areas.

The areas in which differences of ERD were identified between strong (TPD) and weak (TTFD) stimuli, were considered to be the cortical regions related to the strength of odor stimuli. The strong stimulus induced ERD in the temporal, parietal and occipital lobes in the left hemisphere, while the weak stimulus induced ERD in the right hemisphere. Though it is difficult to explain this finding, at least for odor perception, the left hemisphere is more sensitive to strong stimuli and the right hemisphere is more sensitive when the odor is very weak.

Taken together, the results suggest that (1) neural networks distributed in broad cortical areas including the frontal and parietal lobes are involved in olfactory processing, and (2) cortical processing of strong and weak odor perception may be in different areas.

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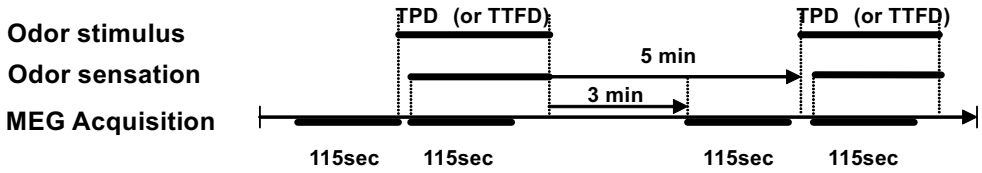

Figure 1: Experimental time course: Before the intravenous infusion of TPD, 115-sec recordings were made. While the subjects smelled the odor, 115-sec recordings were made. Three minutes after the subjects did not perceive the odor, 115-sec recordings were made. The same time as the subjects had perceived the odor of TPD, 115-sec recordings were made after the intravenous infusion of TTFD. The order of TPD and TTFD was randomized in each subject.

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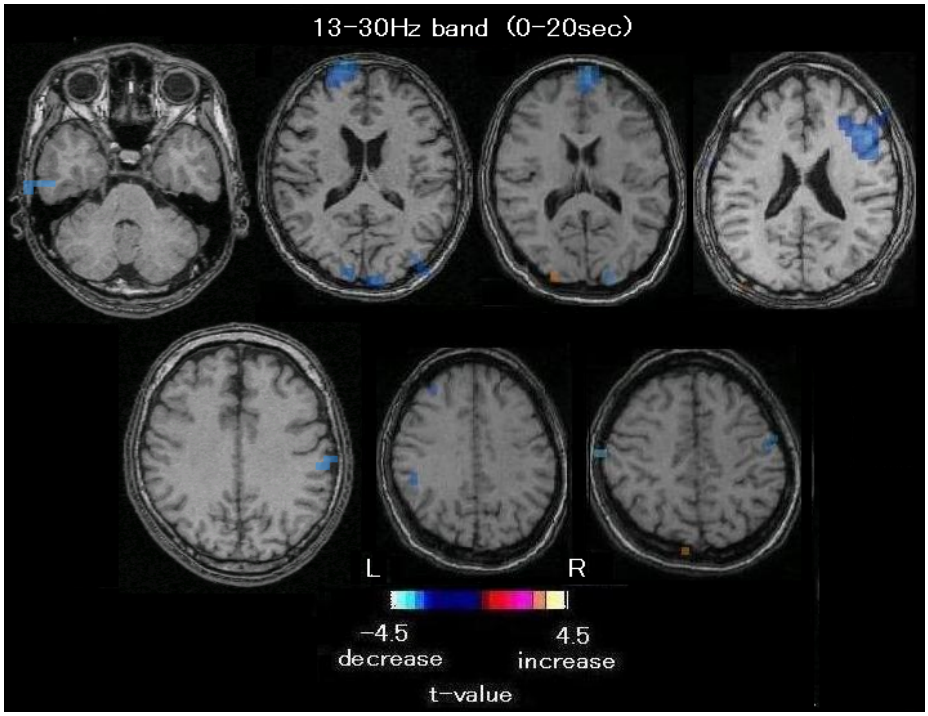

Figure 2: ERD and ERS in the beta band (13-30 Hz): Representative SAM statistical parametric maps in the beta (13-30 Hz) band indicating significant source power changes as color voxels for one subject (subject 1). Source power increase (ERS) and decrease (ERD) is represented by red and blue, respectively. In this subject, ERD was found in the following areas: precentral gyrus in the right hemisphere, bilateral superior and middle frontal gyrus, postcentral gyrus in the right hemisphere, inferior temporal gyrus in the left hemisphere and bilateral occipital gyri.

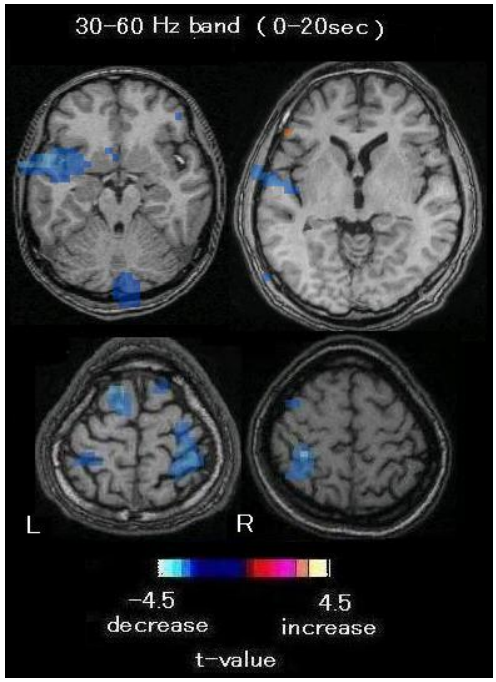

Figure 3: ERD and ERS in the low gamma (30-60 Hz): Representative SAM statistical parametric maps in the low gamma (30-60 Hz) band indicating significant source power changes as color voxels for one subject (subject 2). Source power increase (ERS) and decrease (ERD) is represented by red and blue, respectively. In this subject, ERD was found in the following areas: bilateral superior and middle frontal gyrus, inferior frontal gyrus in the right hemisphere, bilateral postcentral gyrus, superior temporal gyrus in the left hemisphere, bilateral superior parietal lobule and cerebellum.