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

Ai Miyanari*#, Yoshiki Kaneoke*+, Aya Ihara*, Shoko Watanabe*+, Yasuhiro Osaki^, Takeshi Kubo^, Amami Kato~, Toshiki Yoshimine~, Yasuyuki Sagara#, and Ryusuke Kakigi*+%

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; 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. 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 (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 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-

* Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan.
+ Department of Physiological Sciences, School of life Sciences, The Graduate University for Advanced Studies, Hayama, Kanagawa, Japan.
^ Department of Otorhinolaryngology, Osaka University Graduate School of Medicine, Osaka, Japan.
~ Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan.
# Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan.
% RISTEX, JST, Japan.
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Correspondence and reprint requests should be addressed to Ryusuke Kakigi, M.D., Ph.D., Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, 444-8585, Japan.
Fax: +81-564-52-7913
E-mail: kakigi@nips.ac.jp

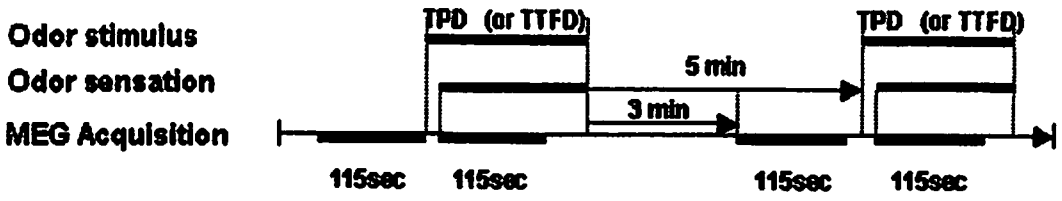


Figure 1. Experimental time course: Before the intravenous infusion of TPD, 115-sec recordings were made. While the subjects smelled the odor, 115-sec recordings were made. Three minutes after the subjects did not perceive the odor, 115-sec recordings were made. At the same time as the subjects perceived 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.

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 (Magnetom 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 headsets 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

each subject. In the first trial, the subjects did not perceive any odorants before TPD was instilled; in the second, the subjects perceived the odor after TPD was instilled; in the third, the subjects did not perceive any odorants before TTFD was instilled; and in the fourth, the subjects perceived the odor after TTFD was instilled. Each trial lasted 115 seconds including 5 seconds prior to the onset of the trial. It was not necessary to be concerned about habituation, since we confirmed that subjects felt the same degree of odor after a period of three minutes in a pilot study.

### SAMs

SAM is based on the adaptive beamformer technique. SAM has been used for the analysis of various cortical areas, including visual (Fawcett et al. 2004), auditory (Herdman et al. 2003), somatosensory (Schulz et al. 2004; Ihara et al. 2003; Hirata et al. 2002), motor (Taniguchi et al. 2000) and language (Hirata et al. 2004) functions. Generally, raw MEG data includes environmental and sensor noise as well as signals related to the stimuli. However, the combination of SAM and magnetic shielding reduces the effect of the environmental noise.

SAM synthesizes signals from all the sensors and extracts a signal from one array having a weight to improve the signal-to-noise ratio. A contributor to a specified coordinate within the cerebrum is determined as a weight. In other words, owing to the cancellation of noise from the uncorrelated region, SAM improves the spatial resolution of the brain's activities. Moreover, it estimates tomographic images of source locations statistically from non-averaged MEG data, after the time and area of the activities are specified. SAM does not require averaged MEG data, thus high frequency components are not reduced. These algorithms are summarized elsewhere (Robinson and Vrba et al. 1999; Taniguchi et al. 2000).

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). 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. As described above, SAM is very useful for analyzing the results for each individual, but an analysis of mean values obtained from many individuals, as conducted using a statistical parametric map (SPM) for PET and fMRI studies, cannot be done. However, the incidence of ERD/ERS found for all the subjects was analyzed with a chi-square test for each frequency band in each cortical area for each TPD and TTFD.

### Subjective Assessments of the Odor Stimuli

After the experiment, all subjects evaluated the strength of the odor and palatability for TPD and TTFD according to a five-grade system; (1) considerably weak, (2) weak, (3) neutral, (4) strong and (5) considerably strong for the strength of the odor, and (1) hate, (2) dislike, (3) neutral, (4) like and (5) strongly like for the palatability.

### Monitoring of Respiration

All subjects practiced nasal breathing at a constant rate before the experiment. During the experiment, to ascertain whether or not the subjects' breathing was constant throughout the experiment, their respirations were monitored with a nasal thermistor(respirator pickup TR-611T, Nihon Kohden, Japan), and recorded with the MEG system. We had confirmed in advance that the monitoring of respiration did not disturb magnetic field recordings.

### Statistical Analysis

The paired t test was used for the statistical analysis of the onset time of smell, duration of smell and dosage of odor sensation. For the statistical analysis of the strength of the odor, palatability and ERD in each area and frequency band, we used the chi square test. For the significant source power changes in 0-20 seconds, we used the paired t test. A $p<0.05$ was considered to be significant in all statistical analyses.

## Results

### Odor Sensation

The onset time was 15.6 ± 5.6 (mean ± SD) seconds for TPD and 59.7 ± 38.1 (mean ± SD) seconds for TTFD.

The duration of smell was 169.3 ± 28.1 (mean ± SD) seconds for TPD and 128.5 ± 75.3 (mean ± SD) seconds for TTFD. The dosage of TPD was 1.15 ± 0.26 (mean ± SD) ml and the dosage of TTFD was 1.24 ± 0.29 (mean ± SD) ml. The paired t test revealed a significant difference in the mean of onset time ($P < 0.05$), but not the duration of smell ($P = 0.147$) or dosage ($P = 0.272$) between TPD and TTFD (figure 2).

All the subjects smelled a drastic odor in their expired breath after the intravenous infusion, especially TPD. For TPD, one subject felt the odor was weak, two felt it was moderate, three felt it was strong and three felt it was considerably strong. For TTFD, four subjects felt the smell was considerably weak and five felt it was weak. The chi square test revealed that the strength of the odor differed significantly ($P < 0.05$) but palatability did not ($P = 0.717$) between TPD and TTFD (figure 3).

### Respiration

In each trial, we calculated the mean and standard deviation of the breathing frequency. The results were the following in order of the trials: 12.9 ± 2.1, 13.4 ± 2.7, 13.1 ± 2.2 and 12.8 ± 2.9 (cycles per minute). Multiple comparisons using the paired t test with Bonferroni correction revealed that there was no significant difference in the mean respiratory rate in each trial.

### MEG Analysis

Overall, ERD was observed but ERS was not. Figures 4 and 5 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. Table I shows the number of subjects who showed a significant ERD out of all nine subjects. Delta, theta and alpha bands showed no significant ERD or ERS.

*Frontal Lobe*

In the beta band (13-30 Hz), ERD was found in the bilateral precentral, superior frontal and middle frontal gyri cortical areas. In the low gamma band (30-60 Hz), ERD was found in the left precentral gyrus, bilateral superior frontal and middle frontal gyri and right inferior frontal gyrus. In the high gamma band (60-100 Hz), ERD was found in the left middle and inferior frontal gyri. In high gamma band 2 (100-200 Hz), ERD was found in the left middle frontal gyri and right inferior frontal gyrus. No superiority of cerebral hemisphere was detectable from the difference in the strength of stimuli. There were some differences between TPD and TTFD stimulation, the most remarkable being that ERD was identified in the high gamma (60-100 Hz) and high gamma 2 (100-200 Hz) bands following TPD in the middle and inferior frontal gyri in the left hemisphere.

*Parietal Lobe*

In the beta (13-30 Hz) band, ERD was found in the right post central gyrus. In the low gamma band (30-60 Hz), ERD was found in the bilateral post central gyri and superior parietal lobule. In high gamma band 2 (100-200 Hz), ERD was found in the left superior parietal lobule. The strong stimulus (TPD) induced ERD only in the left parietal lobe while the weak stimulus (TTFD) induced ERD only in the right parietal lobe.

*Temporal Lobe*

In the beta band (13-30 Hz), ERD was found in the left inferior temporal gyrus. In the low gamma band (30-60 Hz), ERD was found in the left superior temporal gyrus. In the high gamma band (60-100 Hz), ERD was found in the bilateral superior temporal and inferior temporal gyri. In high gamma band 2 (100-200 Hz), ERD was found in the right superior temporal gyrus. There were clear differences between TPD and TTFD. ERD in the left temporal lobe was induced only by the strong stimulus (TPD) whereas ERD in the right temporal lobe was induced only by the weak stimulus (TTFD).

*Occipital Lobe*

In the beta band (13-30 Hz), ERD was found in the bilateral occipital gyri. In the high gamma band (60-100 Hz), ERD was found in the bilateral occipital gyri. In high gamma band 2 (100-200 Hz), ERD was found in the left occipital gyrus. The strong stimulus (TPD) induced ERD only in the left occipital lobe whereas the weak stimulus (TTFD) induced ERD only in the right occipital lobe.

## 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). For recording the changes of each frequency band, various EEG findings have been reported: theta band decreased (Stacher et al. 1979), theta band increased (Klemm et al. 1992), alpha band decreased (Lorig et al. 1991), alpha band unchanged (Klemm et al. 1992) and alpha band increased (Brauchli et al. 1995). However, since the spatial resolution of EEG is not high, it is difficult to localize activated regions. Since MEG has a theoretical advantage in identifying the localization of cortical activities with a high spatial resolution as compared with EEG, we may expect to be able to identify more exactly the anatomical regions related to odor stimuli, as shown in this study. However, since it is difficult for MEG to detect activities

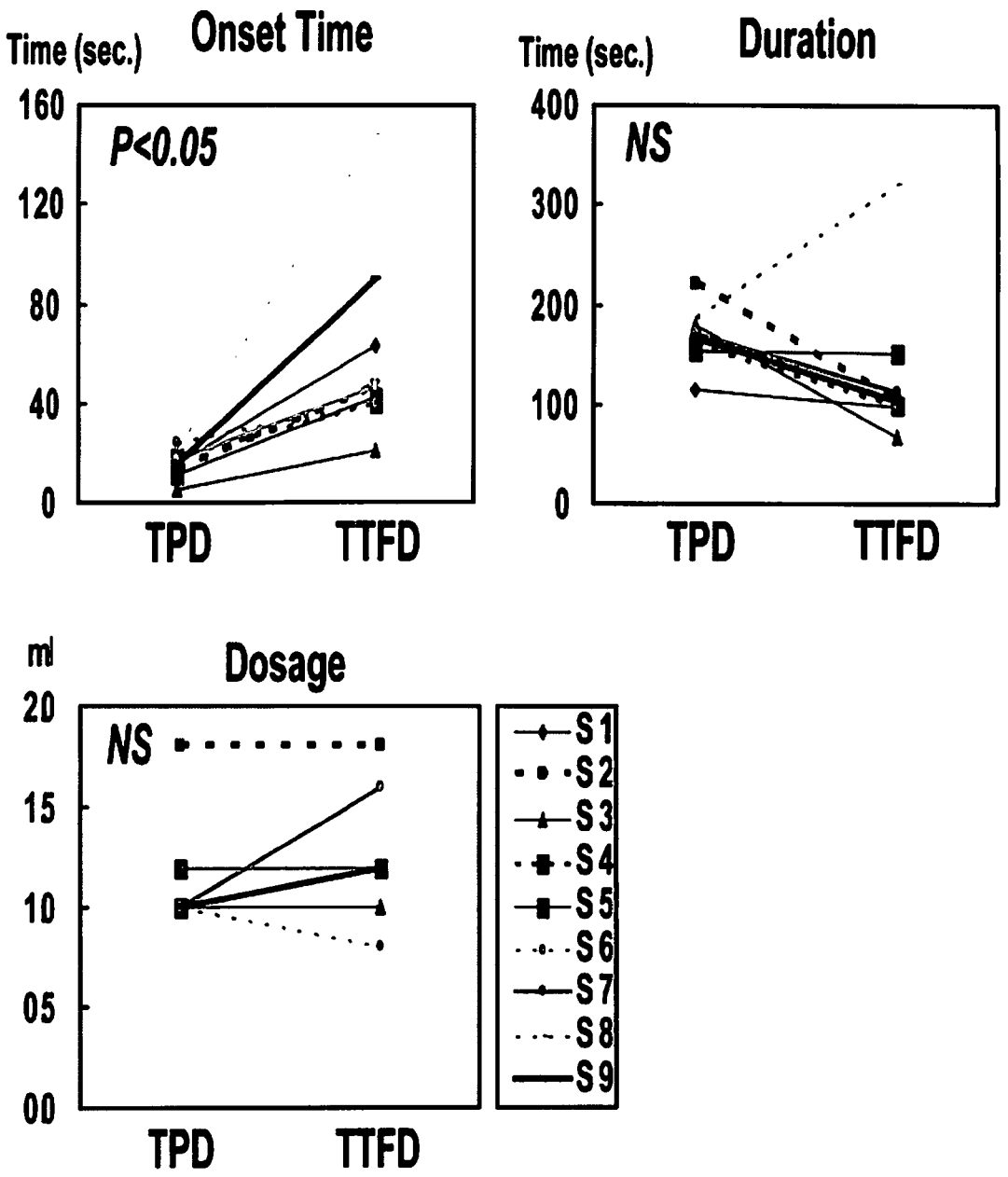


Figure 2. Onset time, Duration and Dosage: Values for onset time, duration of smell, and dosage of TPD and TTFD were obtained from 9 subjects. The difference in the mean of onset time between TPD and TTFD was significant ($P < 0.05$).

in deep brain regions, so-called olfactory areas such as the piriform cortex and surrounding olfactory cortex in the temporal and frontal lobe and the orbitofrontal cortex in the frontal lobe, which have been examined by PET and fMRI (Zatorre et al. 1992; Koizuka et al. 1994; Jones-Gotman et al. 1997; Small et al. 1997; Sobel et al. 1998; Cerf-Ducastel et al. 2001; Djordjevic et al. 2005; Zelano et al. 2005; Djordjevic et al. 2005), could not be clearly recorded using MEG. Instead, since MEG has a high temporal and spatial resolution for detecting physiological changes of neuronal activities, it is occasionally possible to detect subtle changes of the neuronal re-

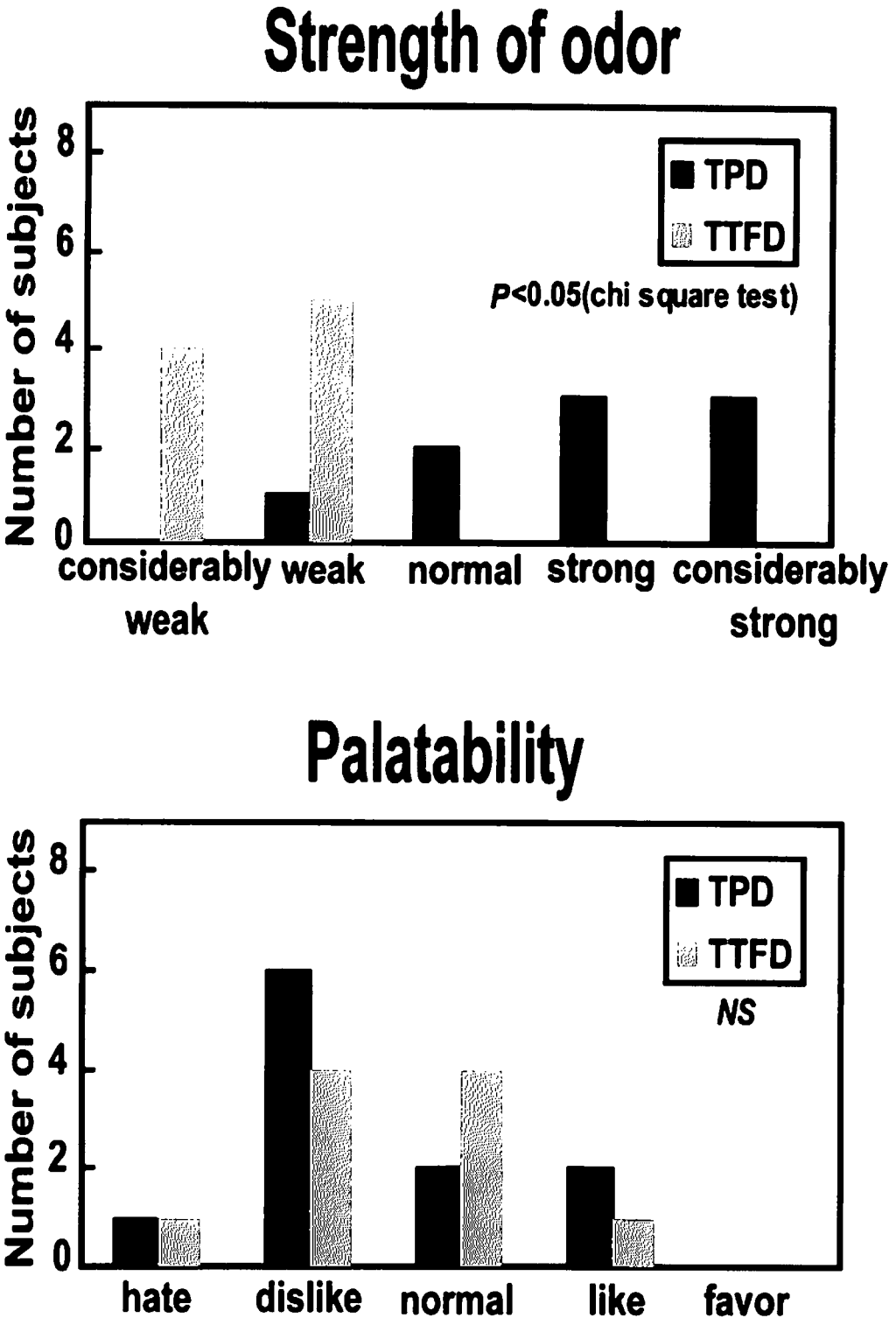


Figure 3. Evaluation of Strength and Palatability. Subjective assessments of the strength of the odor and palatability were obtained from 9 subjects. The strength of the odor was significantly ($P < 0.05$) different between TPD and TTFD.

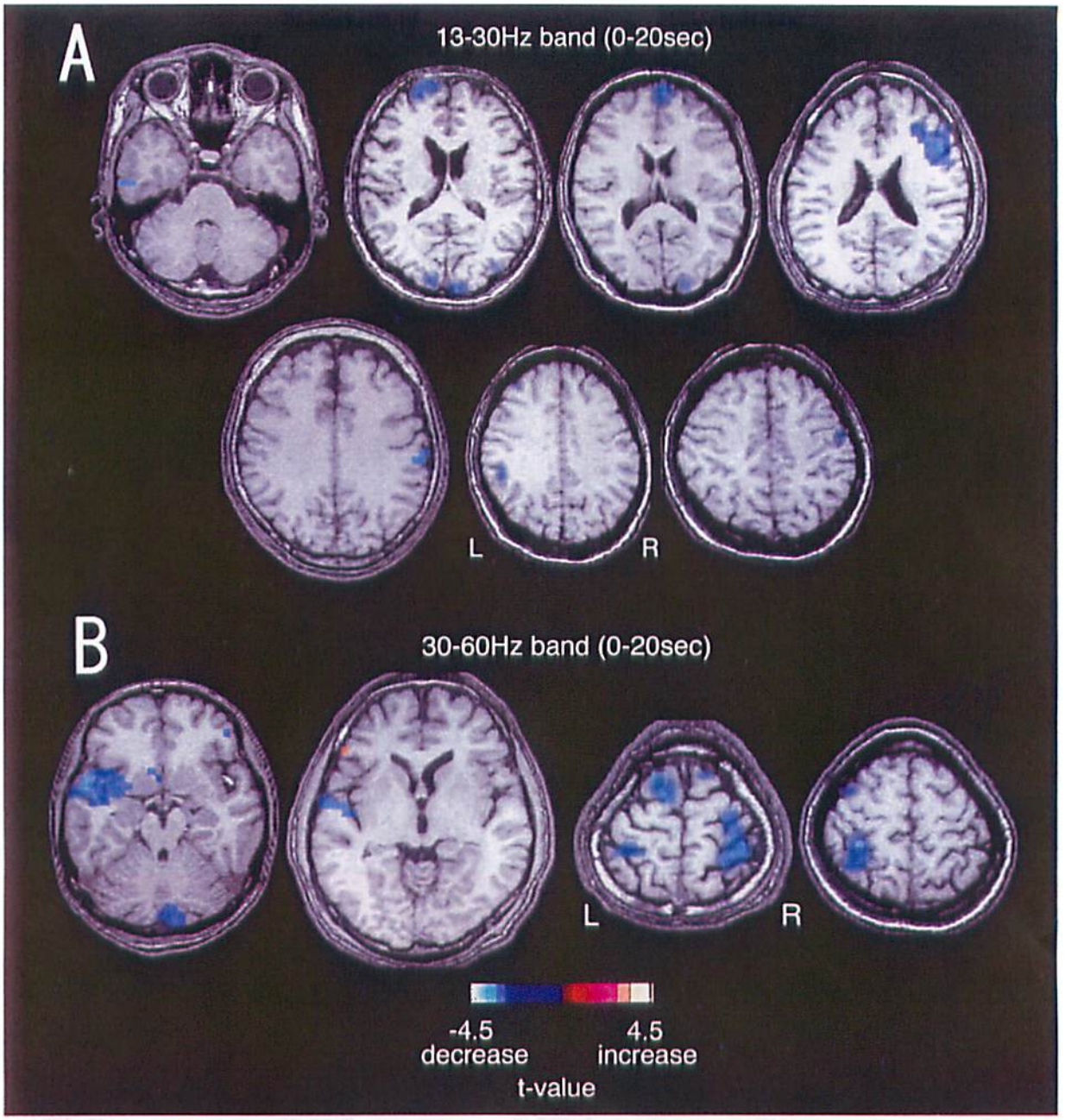


Figure 4. ERD and ERS in the beta band (13-30 Hz) (A) and low gamma (30-60 Hz) band (B): Representative SAM statistical parametric maps in the beta (13-30 Hz) band indicating significant source power changes as color voxels for one subject (subject 1). A source power increase (ERS) and decrease (ERD) 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 gyri in the right hemisphere, inferior temporal gyrus in the left hemisphere and bilateral occipital gyri. 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). In this subject, ERD was found in the following areas: bilateral superior and middle frontal gyri, inferior frontal gyrus in the right hemisphere, bilateral postcentral gyri, superior temporal gyrus in the left hemisphere, bilateral superior parietal lobules and cerebellum.

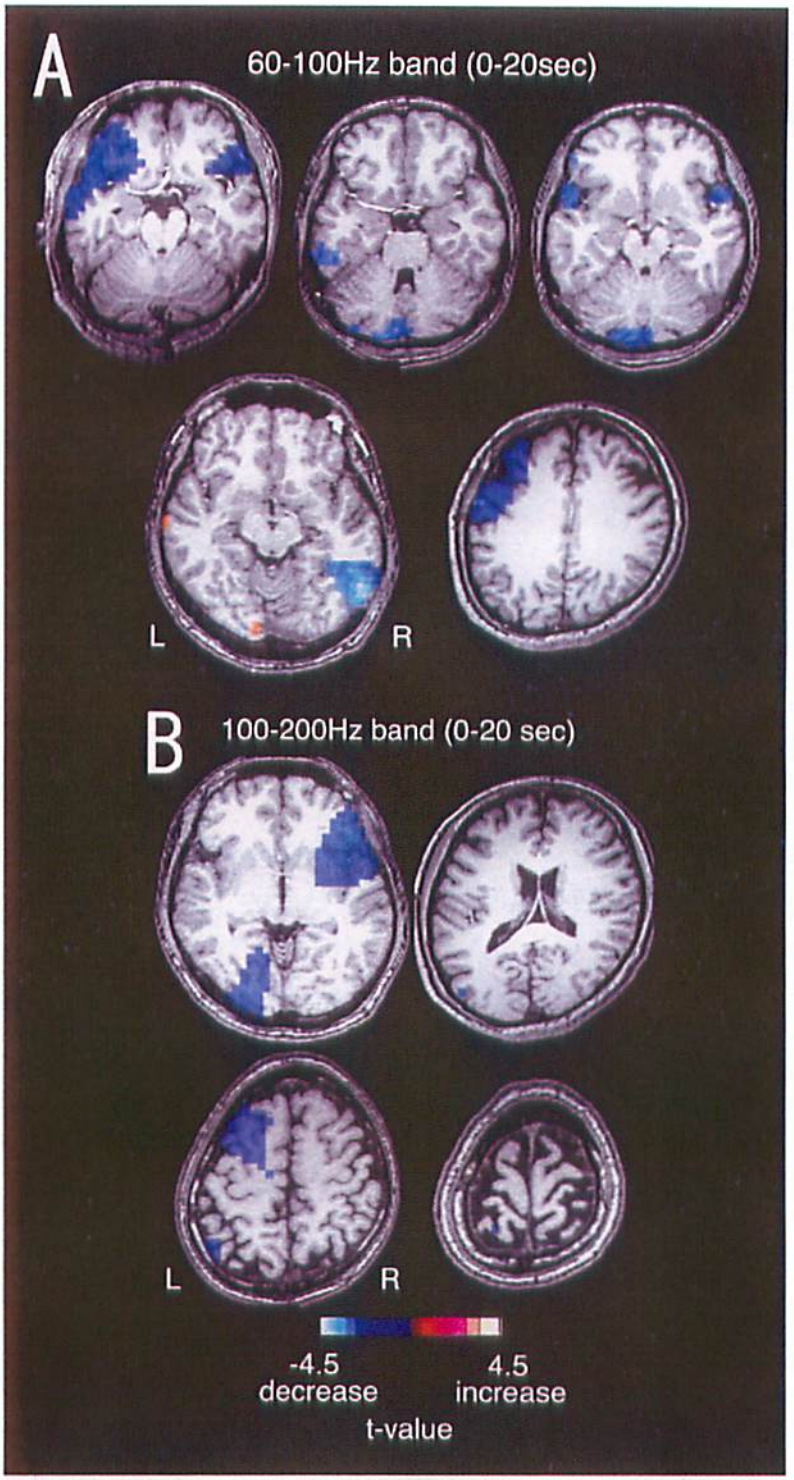


Figure 5. ERD and ERS in the high gamma (60-100 Hz) band (A) and high gamma 2 (100-200 Hz) band (B): Representative SAM statistical parametric maps in the high gamma (60-100 Hz) band indicating significant source power changes as color voxels for one subject (subject 3). A source power increase (ERS) and decrease (ERD) is represented by red and blue, respectively. In this subject, ERD was found in the following areas: middle and inferior frontal gyri in the left hemisphere, bilateral superior and inferior temporal gyri and cerebellum. Representative SAM statistical parametric maps in the high gamma 2 (100-200 Hz) band indicating significant source power changes as color voxels for one subject (subject 4). In this subject, ERD was found in the following areas: middle frontal gyrus in the left hemisphere, inferior frontal gyrus in the right hemisphere, superior temporal gyrus in the right hemisphere, superior parietal lobule in the left hemisphere, and occipital gyri in the left hemisphere.

sponse in cortical areas which could not be detected by blood flow change.

The ERD was observed in response to both strong and weak odor stimuli in the following areas, which were considered to be the locations related to olfactory processing: (1) beta band (13-30 Hz) in the right precentral gyrus, and superior and middle frontal gyri in both hemispheres, (2) low gamma band (30-60 Hz) in the left superior frontal gyrus and parietal lobule and middle frontal gyri in both hemispheres, and (3) high gamma band 2 (100-200 Hz) in the right inferior frontal gyrus. 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), 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 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 ERD in the right precentral gyrus was an interesting finding, since there was no performance of movement in the present study. It is known that the 20-Hz oscillation recorded from the precentral sulcus is closely related to motor function (Hari and Salmelin 1997; Tamura et al. 2005).

There has been much interest in the low gamma band oscillation (30-60 Hz), which was induced in relation to the perception of sensory stimuli, such as olfactory (Breesseler and Freeman 1980), visual (Gray et al. 1989), auditory (Franowicz et al. 1995) and somatosensory (MacDonald et al. 1995; Ihara et al. 2003) and the performance of movement (Pfurtscheller and Neuper 1992; Pfurtscheller et al. 1993). It is of interest whether the changes in the left superior frontal gyrus and middle frontal gyrus reflect activities in the olfactory bulb at around 40 Hz, since synchronized gamma band oscillation might be related to the binding of information between spatially separated cell assemblies, which reflects the activity of the cortico-cortical networks at a higher level of processing (Gray et al. 1989; Engel et al. 1991). However, there is another possibility, that the results simply reflect the changes of cortical activities in such regions. The finding that the ERD was identified in the superior parietal lobule in the left hemisphere is interesting, since no previous neuroimaging and electrophysiological studies found activities in these regions following odor stimulation. Though we cannot ascertain the reason for this finding, the superior parietal lobule may play important roles in higher functions after the frontal lobes are activated. The ERD of high gamma band 2 (100-200 Hz) was identified in the right inferior frontal gyrus. The meaning of these changes is still unclear and will require further study.

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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