Chem. Senses 27: 629–634, 2002

Gustatory Evoked Cortical Activity in Humans Studied by Simultaneous EEG and MEG Recording

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Abstract

Evoked potentials are widely used in clinical medicine for objective evaluation of sensory disturbances. However, gustatory evoked potentials (GEPs) have not been extensively studied due to lack of agreement among investigators regarding the waveforms. In this study GEPs and gustatory magnetic fields (GEMfs) were simultaneously recorded from five subjects in response to 0.3 M NaCl in an attempt to establish GEP recording as an objective gustatometer. Each subject received a total of 240 stimulus presentations over six sessions. Three GEP components (P1, N1 and P2) were observed and correlated with their corresponding equivalent current dipoles (ECD1, ECD2 and ECD3, respectively). ECD1 was localized to area G in all subjects, P1 being the indicator of intact gustatory projection to area G. No significant GEP activity was detected during the time preceding P1, which suggests that there was no activity in cortical gyri other than that detected by magnetoencephalography. ECD2 and ECD3 were localized to various cortical structures, including the inferior insula and the superior temporal sulcus, indicating that N1 and P2 reflect higher order gustatory functions. The present results indicate that measurement of GEPs may be useful for objective evaluation of gustatory disturbance.

Introduction

It is well known from clinical observation that brain damage and aging often result in gustatory disorders (Lee *et al*., 1998; Onoda and Ikeda, 1999; Aglioti *et al*., 2000). So far, however, an objective medical examination of gustatory function has not been carried out. Electroencephalography (EEG) is a useful and established tool for objective examination of functional disturbances of various sensory modalities, but it has seldom been applied to subjects with gustatory disturbances. This is because, in the past, the difficulty involved in adequately controlling the necessary liquid stimuli led to inconsistent measurements of gustatory evoked potentials (GEPs) (Funakoshi and Kawamura, 1971; Kobal, 1985; Plattig *et al*., 1989; Prescott, 1989). To date, there has also been no agreement between investigators regarding the sequence of potentials to be measured.

Among the requirements originally proposed by Evans *et al.* (Evans *et al.*, 1993) regarding stimulation to record chemosensory evoked potentials, stimuli should be in the form of a square wave with a rise time to 70% of the maximum concentration of <50 ms. Kobayakawa *et al.* (Kobayakawa *et al*., 1996) developed a gustatory stimulator which fully meets this requirement. When they previously located human gustatory areas by magnetoencephalography (MEG), a recently introduced technique with high temporal and spatial resolution, their stimulating system was found to be useful for activating gustatory evoked magnetic fields (GEMfs) without contamination due to tactile stimulation (Kobayakawa *et al*., 1996). However, due to the expensive running costs of the MEG system and the requirement for a magnetically shielded room, the use of MEG systems for gustatometry in clinical practice is practically unfeasible. Meanwhile, EEG has the same superior temporal resolution as MEG, but with far lower running costs. Repetitive presentations of gustatory stimuli are necessary to obtain clear GEMfs or GEPs. Roughly 40 stimulus presentations, taking ~30 min, are enough to obtain GEMfs, but several hundred are most likely required to collect adequate GEPs, which would require the subjects to be restrained for several hours. However, EEGs obtained from the same subject over several days can be averaged together if the electrodes are carefully placed at the same position for each set of recordings. Used

in this way, EEG is much more practical than MEG for use in the clinical field.

Previously, Kobayakawa *et al*. (Kobayakawa *et al*., 1996) located the primary gustatory area, area G, at the transition between the parietal operculum and the insula of the cerebral cortex in humans by estimating the location of the first equivalent current dipole (ECD) from GEMfs. Because MEG is incapable of detecting electrical current which is vertically oriented to the brain surface (Gryzpan and Geselowitz, 1973), while EEG signals reflect cortical activities of gyri and sulci, simultaneous recording of EEG and MEG may reveal information about cortical evoked activity that might be missed by MEG alone.

The aim of the present study was twofold: (i) to obtain fundamental data regarding GEPs in order to establish an objective gustatometer; (ii) to investigate whether GEPs yield information about possible cortical activities of gyri not detected by MEG. To successfully accomplish this, we needed to measure GEPs induced by an appropriate stimulator as well as to clarify the sources of activities of recorded GEP peaks through simultaneous measurement of GEMfs.

Materials and methods

Subjects

Five healthy subjects (three females and two males, aged 25–30 years, mean 27 years) participated in this experiment. Each subject was required to attend six identical experimental sessions. Each session was held on a different day or with an interval of at least 2 h if on the same day. The study was conducted in accordance with the revised version of the Helsinki declaration and was approved by the National Institute of Advanced Industrial Science and Technology, Japan.

Stimulation

A 0.3 M solution of NaCl was used as the gustatory stimulus. The methods of gustatory stimulation have previously been described in detail (Kobayakawa *et al*., 1996). Briefly, for each subject a gustatory but non-tactile stimulator with a rapid rise-time was used to deliver taste solutions to the tongue. The deionized water and the gustatory solution, separated by a small amount of air, were delivered via a Teflon tube at a rate of 140 ml/min. Solenoid valves controlled by a PC switched between deionized water, gustatory solution and air. Stimuli were presented through a hole (7 × 2.8 mm) situated in the wall of the tube. The subject's tongue was firmly fixed to the hole by the small amount of negative pressure generated by the flow of liquid and air in the tube. The triggering time points were calculated off-line, based on signals from two optical sensors placed as close as possible to the subject's mouth.

Each 400 ms stimulus was presented 40 times with an inter-stimulus interval of 30 s during each session. The gustatory solution and water were kept at 36°C, approximately the same temperature as that of the tongue. The subjects were asked to show a perceived intensity of saltiness between 0 (not detectable) and 5 (very strong) using their fingers a few seconds after each stimulus presentation. This evaluation was used to confirm that gustatory adaptation did not occur. After every recording session, the subjects were asked about the stimulus quality and confirmed no difference in temperature between water and gustatory solution.

Recording

EEG measurements were recorded from five sites (Fz, Cz, Pz, T3 and T4), with reference to A1 + A2 based on the international 10–20 method, using a conventional EEG recording system. GEMfs were measured using a 64 channel whole head SQUID system (CTF System Inc., Canada). Both GEPs and GEMfs were recorded simultaneously. The signals were digitized at a sampling rate of 250 Hz and filtered on-line with a 100 Hz low-pass filter and off-line with a 40 Hz low-pass filter. For EEG signals, a 0.53 Hz high-pass filter was also used. A pre-triggering control period of 400 ms was used and the total duration of the recording per stimulus presentation was 2 s. The measurements of peak and mean amplitude were referred to a pre-stimulus baseline. Any records contaminated by eye movements were rejected from the averages. More than 80% of the 40 records were available every session.

Data processing

The recorded GEP signals were averaged every session (~40 stimulus presentations), and the averaged data were further averaged over six sessions to obtain the peak latency and amplitude of all sessions for each subject. The grand averaged GEPs were also obtained.

Several ECDs were selected for each GEP peak latency every session using MEG data. ECDs were searched for within 50 ms around the peak latency of an early GEP component and within 100 ms for later components, based on the following requirements: (i) >80% fit with estimation; (ii) more than 50 ms stability; (iii) suitable power between 10 and 100 nA/m. The estimated ECD locations were superimposed on the corresponding axial, coronal and sagittal MRI images. The cortical structures where ECDs were located were referred to an atlas of the human brain (Mai *et al*., 1997).

Results

After averaging the GEPs recorded over six sessions, two positive peaks (P1 and P2) were observed for all five subjects and one negative peak (N1) was noted in four out of five. Figure 1a–e shows averaged waves recorded at Cz in five subjects and Figure 1f shows a grand averaged waveform from all subjects in order to display every peak.

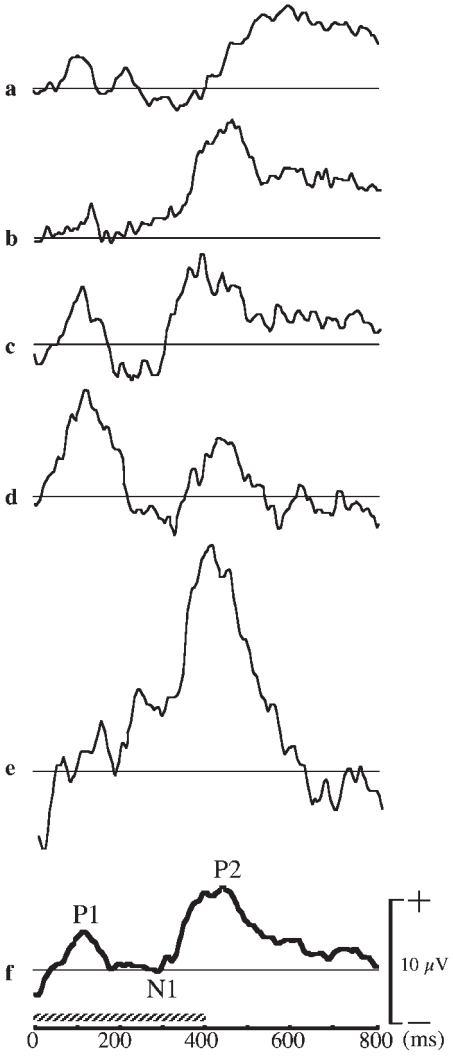

Figure 1 Gustatory evoked potentials recorded at Cz with reference to A1 + A2. Potentials were averaged over six sessions with 40 stimulus presentations per session. Taste stimulus 0.3 M NaCl. **(a–e)** GEPs obtained from each of the five subjects. **(f)** A grand average of the data from all 30 sessions (5 subjects ´ 6 sessions). Three components, P1, N1 and P2, are clearly noticeable. The horizontal oblique dotted line at the bottom indicates the period of gustatory stimulation (400 ms).

The averaged latency and amplitude of P1 were 126.67 ± 31.95 ms and 5.91 ± 4.31 μV, respectively (n = 5). Although the P1 component was not clearly detected in the wave averaged from 40 stimulus presentations, it became clear after averaging over six sessions (240 stimulus presentations) for every subject. The N1 component was revealed in four of the five subjects after averaging over six sessions, with an averaged latency and amplitude of 262.68 ± 23.86 ms and –3.01 ± 3.64 μV (n = 4). The P2 component could be detected after averaging signals over 40 stimulus presentations for every subject and became more prominent after averaging over six sessions. The averaged latency and amplitude of P2 were 431.57 ± 44.19 ms and 10.65 ± 6.90 μV, respectively (n = 5). This component displayed remarkably

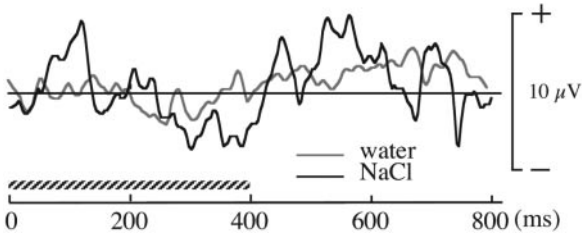

Figure 2 Comparison between responses to water and 0.3 M NaCl stimulation at Cz with reference to A1 + A2. Potentials were averaged over 40 stimulus presentations. The horizontal oblique dotted line at the bottom indicates the period of gustatory stimulation (400 ms). Water following an air bubble did not evoke potentials noticeable at the scalp. Subject no. 1.

high amplitude and was quite long lived, lasting on the order of 200 ms. All components displayed the highest amplitude at Cz among the five recording sites in all subjects. GEPs from the left and right hemispheres were recorded only at T3 and T4. No differences in P1 latency (T3, 104.8 ± 8.67 ms; T4, 114.4 ± 4.56 ms; n = 5) or amplitude (T3, 0.69 ± 0.98 μV; T4, 0.41 ± 1.66 μV; n = 5) were observed between the two recording sites (P > 0.05, df = 4, Student's t-test n.s.).

To confirm that the aforementioned GEPs were uniquely evoked by NaCl, we examined a sequence of the potentials evoked by water and compared it with the GEPs induced by NaCl (Figure 2). No significant change in potentials was noticed with water stimulation following an air bubble.

The ECDs around each GEP peak latency were examined (Figure 3Aa,Ab). ECD1 was successfully estimated in all 30 sessions (5 subjects × 6 sessions) near the P1 latency, and no activation was found before P1 and ECD1. The averaged latency of ECD1 was 125.87 ± 32.45 ms in both hemispheres (n = 5), very similar to the P1 latency (126.67 ± 31.95 ms, n = 5) (P > 0.05, df = 4, Student's t-test n.s.). ECD2 could be estimated in 20 sessions in the left hemisphere and in 19 sessions in the right hemisphere, with averaged latencies of 276.68 ± 45.85 (n = 4) and 277.1 ± 47.75 ms (n = 4), respectively. ECD3 could be estimated in 27 sessions in the left hemisphere and in 29 sessions in the right hemisphere, with averaged latencies of 439.36 ± 44.22 (n = 5) and 436.93 ± 44.22 ms (n = 5), respectively. The direction of the ECDs in area G, the region in which all of the ECDs were most commonly located, was in most cases upward (90% of sessions for ECD1, 67.46% for ECD2 and 95.84% for ECD3).

Once the ECDs were pinpointed, they were then overlaid on coronal anatomical MR images, as in Figure 3B. The cortical activated regions associated with ECD1, ECD2 and ECD3 from all 30 sessions are shown in Table 1. ECD1 was successfully extrapolated (100% of 30 sessions in both hemispheres). It was localized to area G most frequently in all extrapolated areas (53.33% in the left hemisphere, 66.67% in the right hemisphere), followed by the inferior part of the pre-central sulcus and the central sulcus (30% in the left hemisphere, 16.67% in the right hemisphere) (Table 1).

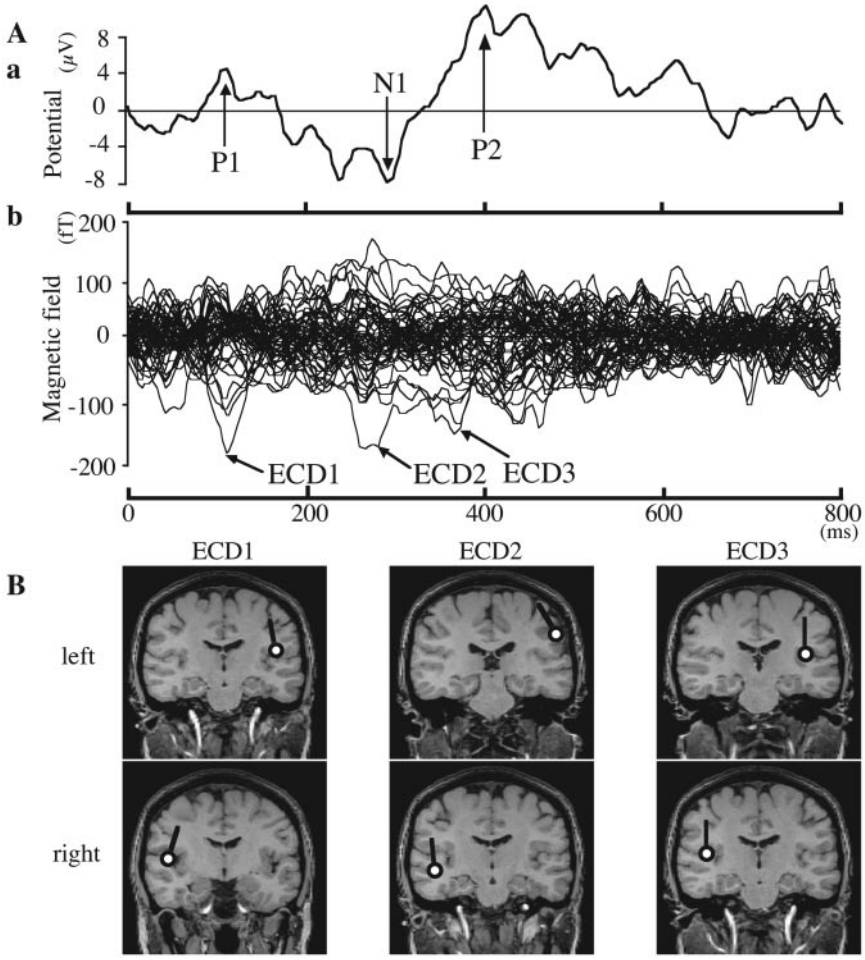

Figure 3 Simultaneously recorded GEPs **(Aa)** and GEMfs **(Ab)** over 40 stimulus presentations and the estimated locations of ECDs in the cortex **(B)**. P1, N1 and P2 were designated as the three components of the GEPs (Aa) and correspondingly ECD1–ECD3 are given as the designations of the GEMfs (Ab). The latency of each of the GEP components was 104 (P1), 292 (N1) and 396 ms (P2). Similarly, the latency of each of the ECDs was 96 (ECD1), 284 (ECD2) and 392 ms (ECD3). The locations of the ECDs were plotted on coronal MR images (B). Blank circles indicate the locations of activation and solid lines display the direction of electrical current. ECD1 was localized to area G in both hemispheres. ECD2 was localized to the central sulcus in the left hemisphere and the superior temporal sulcus in the right hemisphere. ECD3 was localized to area G in both hemispheres. Subject no. 3.

Compared with ECD1, the anatomical position corresponding to ECD2 was less successfully extrapolated (66.67% of 30 sessions in the left hemisphere, 63.33% in the right hemisphere) and tended to show more variation, being localized to the superior temporal sulcus more frequently (15.38% of 39 sessions in both hemispheres) in comparison with ECD1 (1.67% of 60 sessions in both hemispheres). ECD2 was most frequently localized to area G (35% of 20 sessions in the left hemisphere, 47.37% of 19 sessions in the right hemisphere) (Table 1).

The success rate for pinpointing the anatomical location of ECD3 was higher than for ECD2 (90% of 30 sessions in the left hemisphere, 96.67% in the right hemisphere). The percentage localization of ECD3 to area G (44.44% of 27 sessions in the left hemisphere, 41.38% of 29 sessions in the right hemisphere) was the highest among localized areas, but smaller than that for other ECDs. ECD3 was more frequently (21.43% of 56 sessions in both hemispheres) localized to the inferior insula and the superior temporal sulcus than ECD1 (6.67% of 60 sessions in both hemispheres) (Table 1).

Discussion

In this study gustatory evoked activity in the cerebral cortex was examined by simultaneous EEG and MEG recording. Using a stimulator designed by Kobayakawa to meet Evan's original requirements (Kobayakawa *et al.*, 1996), we succeeded in identifying three GEP components. We also clarified the source of each component based on the relevant ECDs estimated from the GEMfs.

Although tactile stimulation of the tongue evokes potentials with a latency similar to the P1 at the secondary somatosensory response (Fitzsimons *et al.*, 1999), a small bubble of air applied at the stimulus point did not elicit any potential change at the scalp. This indicates that the

Table 1 The cortical regions and the number of sessions in which the ECDs were localized

ECD1	*n*	ECD2	*n*	ECD3	*n*
Left hemisphere					
Area G	16	area G	7	area G	12
PCs	5	cs	5	PCs	7
cs	4	PCs	1	cs	2
POCs	2	iIns	3	iIns	3
iIns	1	sts	2	Ins	1
sfs	1	sfs	1	sts	1
sts	1	Hi	1	cos	1
Total	30		20		27
Right hemisphere					
Area G	20	area G	9	area G	12
PCs	5	cs	2	cs	1
POCs	1	sts	4	iIns	4
Op	1	iIns	1	sts	4
iIns	2	Fop	1	PAR	3
PAR	1	PAR	1	PHs	2
		Hi	1	cgs	2
				its	1
Total	30		19		29

Fop, frontal operculum; area G, the primary gustatory area; Hi, hippocampus; iIns, inferior insula cortex; Ins, insular cortex; Op, Rolandic operculum; PAR, posterior ascending ramus of Sylvian fissure; PCs, pre-central sulcus; PHs, parahippocampus sulcus; POCs, post-central sulcus; cos, collateral sulcus; cgs, cingulate sulcus; cs, central sulcus; its, inferior temporal sulcus; sfs, superior frontal sulcus; sts, superior temporal sulcus.

recorded GEPs represent exclusively gustatory, and not tactile, responses to the stimulus, confirming the specificity of the stimulator. The contribution of tactile interference to the formation of GEMfs has also previously been denied (Kobayakawa *et al*., 1996).

GEP components

For all but one of the five subjects the P1, N1 and P2 components of the gustatory evoked activity were noticeable after averaging the potentials (240 stimulus presentations in six sessions). The averaged latencies of the P1, N1 and P2 components were 126.67 ± 31.95 (n = 5), 262.68 ± 23.86 (n = 4) and 431.57 ± 44.19 ms (n = 5), respectively, shorter than previously reported (Funakoshi and Kawamura, 1971; Plattig *et al*., 1989; Prescott, 1989). The difference can be ascribed to a slower rise time of the gustatory stimulation used by the previous investigators. Kobal (Kobal, 1985), using gaseous stimuli, reported that the same three components, P1 (180 ms), N1 (260 ms) and P2 (400 ms), had peaks comparable to those of the present study. In every subject the amplitude of the potentials evoked was largest at Cz for all components at the five recording sites, in agreement with Kobal (Kobal, 1985). None of the components of the GEPs differed in amplitude and latency between T3 and T4, suggesting no prominent laterality of gustatory projection from the tip of the tongue to the cortex.

Averaging the 40 records from any single session was not sufficient to reveal the P1 component, which suggests that a larger number of stimulus presentations is most likely required to raise the signal to noise ratio to the point where the P1 component may be detected. The previous studies also suffered from the same difficulty. Since a long inter-stimulus interval is needed to prevent adaptation, the maximum possible number of stimulus presentations per session is extremely limited in comparison with other sensory modalities, e.g. audition and vision. Retaining a sufficiently long experimental time for a session (~20 min), we conducted six sessions at one or two sessions per day and obtained a total of approximately 240 stimulus presentations. With this amount of data, we were able to isolate the P1 component clearly for every subject. Thus, >200 stimulus presentations are required to clearly obtain the earliest GEP component. Since this repetitive stimulation method did not place subjects under restraint for >20 min per session, it proved to be quite tolerable, an important clinical consideration. Forty stimulus presentations were sufficient, on the other hand, to obtain a clear P2 component. Hardest to detect was the N1 component. Even using the data averaged over six sessions, it could only be detected in four of the five subjects.

Comparison of GEPs and GEMfs

ECD1 was most commonly found to originate from area G, followed by the feet of the pre- and post-central sulci and the central sulcus. This was consistent with previously reported data (Faurion *et al*., 1998; Kobayakawa *et al*., 1999). The primary responses of both GEPs and GEMfs were observed to have similar latencies (P1, 126.67 ± 31.95 ms; ECD1, 125.87 ± 32.45 ms; n = 5) and no remarkable potential change was detected before P1. ECD1 was located near the center of the anterior–posterior line in both hemispheres and was directed mainly upward on either side of the hemisphere. EEG potential changes due to ECD1 on both sides may be summated to yield the maximum amplitude at Cz and the polarity of this maximum amplitude was most often positive, consistent with the GEP data. This indicates that both P1 and ECD1 are generated from the same source and that P1 reflects the primary gustatory response.

Based on ECD2 and ECD3, the current generators for N1 and P2 were localized to area G or the central sulcus in about a half of the sessions, less frequently than P1. Typically, they were found to be located in a more diverse group of regions than ECD1. Since several regions, including area G, were sometimes activated simultaneously during N1 and P2, it is not clear how the polarity of the N1 and P2 components were determined. Interestingly, ECD2 and ECD3, unlike ECD1, were significantly more likely to be localized to the right, rather than the left, superior temporal sulcus.

Kettenmann *et al*. (Kettenmann *et al*., 1997) also noted late activation of the superior temporal sulcus after olfactory stimulation and suggested that this region was one of the main cortical areas involved in olfactory cognition. Activation of the inferior insula was more commonly found to be associated with ECD3 than ECD1 or ECD2, consistent with the reports of fMRI studies that this region was likely to be involved in gustatory cognitive processing (Faurion *et al*., 1999; Cerf *et al*., 2001). Thus, the N1 and P2 components, corresponding to ECD2 and ECD3, probably reflect higher gustatory functions. In terms of clinical screening, detection of the P1 component most likely confirms the intact projection of gustatory information to the primary cortex, whereas the P2 component is possibly a good marker for higher levels of gustatory functions.

Kobayakawa *et al*. (Kobayakawa *et al*., 1996) placed the location of the human gustatory area at the transition between the parietal operculum and the insula cortex, which corresponds to area G in subhuman primates (Ogawa *et al*., 1985). However, MEG measurement is not capable of recording cortical activation of gyri where the electric current generated is oriented vertically to the brain surface (Gryzpan and Geselowitz, 1973). Thus, measurement of cortical activities by MEG only still left the possibility that certain cortical gyri might have been activated by gustatory stimulation with a shorter latency than area G. In contrast, EEG signals accurately reflect the cortical activities of gyri and sulci. By simultaneous recording of EEG and MEG, we obtained data for P1 and ECD1 which demonstrated consistent latency and electromagnetic characters. Although we do not deny that some cortical gyri are activated by gustatory stimulation with the same latency as area G or the central sulcus, no significant changes in the GEPs were found in the time period preceding the P1 component and ECD1. Our results indicate that gustatory information first arrives in the cortex at area G and the central sulcus, as detected by MEG, but probably not at the crown of any cortical gyri, to produce the P1 component of the GEPs. It is not clear whether any cortical gyri are activated during the surveyed time period after the stimulation (say 800 ms), since the later components (N1 and P2) probably result from the ECDs, as calculated from the GEMfs.

In the present study we used 0.3 M NaCl as a stimulus. Future work will be needed to examine whether the amplitudes and latencies of the GEP peaks are dependent on the concentration or the quality of the stimulus. Information from such studies, now in progress, are likely to lead to improvements in technique as well as to provide new information as to the nature of GEPs.

Acknowledgements

This research was supported by the Industrial Technology Research Grant Program for NEDO (New Energy and Industrial Technology Development Organization). We would like to thank Ms Aiko Kitajima, who provided technical assistance.

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Accepted May 30, 2002