Journal of Oral Rehabilitation 2007 **34**; 487–496

Analysis of brain activity immediately before conscious teeth clenching using magnetoencephalographic method

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SUMMARY **The reasons for unconscious teeth clenching have not been clarified. The long-term goal of our project was the elucidation of processing in the brain immediately before unconscious teeth clenching, in order to clarify its significance in humans. The objective of the present study was to establish a magnetoencephalographic (MEG) method of measuring brain activity immediately before clenching, and to clarify the time-course of brain activity immediately before conscious clenching. We measured the MEG signal in six subjects before, during and after clenching in a protocol that restricted head movement <5 mm. We derived tomographic estimates of brain activity for each time slice of data, as well as time courses for regional brain activations. Analysis of the tomographic images and time courses yielded statistical maps of activity in the motor, pre-motor and somatosensory cortices immediately before clenching in all subjects. Activations were found bilaterally, but with a strong unilateral bias in most subjects. Our results demonstrate that the MEG procedures, we have introduced are capable of measuring brain activity immediately before clenching, and indicate that analysis should begin from at least 200 ms before electromyogram onset.**

KEYWORDS: **clenching, magnetoencephalography, magnetic field tomography, regions of interest**

Accepted for publication 12 January 2007

Introduction

One of the main goals of dentistry is to preserve lifelong healthy masticatory function. Biting is a coordinated function requiring extensive motor control, and integrating the action of muscles involved in biting with the peripheral sensory functions of the mouth (1). The act of biting is not only important for chewing food but also has a wider significance in the animal. Hori *et al.* (2, 3) have suggested a possible anti-stress effect of biting. People unconsciously clench their teeth in daily life, but the reasons for this unconscious clenching have not been clarified. Although the cerebral regions that are active during mastication and clenching have been investigated by functional magnetic resonance imaging (fMRI) (4–8) and positron emission tomography (PET) (9), these reports were unable to show how the brain activity evolves over time, from mandibular stasis to movement. Brain activity along the time axis during chewing and tooth tapping has been investigated by electroencephalography (EEG) (10, 11). Although EEG can identify focal isolated activations, its localization accuracy depends critically on the conductivity of the intervening tissue and skull between the generators and the sensors. In our work, we used magnetic field tomography (MFT) analysis of magnetoencephalographic (MEG) signals, which has been shown to accurately localize brain activity with simple models of head conductivity (12). MEG detects the weak magnetic fields generated by cerebral electrical activity in the brain, with the same high-temporal resolution as EEG. Both MEG and EEG signals are susceptible to noise contamination by muscle activity, head movement and blinking, the problems which must be addressed in order to obtain good measurements. MEG studies have reported somatosensory tasks related

 doi: 10.1111/j.1365-2842.2007.01736.x

to jaw movement (13–17), motor tasks related to swallowing (18) and the readiness potentials immediately before jaw movements (19). However, chewing and tapping are rhythmic, repetitive movements (20), and their brain activity profiles may differ from that of clenching, which is induced by central command. MEG has also been applied to the study of motor tasks, such as bilateral finger movements (21–24), but these studies investigated the simultaneous movement of two bilateral digits. Clenching-related brain activity may be different from finger movement because the bilateral masticatory muscles move only a single unit, the mandible, during clenching.

The long-term goal of our project was the elucidation of processing in the brain immediately before unconscious teeth clenching in order to clarify its significance in humans. The objective of the present study was to establish an MEG method of measuring brain activity immediately before clenching, and to clarify the time-course of brain activity immediately before conscious clenching.

Materials and methods

Pilot study

A pilot study was carried out with an analysis of head movement before and after teeth clenching in two subjects, using the head localization system of the MEG equipment. Visual cues for rest and for clenching were presented to the subject in a semi-random order at between 2 and 4 s intervals. We set out to find the optimum number of trials per run. The number of trials was set at 20, 25 or 30 in one run. Each subject carried out five runs for each of the trials, and head movement was measured before and after each run. The head movement for 20 trials in one run was 0·1–0·2 cm, and for 25 trials in one run was 0·1–0·3 cm. But the head movement for 30 trials in one run showed that nearly half of the runs were over 0·5 cm for each subject. MEG signals are susceptible to noise contamination by muscle activity, head movement and blinking, the problems which must be addressed in order to obtain good measurements. It was important for us to evaluate the effect of head movement and muscle activity. For head movement, we estimated the difference between the main run and the control run. For the muscle activity, a region of interest (ROI) was set inside the source space as close as possible to the masseter muscle region to monitor the masticatory muscle activity as captured by MEG.

Main study

The subjects were six, right-handed males (19–54 years of age), with no history of neurological disorders and without abnormality in stomatognathic function. The RIKEN Ethical Committee had given prior approval for the study. MEG recordings were taken with a whole-head Omega Biomagnetometer 151-channel system*. Electrodes for measuring electrooculogram (EOG) and electrocardiogram (ECG) were used for monitoring the eye movement and heart activity respectively. In addition, the electromyogram (EMG) was recorded with electrodes placed on the central regions of the bilateral masseter muscles, thus monitoring masticatory muscle activities. The EMG, EOG and ECG signals were measured simultaneously with the signal from the 151 MEG channels (the first-order gradiometers), at a sampling rate of 1250 Hz, and low-pass filtered by firmware at 400 Hz. The operator explained the task to the subject before the experiment and allowed him to practice simple clenching. The instructions given were, 'the visual cues consist of two images ''+'' and ''+ and C.'' When ''+'' appears at the center of the screen, please relax but remain fixating on the cross. When ''+ and C'' appear at the center of the screen, then clench your teeth in the way that you have practiced'. Clenching was initiated from the mandibular rest position. The movement paradigm used visual cues projected onto a screen (2·70 ° in height and 2·32 °in width) situated 60 cm in front of the subject. We set the luminance of the screen to about 25 candela m^{-1}, which was comfortable for the subject.

A single trial consisted of maintained clenching for 2 s, followed by a semi-randomized interval of 2–4 s, with 25 trials performed in a single run (Fig. 1). Each subject performed a total of 125 trials over five runs. The subjects also performed five more runs as a control with the same visual cue, but with no teeth clenching. The exact onset of the visual cue was recorded together with the MEG signal, using a photodiode fixed to the screen (25). Before and after each run, the localization coils placed on the nasion and on the left and right pre-auricular points were activated. The locations of these signals were used to determine if the head had moved

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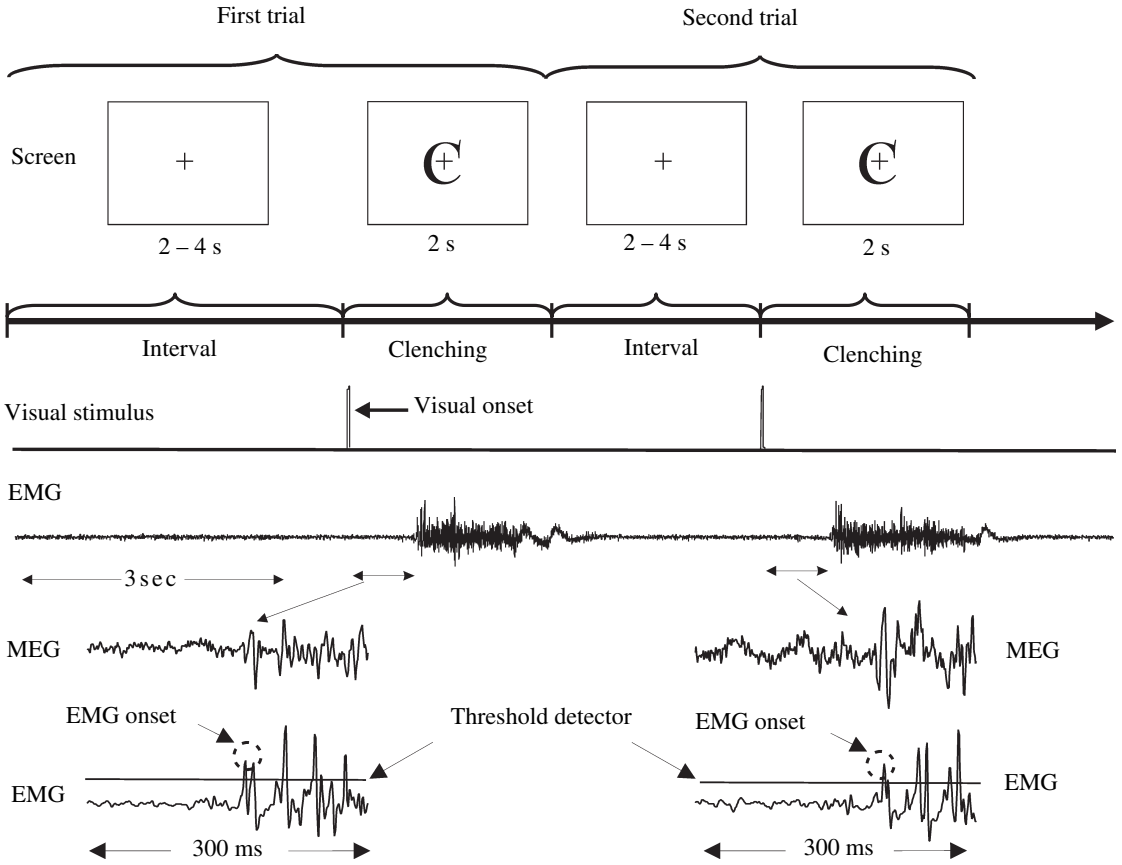

Fig. 1. The task procedure with visual cues. A single trial consisted of maintained clenching for 2 s followed by a semi-randomized interval of 2–4 s, with 25 trials performed in a single run. The figure shows the sequence of events schematically in the top two rows. The next two rows show the stimulus channel (marking the visual cue onset) and an electromyogram (EMG) channel. The last two rows show expanded views of an magnetoencephalographic and EMG channel for the 300 ms periods, following the two visual cues in the display period. The threshold level for detecting EMG onset is also shown together with the EMG traces in the last row.

during the run. If the head had indeed moved 5 mm or more, the measurement was repeated. The subject's head was not fixed during the measurement to avoid stress. The subject's head shape (including the localization coils) was scanned using a 3D digitizer[†] and a 3D camera system[‡]. After the experiment, the digitized head shape was fitted to the MR image to get a transformation matrix between the coil- and MRI-based coordinate systems using Rapid Form software[§] and an in-house developed software (26). The accuracy of co-registration was found to be within 3 mm. Before the main data analysis, we eliminated noisy channels and trials contaminated by artifacts. The raw data were processed using the third gradient and by removal of the direct current (DC) baseline. The third gradient is constructed in software using additional measurements from reference channels further away from the head, than the 151 first-order gradiometers that make up the main set of MEG sensors. To determine the clenching onset latency, the raw data were low-pass filtered at 200 Hz and high-pass filtered at 14 Hz, a threshold detector was set and the latency at which the EMG signal crossed this threshold was marked for each trial. The latency from the visual onset (VO) to the EMG onset (EO) was then determined for each trial, and the mean and standard deviation (SD) were calculated for each subject. Trials with a value exceeding ± 2 SD were excluded from the analysis. One subject was excluded from the analysis because of excessive blinking, immediately after the visual cue. As the latency tended to increase, when blinking occurred between the visual cue and EMG onsets and on the first trial of each run,

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these trials were excluded from the analysis. For the main analysis, the raw MEG data were processed again by taking the third gradient, removing the DC component and high-pass filtering at 1·026 Hz. Two, separate, average MEG signals were computed for each run. The first signal was computed after averaging the artifact-free single trials of each run aligned to VO. It extended from −300 to 600 ms with VO set at zero. The second average was computed from single trials aligned to EO from −600 to 300 ms with EO set at zero. We used MFT (27) to obtain a tomographic reconstruction of brain activity, for each time slice of the VO and EO average signal, for each subject and run. Four separate MFT computations were used with separate source spaces ($17 \times 17 \times 11$ grid points in each) covering the left and right hemispheres and top and back of the brain. For each source space, the 90 channels providing the best coverage were used, with the lead fields computed for a conducting sphere abutting the inner surface of the skull around the source space. MFT was used to obtain three-dimensional distributions of the primary current density, $J(r, t)$ at each grid point in the brain, and the reconstruction was performed completely independently at each time slice. The time slices for reconstruction were taken from the averaged MEG signal. The combination of the reconstructions from all four source spaces used MFT solutions defined from the sensitivity profiles of the sensors (28).

Student's *t*-test was applied in a voxel-by-voxel analysis using the MFT values to identify statistically significant changes in activity. Statistical parametric maps (SPMs) (29) were used to identify significant differences in the brain activity between pre- and post-visual stimuli. Student's *t*-test was computed across runs for each subject, using a running window of 48 ms width, and was used to compare the two conditions. We reported *P*-values that included the conservative Bonferroni correction for multiple voxel comparisons. The data for each subject were transformed to a common Talairach space (30), and common statistically significant changes in activity ($P < 0{\cdot}01$) were identified for each time window. These changes in activity were displayed on the MR image of one subject after the appropriate inverse transformation from the Talairach space. Probe ROI (pROIs) were defined for each subject in the left and right motor, pre-motor, somatosensory and visual cortices. These pROIs were defined either according to the common activations identified by MFT or by reference to the anatomical locations in Penfield's report (31). An activation curve (32) was computed for each pROI from the MFT data (using all grid points within the ROI). Separate pROIs were computed for VO and EO for each subject. The most representative pROI for each area was selected as the final ROI for that region for each subject. In addition, an ROI was set inside the source space as close as possible to the masseter muscle region to monitor the masticatory muscle activity as captured by MEG. The coordinates of all ROIs in the brain were transformed to Tarailach coordinates in each subject, and the coordinates of each ROI of all subjects were averaged.

The onset latency and first peak latency from the VO to the onset, and first peak response of the visual, motor, pre-motor and somatosensory areas were detected from the activation curves of the VO-based averages for each subject. We, then, determined the latency between these two peaks, independently for the left and right hemispheres for these areas. To determine the threshold, the algorithm computed a threshold amplitude value exceeding ±3 SD of the integrated activation curve in the 300 ms preceding the visual stimulus. The onset delay and first peak delay, between left and right hemispheres for each area, were detected by the onset latency and first peak latency. Using this measurement, the significant difference of the delay for each area was computed using a two-way analysis of variance (ANOVA) (by area and subject), and a *post-hoc* test.

Results

Table 1 shows the mean and SD values for the clenching onset latency relative to the cue onset (time from VO to EO), and the mean distance of head movement after measurement, for the five individual subjects. The

Table 1. Mean and standard deviation of latency from visual onset to electromyogram onset and mean of head movement

	Latency		Head movement	
	Mean (ms)	SD (ms)	Main run (mm)	Control run (mm)
Subject 1	264	63	1·7	1·3
Subject 2	303	82	4·5	2·8
Subject 3	388	116	2·1	4·3
Subject 4	160	48	1·4	1·6
Subject 5	391	110	1·5	0·9
Avg.	305	129	2·2	2·2

range of clenching latencies was 160–400 ms. The head movement range values were 1·4–4·5 mm in the main run, and 0·9–4·3 mm in the control run, showing no significant difference in any subject. Repetition because of head movement was necessary in only two trials in the main run out of all subjects, giving an overall measurement success rate of >90%.

Figure 2a–d shows maps of statistically significant changes in activity common for all subjects ($P < 0{\cdot}01$), projected back on to the axial and sagittal MR images of one subject. Figure 2a and b shows the common activations computed from the MFT solutions of the EO-based average MEG signal with 48 ms latency windows. Common (for all five subjects) statistically significant increases in activity are identified in motor, pre-motor and somatosensory cortex from 112 ms, before EO. Figure 2c and d shows the common activations computed from the MFT solutions of the VO-based average. Common statistically significant increases in right pre-motor/motor cortex are identified as early as 140 ms after VO, and bilaterally afterwards (Fig. 2c and d). Common statistically significant activity was also identified in the visual cortex from 140 ms (not shown). Figure 3 shows typical activation curves for each ROI for one subject. Figure 3a shows the ROI activation curves of the VO-based average from the right hemisphere, and Fig. 3b from the left hemisphere. Visual cortical activity was detected about 120 ms after VO. A similar ROI activation curve of the visual cortex was obtained from the control run. In the motor, pre-motor and somatosensory cortices, activities were noted within about 100 ms after the visual cortical activity. Figure 3c shows the ROI activation curves of the EO-based average from the right hemisphere. Motor, pre-motor and somatosensory cortical activities were noted from −120 ms before EO. Figure 3d shows the

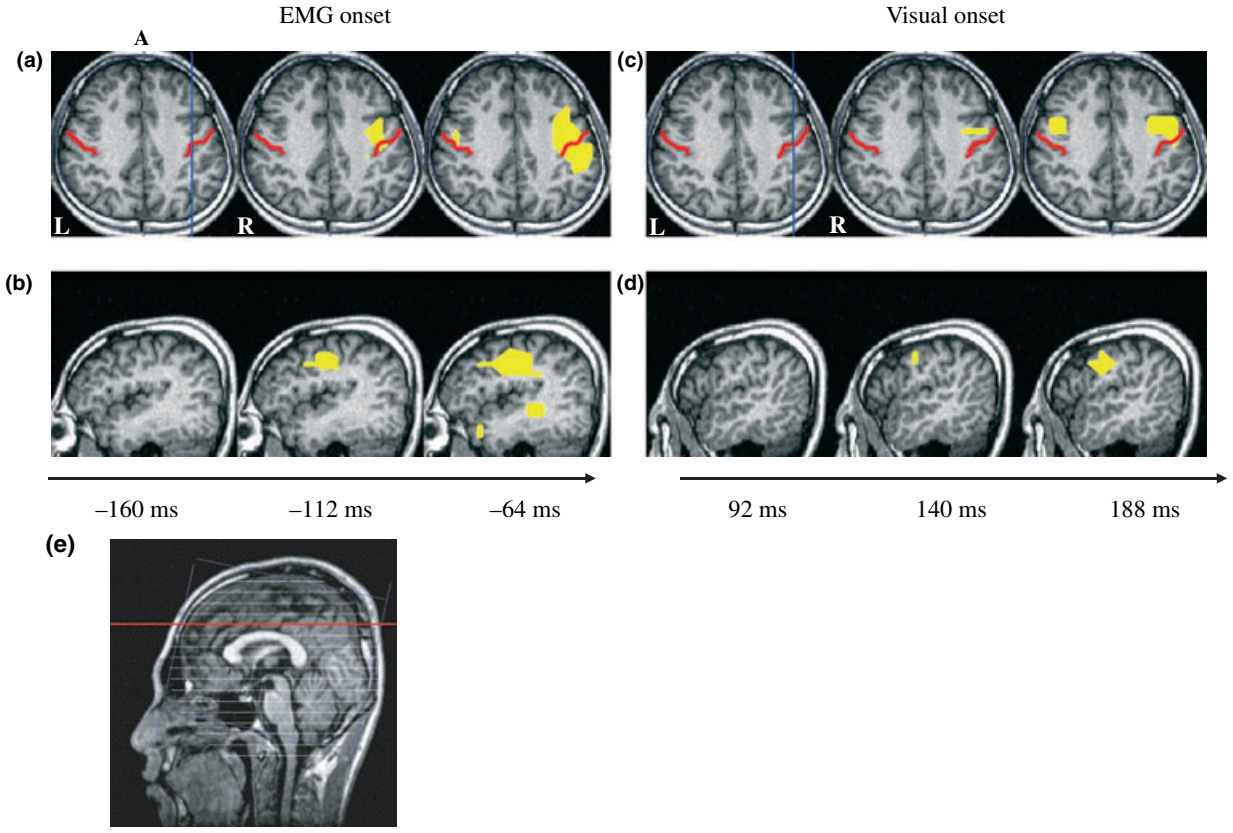

Fig. 2. Statistical parametric maps of significant change of activity ($P < 0{\cdot}01$ for all subjects). (a, b) The statistical maps on the axial and sagittal magnetic resonance (MR) images with the origin of the time axis set to the electromyogram onset. (c, d) The statistical maps on the axial and sagittal MR images with the origin of the time axis set to the visual cue onset. The red line in (a) and (c) is the central sulcus. The blue line in (a) and (c) shows the sagittal sections below. The red line in (e) shows the axial planes in (a) and (c). Coordinates are given in Table 2.

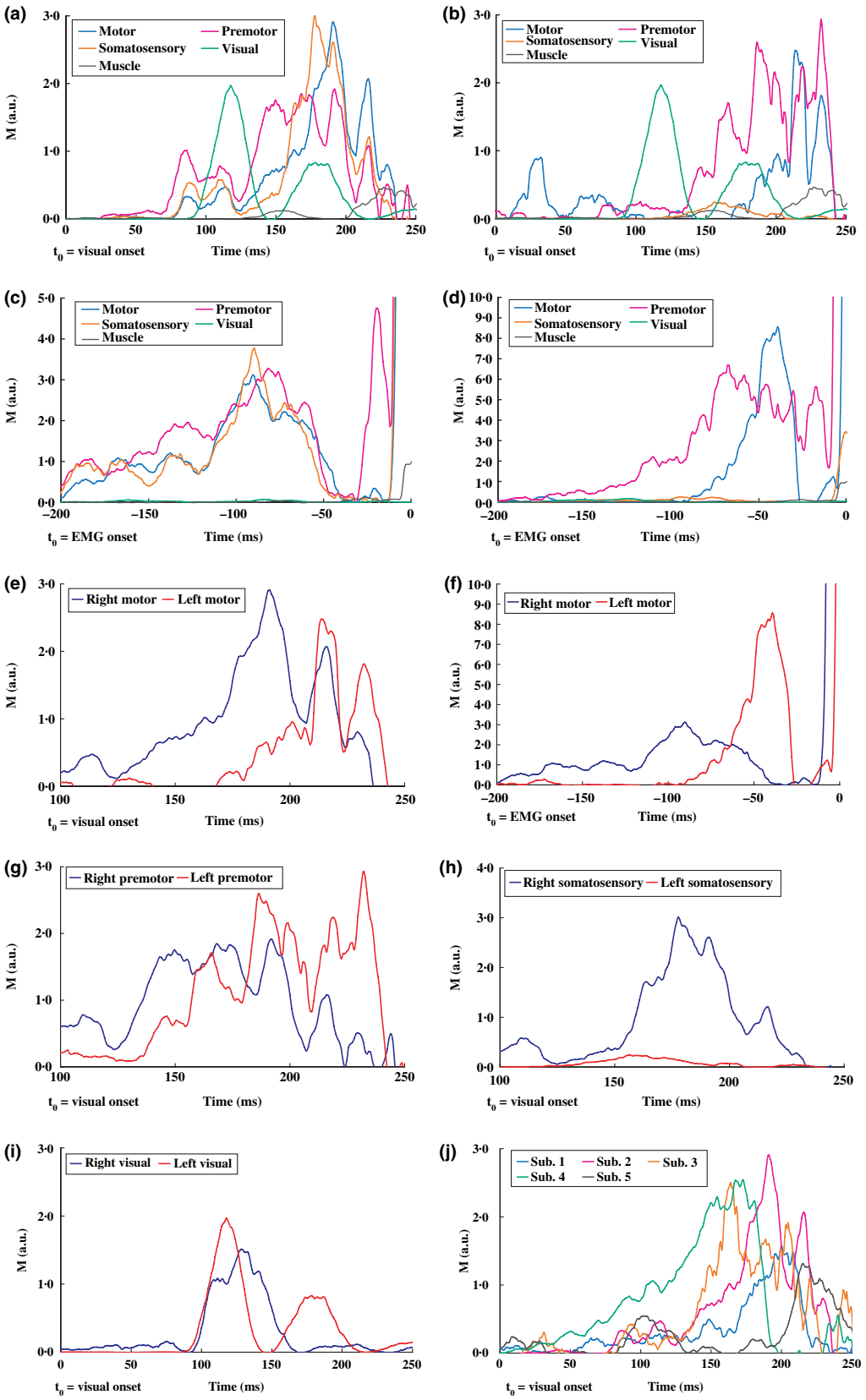

Fig. 3. Typical activation curves for subject 2. (a, c) The activations for regions of interest (ROIs) in the right hemisphere. (b, d) The activations for ROIs in the left hemisphere. (e, f) Direct comparison of left and right motor ROI activity. Direct comparisons of activations in the left and right hemisphere (g) pre-motor, (h) somatosensory, (i) visual cortex. (j) Activation of right motor cortex for each subject. The origin of the time axis is set to the visual cue onset for (a), (b), (e), (g), (h) and (i) and to the electromyogram (EMG) onset for (c), (d) and (f). On the *y*-axis, 'a.u.' stands for arbitrary units. The muscle ROI was set as close as possible to the masseter muscle region to monitor the masticatory muscle activity captured by the MEG and used as the EMG onset signal.

Table 2. Mean and standard deviation of the Talairach coordinates for each region

		Talairach coordinates		
R/L	Region	*x*	*y*	*z*
R	Motor cortex	41·5 (9·0)	−10·5 (8·0)	45·3 (8·5)
R	Somatosensory cortex	43 (6·5)	−23·5 (11·4)	46·3 (7·1)
R	Pre-motor cortex	34·8 (10·8)	10·3 (8·8)	45·5 (8·5)
L	Motor cortex	−47·8 (9·8)	−11·8 (10·4)	36 (5·8)
L	Somatosensory cortex	−45 (9·8)	−30·5 (8·4)	38·8 (10·5)
L	Pre-motor cortex	−40·5 (7·3)	12·3 (10·1)	32·8 (7·8)

R, right; L, left.

ROI activation curves of the EO-based average from the left hemisphere. Note that the ROIs describing muscle activation (dashed line) in Fig. 3a–d show no strong activity before clenching onset. Figure 3e shows a direct comparison of the left and right motor cortical ROI activation curves of the VO-based average and Fig. 3f of the EO-based average. Activity is clearly seen in both motor cortices, but the right motor cortex is activated more and earlier (Fig. 3e and f). Figure 3g–i shows, respectively, a direct comparison of the left and right pre-motor, somatosensory and visual cortical ROI activation curves of the VO-based average for one subject. These waveforms comparing the left and right are not entirely symmetrical. Figure 3j shows the activity of right motor cortical ROI activation curves of the VO-based average in each subject. The coordinates of each ROI were transferred to Talairach space averaged across all five subjects (Table 2).

Table 3a shows the onset delay and Table 3b shows the first peak delay between two hemispheres for each area. ANOVA showed significant difference for the onset delay [$F(3,12) = 6{\cdot}5$; $P < 0{\cdot}01$] and the first peak delay of each area [$F(3,12) = 4{\cdot}5$; $P < 0{\cdot}03$]. The *post-hoc* test showed a significant difference for the onset delay between visual cortex and motor cortex ($P < 0{\cdot}03$), and no significant difference for the first peak delay.

Table 3. (A) The onset delay between two hemispheres for each area. (B) The first peak delay between two hemispheres for each area

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
A					
Visual	3	6	3	4	5
Pre-motor	2	10	10	2	4
Motor	32	43	18	18	8
Somatosensory	30	13	25	7	5
B					
Visual	7	8	4	9	7
Pre-motor	30	2	4	7	3
Motor	36	10	11	25	17
Somatosensory	20	8	6	20	16

ANOVA showed significant difference for the onset delay for each area [$F(3,12) = 6{\cdot}5$; $P < 0{\cdot}01$], and the first peak delay for each area [$F(3,12) = 4{\cdot}5$; $P < 0{\cdot}03$]. The *post-hoc* test showed a significant difference for the onset delay between visual cortex and motor cortex ($P < 0{\cdot}03$), and no significant difference for the first peak delay.

Discussion

The objective of the present study was to establish an MEG method of measuring brain activity immediately before clenching, and to clarify the time course of brain activity immediately before conscious clenching.

In previous reports, the relationship between jaw movement (10, 11) or finger movement (21–24) and brain activity was analysed in time, but the method of cueing subjects was not described and the task onset was not clearly indicated. These movements were mostly rhythmic and repetitive, whereas teeth clenching is neither a rhythmic nor repetitive movement. In this study, we used visual stimulation in the

experimental design, which allowed us to time-lock from the input of visual stimulation to the output of teeth clenching, using the visual or EMG onset timing landmarks for each single trial. Using the corresponding clenching onset latencies (VO and EO) allowed the computation of two average signals. The early stages of visual to motion processing were clearly seen using the VO-based average, revealing the onset of activity in each area. Later stages of processing were better time-locked to the motor output and were clearly seen using the EO-based average.

Head movement posed a potential problem to measuring jaw movement using MEG. However, even with no head support system, repeating a measurement was necessary in only two trials. Movement of the head remained within the pre-specified acceptable range of 5 mm in all trials (Table 1), and no significant difference was noted in comparison with the control run, supporting our claim that the MEG measurements were free of motion artifacts during clenching, without the use of a physical head restraint.

Analysis of the activation curves showed a prominent peak in the visual cortical activity at about 120 ms after the visual cue onset for both the control and main runs (Fig. 3a and b; control not shown). This suggests that the subjects were able to clench on the visual cue and started clenching after the stimulus, resulting in few error tirals and increased reliability in the latency from VO to EO. As the mean latency of all subjects was about 300 ms from VO to EO, the initiation times of the motor, pre-motor and somatosensory cortical activities were about −180 ms immediately before clenching. These findings suggest that the analysis of activation curves should begin at least 200 ms before EO. In earlier EEG and MEG studies, activity was detected from 600 to 1500 ms before the EMG onset, for chewing and tapping (11, 19). In those studies, a self-paced task was used, in which MEG signals were averaged by movement output but not by sensory-visual input. No large MEG component that could be attributed to masticatory muscle activity was detected before EO, indicating that such noise contribution because of masticatory muscle activity did not affect the analysed period.

Bilateral cortical activity was noted in previous reports on time-course activation before jaw movement (10, 11, 19), but the reported results referred to EEG traces and could not unambiguously relate to activity in motor structures or muscles. One MEG study (19) used dipole localization with a single source describing the activity in each hemisphere. With this method, the time course of the equivalent source is influenced by somatosensory, motor, pre-motor and possible muscle activity. Bilateral finger movement has been studied with MEG and in some cases regional time courses were computed (21–24). However, the results are difficult to compare with ours, because, despite a common bilateral symmetry in the two movements, there is essential difference in the coordinating parts of the left and right hand in bimanual finger movements, as compared with controlling jaw movements. Our results found bilateral cortical activation before teeth clenching as shown in Figs 2 and 3, although this activity was seldom symmetrical, and there was a subject difference in the side of early activation of the motor cortex. The tomographic solutions allowed us to compute SPMs across the brain. In both cases, increases in activity were found in both hemispheres (Fig. 2a and c). These activations were in the inferior aspects of the central sulcus. Penfield (31)reported isolated activations in the dorsal aspects of the sensorimotor cortex. We found no significant activity in the dorsal areas either on the posterior or anterior banks of the central sulcus corresponding, respectively, to the sensory and motor cortex for the hand and foot. Furthermore, in our study, we did not observe widespread sensory activity before clenching. The widespread sensory and parietal activity reported in the clenching study using fMRI (4) was very likely generated by sensory feedback after clenching.

In previous EEG and MEG studies, readiness potentials were judged to be symmetrical before the jaw opening and jaw-closing movements from rather limited signal topographies (11, 19). In contrast, previous studies reported asymmetrical masticatory activity with fMRI (6) and asymmetrical swallowing with MEG (18). In our study as well, the activity was not entirely symmetrical when analysed on the time axis, as shown in Fig. 3e–h and in the statistics (Table 3). Our study, therefore, suggests that the brain activity associated with clenching is not symmetrical, and that the activation of one hemisphere precedes the other, despite the fact that the bilateral masticatory muscles move the mandible as a single unit.

Conclusions

Based on these findings, we concluded that the MEG procedures, we used, were capable of measuring brain

activity immediately before teeth clenching, and showed that the analysis should begin from at least 200 ms before EMG onset. In addition, immediately before teeth clenching, the cerebral activity was asymmetrical in the motor, pre-motor and somatosensory cortices.

Acknowledgments

We thank Prof. Misao Kawara, Director of Department of Clinical Oral Physiology, Nihon University School of Dentistry at Matsudo, Dr Daniel Palomo for editing assistance and the staff of Laboratory for Human Brain Dynamics, RIKEN, BSI for their continuous support to this work.

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