ORAL DISEASES

Oral Diseases (2011) 17, 407–413 doi:10.1111/j.1601-0825.2010.01767.x

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ORIGINAL ARTICLE

Quantitative analysis of masticatory activity during unilateral mastication using muscle fMRI

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OBJECTIVE: Quantitative analysis of the activities of all masticatory muscles is required to elucidate the mechanism of stomatognathic dysfunction. Electromyography can be used to record the activity of masticatory muscles, but quantification of the overall activity of every masticatory muscle has not been accomplished because of methodological limitations. In this study, we used muscle functional magnetic resonance imaging for simultaneous quantification of the overall activities of the masseter, medial pterygoid and lateral pterygoid muscles during unilateral gum chewing.

METHODS: Seven healthy male volunteers participated in the study. We evaluated changes in the mean proton transverse relaxation time in the bilateral masseter, medial pterygoid and lateral pterygoid muscles before and after unilateral gum chewing, and to quantify the overall activity of these muscles simultaneously during unilateral gum chewing.

RESULTS: After 5 min of chewing, the activity of the ipsilateral masseter was highest among the six muscles, followed by the ipsilateral medial pterygoid, contralateral lateral pterygoid and contralateral masseter muscles.

CONCLUSION: These results affirm the importance of the ipsilateral masseter muscle and quantitatively demonstrate the important contribution of the ipsilateral medial pterygoid and contralateral lateral pterygoid muscles during unilateral mastication.

Oral Diseases (2011) **17**, 407–413

Keywords: MRI; masticatory muscle; activity; quantification

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Received 2 June 2010; revised 23 August 2010; accepted 15 September 2010

Introduction

Physiologic stomatognathic functions such as mastication and deglutition require balanced and coordinated activities of the masticatory muscles on the left and right sides. A disruption of this balance may lead to dysfunctions of the stomatognathic system such as temporomandibular disorder. Quantitative analysis of the activities of all masticatory muscles is desirable to elucidate better the mechanism of masticatory function and dysfunction.

Electromyography is the general approach for studying masticatory activity and is commonly used for analysis of the masseter and temporal muscles, which are easily accessible from the skin surface. However, the activity of the medial and lateral pterygoid muscles is less well understood (Hannam and McMillan, 1994), as surface electromyography cannot be used and alternative approaches require use of a wire or needle and are difficult to perform. The anatomic locations of these muscles are deep below the skin surface and determining the electrode location is difficult. Furthermore, intramuscular electromyographic recording evaluates the activity only in a limited region of a muscle and cannot quantify its overall activity.

Muscle functional magnetic resonance imaging (mfMRI) can be used to quantify the overall activity of a particular set of muscles simultaneously. This technique makes use of the exercise-induced increase in the proton transverse relaxation time (T2) in 3-dimensional MR images of muscle, and has the advantage of being non-invasive and allowing simultaneous evaluation of all muscles within the acquired MR images, including deep muscles such as pterygoid muscles. mfMRI has been used to examine the activity of limb skeletal muscles, in which exercise-induced shifts in T2 correlate with exercise intensity and workload (Adams *et al*, 1992; Sloniger *et al*, 1997; Meyer and Prior, 2000; Saunders *et al*, 2000; Kinugasa and Akima, 2005; Segal and Song, 2005). In previous studies of masticatory muscles, the mean signal intensities (not the T2 value) in selected parts of the left masseter, medial pterygoid, and

temporal muscles have been measured on T2-weighted MR images obtained before and after maximal clenching (Gan *et al*, 2000), but changes of the mean T2 value over all the bilateral masticatory muscles have not been examined. It is possible to compare T2 values as measures of muscle activity among a number of subjects because the T2 value is a tissue-specific parameter that differs from signal intensity and is not affected by the machine parameters. The T2 value has been reported as an index of muscle activity in most previous studies (Adams *et al*, 1992; Sloniger *et al*, 1997; Meyer and Prior, 2000; Saunders *et al*, 2000; Kinugasa and Akima, 2005; Segal and Song, 2005).

The present study was designed to evaluate changes in the mean T2 in the bilateral masseter, medial pterygoid, and lateral pterygoid muscles before and after unilateral gum chewing, and to quantify the overall activity of these muscles simultaneously during unilateral gum chewing. The bilateral temporal muscles were excluded from the analysis because the superior parts of these muscles could not be included in the collected thin (3.0-mm thick, no gap) slice axial MR images.

Materials and methods

Subjects

Seven healthy male volunteers who had no missing teeth and no functional malocclusion participated in the study. The subjects were aged 25–47 years old (mean age 32.7 ± 7.3 years old) and had no symptoms of stomatognathic dysfunction or other general disease affecting the neuromuscular system. The chewing side preference was determined by interview. Two subjects had a bilateral chewing side preference, three subjects had a right-side preference, and two subjects had a left-side preference. Written informed consent was obtained from each subject after a full explanation of the study was provided. The study was approved by the Ethical Committee of Tohoku University Graduate School of Dentistry.

Magnetic resonance imaging

Each subject was instructed to chew three pieces of chewing gum (Freezone, Lotte, Tokyo, Japan) simultaneously in the left dental arches at their preferred constant chewing rate. Each piece of gum had a standard size and weight ($72 \times 19 \times 1.5$ mm, 2.85 g). High-level activation of the target muscle is needed to evaluate muscle activity with mfMRI because there is minimal or no change in the T2 time at low levels of muscle fiber activation (Segal, 2007). In a preliminary study, T2 changes that could be evaluated statistically in the masticatory muscles were recorded while chewing three pieces of gum. Left-side chewing was used to allow simple comparison with our previous study, in which we simultaneously quantified the overall activity of individual masticatory muscles during left lateral excursion with ^{18}F-fluorodeoxyglucose-positron emission tomography (Yamaguchi *et al*, 2006). Gum chewing was performed in a supine position on the MR gantry to allow an MRI scan to be obtained immediately after mastication. Starting and stopping of gum chewing were indicated with an auditory cue. T2-weighted MR images were obtained under three conditions: the first MRI scan was performed at rest, and the second and third MRI scans were obtained immediately after 5 min of gum chewing and immediately after 10 min of gum chewing, respectively, separated by 40 min of rest. Transverse head and neck images (25 slices, slice thickness = 3 mm, matrix = 256*256, field of view = 250 mm, pixel size = 0.98*0.98 mm) were obtained with a spin-echo sequence (repetition time: TR = 2500 ms, echo time: TE = 20/80 ms, flip angle = 90°) on a Magnetom Vision Plus 1.5 T system (Siemens, Erlangen, Germany) at Kansei Fukushi Research Center, Tohoku Fukushi University. The location of transverse images was chosen to contain the entire masticatory muscles, except for the temporal muscles. Each participant rested for 40 min between periods of 5 min and 10 min of chewing, as the T2 decay time may be >20 min after cessation of exercise (Gan *et al*, 2000).

Image analysis

Acquired MR images were transferred to a PC workstation and T2 values were calculated for each pixel on images obtained at two echo times (20 and 80 ms) using ImageJ (Research Services Branch, National Institutes of Health, Bethesda, MD, USA) with the following formula: $T2 = (t_b - t_a)/\ln(i_a/i_b)$, where t_a and t_b are the spin echo times, and i_a and i_b are the signal intensity levels.

Volume of interest (VOI) analysis was carried out with ImageJ (Figure 1). VOIs were manually drawn over the bilateral masseter muscles, medial pterygoid muscles, and lateral pterygoid muscles on all slices of TE = 20 ms MR images, which include more anatomic information than TE = 80 ms images. Apparent high-signal areas, such as those due to fat, were manually excluded during tracing of the VOIs. VOIs could not be drawn over the bilateral temporal muscles because the

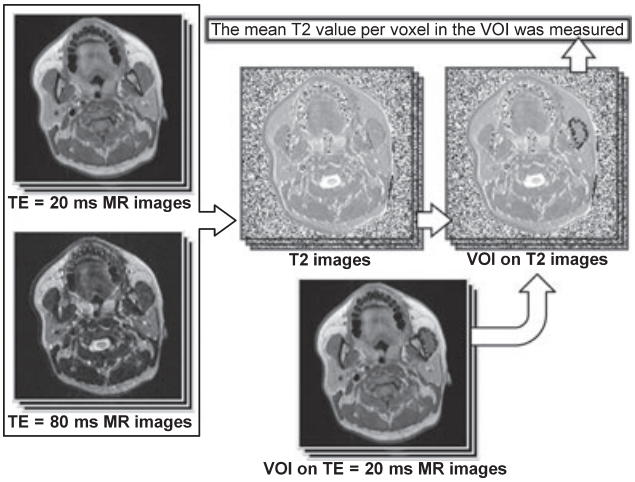

Figure 1 Procedure for volume of interest (VOI) analysis, using the left masseter muscle as an example. Representative images are shown at the same slice level in the same subject

superior parts of these muscles did not appear in the collected MR images. As a reference, VOIs were also drawn over the mandibular condyle marrows. VOIs were applied to the corresponding reconstructed T2 images and the mean T2 values per voxel in each VOI were measured with ImageJ. A mean ΔT2 for each VOI was calculated from the mean T2 after chewing minus the resting T2.

Statistical analysis

Statistical analysis was performed with Dr. SPSS II (SPSS Japan, Tokyo, Japan). The within-subject variation of the mean T2 value of each VOI in MR images of each subject was analyzed with a one-factor repeated-measures ANOVA for each acquisition condition (at rest, and after 5 and 10 min of chewing). Significant differences among acquisition conditions were examined using post hoc Bonferroni tests, and significant differences in mean ΔT2 values among different muscle VOIs for each acquisition condition were examined with a one-factor ANOVA and the Games/Howell method. The null hypothesis was rejected for $P < 0.05$.

Results

Changes of signal intensity in T2-weighted MR images

A visual comparison of TE = 80 ms MR images in each subject at rest and after 5 min of chewing showed that the signal intensity increased in the masseter, medial pterygoid, and lateral pterygoid muscles after chewing (Figure 2). The signal intensity clearly increased in the ipsilateral masseter and medial pterygoid muscles, but showed little change in the muscles of the posterior region of the neck.

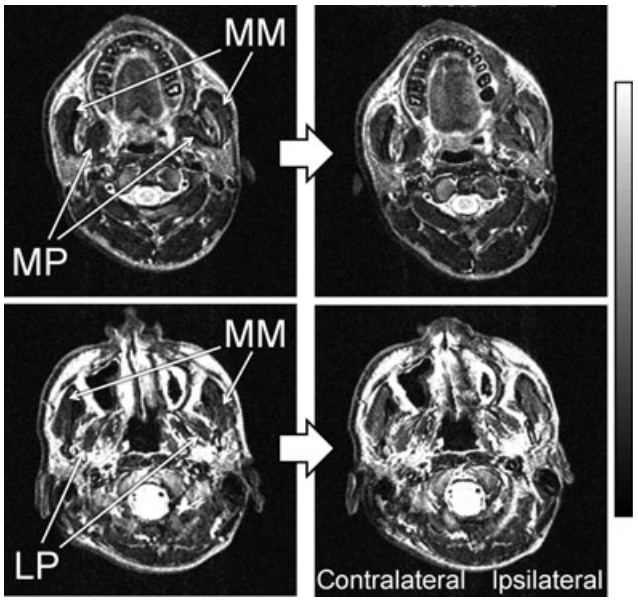

Figure 2 Representative axial TE = 80 ms MR images of the head and neck at rest (left) and after 5 min of left side chewing (right). Black-white scales depict the MR signal intensity. Note the increased signal intensity of the masticatory muscles following 5 min of gum chewing. MM = masseter muscles, MP = medial pterygoid muscles, LP = lateral pterygoid muscles

Mean T2 value of each VOI

Significant changes in mean T2 values after chewing were found in the ipsilateral masseter ($P < 0.001$), contralateral masseter ($P = 0.010$), ipsilateral medial pterygoid ($P < 0.001$), contralateral medial pterygoid ($P = 0.002$), ipsilateral lateral pterygoid ($P = 0.004$), and contralateral lateral pterygoid muscles ($P = 0.005$) (Table 1). There were no significant changes in mean T2 values for the ipsilateral ($P = 0.360$) and contralateral ($P = 0.658$) mandibular condyle marrows.

The mean T2 value increased with duration of gum chewing in the contralateral masseter, contralateral medial pterygoid, and ipsilateral lateral pterygoid muscles, but leveled off after 5 min of chewing in the ipsilateral masseter and medial pterygoid and contralateral lateral pterygoid muscles (Figure 3a). In the ipsilateral masseter and medial pterygoid muscles, significant differences in mean T2 values were found between rest and after 5 min of chewing ($P = 0.004$ and $P = 0.006$, respectively), and between rest and after 10 min of chewing ($P = 0.014$ and $P = 0.006$, respectively). In the contralateral masseter muscle, significant differences in T2 were observed between rest and after 10 min of chewing ($P = 0.025$), and between 5 and 10 min of chewing ($P = 0.019$). In the contralateral medial pterygoid and ipsilateral and contralateral lateral pterygoid muscles, significant differences in T2 were observed only between rest and 10 min of chewing ($P = 0.011$, $P = 0.023$ and $P = 0.005$, respectively).

Mean ΔT2 values for each muscle

After 5 min of chewing, the mean ΔT2 for the ipsilateral masseter was highest among the six muscles, followed by the ipsilateral medial pterygoid, contralateral lateral pterygoid and contralateral masseter muscles (Table 2 and Figure 3b). The mean ΔT2 values for the ipsilateral lateral pterygoid and contralateral medial pterygoid muscles were clearly lower than those for the other four muscles. A multiple comparison revealed a significantly higher mean ΔT2 value ($P = 0.034$ by the Games/Howell method) in the ipsilateral masseter muscle compared with the contralateral medial pterygoid muscle.

After 10 min of chewing, the mean ΔT2 values of the six muscles showed a tendency to converge and there was no significant difference among the muscles ($P = 0.328$ by one-factor ANOVA).

Discussion

In this study, we provide the first quantification of the overall activities of masticatory muscles focusing on the change in the T2 value in mfMRI. An exercise-induced increase of T2 in MRI has been observed in isolated frog skeletal muscle after isometric contractions with electrical stimulation (Bratton *et al*, 1965) and a similar phenomenon has been found in human subjects (Fleckenstein *et al*, 1988). These increases in T2 are thought

Table 1 Mean T2 values for VOIs

	Masseter		*Medial pterygoid*		*Lateral pterygoid*		*Mandibular condyle marrows*	
	Ipsilateral	*Contralateral*	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*
Rest	33.0 ± 1.2	33.1 ± 1.2	33.5 ± 1.4	33.0 ± 1.9	37.7 ± 3.0	39.1 ± 2.9	38.8 ± 2.9	40.1 ± 2.3
After 5 min chewing	36.4 ± 2.5	35.5 ± 2.6	36.7 ± 2.3	33.8 ± 1.8	38.7 ± 2.9	41.9 ± 4.3	39.3 ± 1.7	39.8 ± 1.8
After 10 min chewing	36.5 ± 2.7	36.3 ± 2.8	36.4 ± 1.6	34.5 ± 2.2	40.4 ± 3.3	41.7 ± 3.0	39.6 ± 1.6	40.5 ± 1.6
P value	< 0.001*	0.010*	< 0.001*	0.002*	0.004*	0.005*	0.360	0.658

Mean ± standard deviation (msec).
*$P < 0.05$ (one-factor repeated-measures ANOVA).

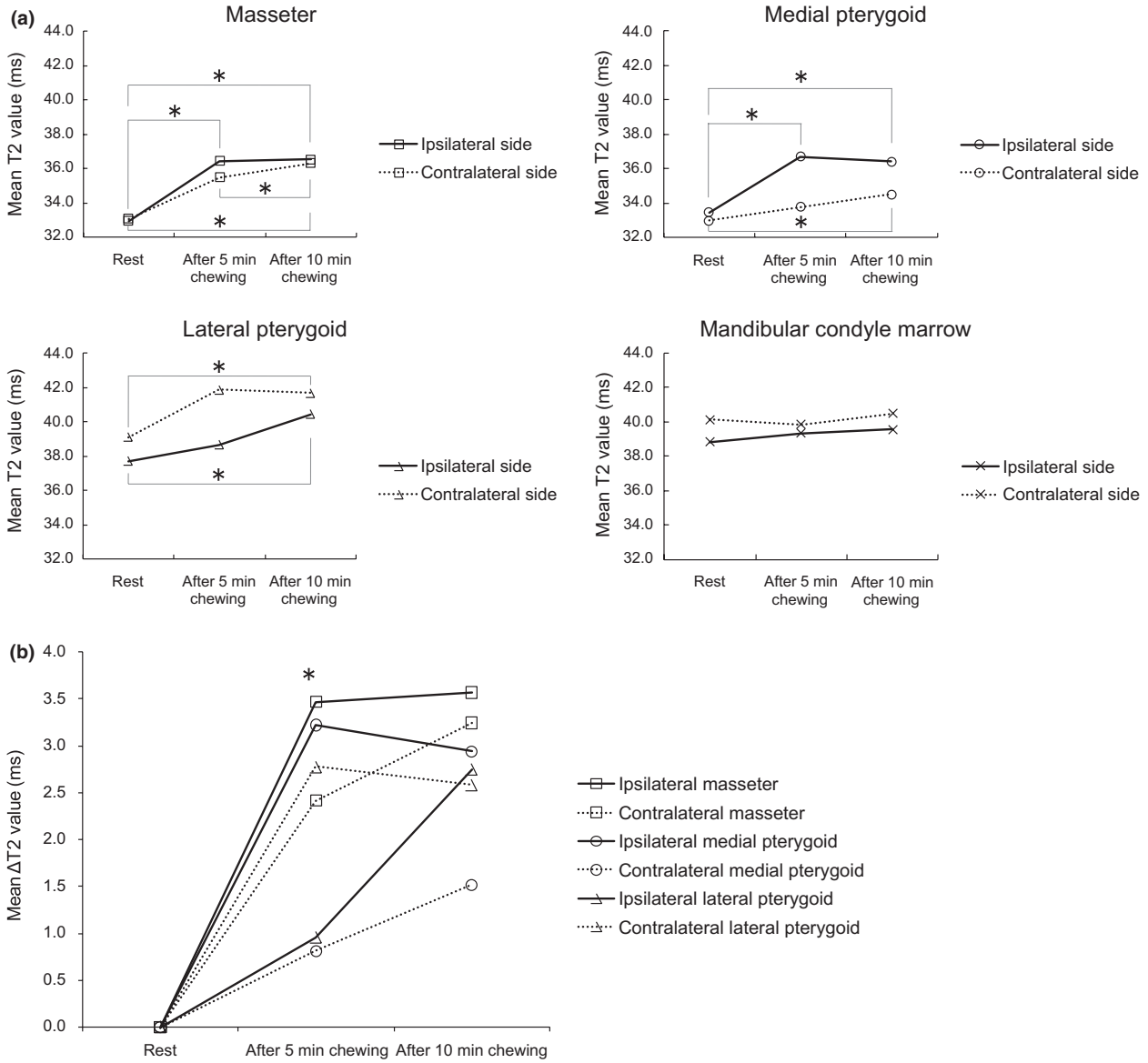

Figure 3 **(a)** Mean T2 for each VOI at rest and after 5 and 10 min of chewing. Statistical significance was tested by a one-factor repeated-measures ANOVA and Bonferroni tests (*$P < 0.05$). **(b)** Mean ΔT2 for the masseter, medial pterygoid and lateral pterygoid muscles at rest and after 5 and 10 min of chewing. * Significantly higher ΔT2 ($P < 0.05$) for the ipsilateral masseter muscle compared to the contralateral medial pterygoid muscle

to be driven primarily by water shifts resulting from transient changes in tissue osmolarity, which depend on accumulation of tissue osmolytes, and particularly intracellular lactate (Akima, 2005). The underlying biophysical cause of the T2 increase in exercised muscle is not fully understood, but exercise-induced shifts in T2

Table 2 Mean ΔT2 for the masseter, medial pterygoid and lateral pterygoid muscles

	Masseter		*Medial pterygoid*		*Lateral pterygoid*	
	Ipsilateral	*Contralateral*	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*
After 5 min chewing	3.5 ± 1.6*	2.4 ± 2.1	3.2 ± 1.6	0.8 ± 0.9	1.0 ± 1.6	2.8 ± 2.3
After 10 min chewing	3.6 ± 2.2	3.2 ± 2.2	2.9 ± 1.5	1.5 ± 0.9	2.7 ± 1.8	2.6 ± 1.3

Mean ± standard deviation (msec).
*$P < 0.05$ versus contralateral medial pterygoid (Games-Howell method).

correlate with physiologic parameters such as integrated electromyography, exercise intensity, number of repetitions, and workload (Adams *et al*, 1992, 1993; Yue *et al*, 1994; Prior *et al*, 1999; Kinugasa and Akima, 2005). mfMRI cannot provide a real-time continuous record of muscle activity, as can be achieved with electromyography (Yue *et al*, 1994). However, it is possible to quantify the overall activity of particular muscles simultaneously after exercise with mfMRI, whereas this cannot be achieved with conventional electromyography.

^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) can also be used to quantify the overall activity of a particular muscle. FDG-PET has been used to evaluate muscle activity by measuring intramuscular variation in glucose metabolism within exercising skeletal muscles (Fujimoto *et al*, 1996; Pappas *et al*, 2001). This approach allows simultaneous quantification of the overall activity of individual masticatory muscles during chewing and lateral excursion (Rikimaru *et al*, 2001; Yamaguchi *et al*, 2006). However, FDG-PET scanning cannot be performed repetitively in an individual subject because of exposure to the ^{18}F radioisotope. Therefore, multiple measurements in the same individual cannot be performed in a FDG-PET study. Furthermore, it is difficult to determine the exact region of muscle in a FDG-PET image due to the limited amount of anatomic information in these images. In contrast, mfMRI scanning is non-invasive, which allows repetitive imaging in individual subjects, and the exact region of muscle can be determined since mfMRI gives functional and anatomic information.

In our subjects, significant changes in T2 induced by gum chewing occurred in the bilateral masseter, medial pterygoid and lateral pterygoid muscles, with little change in the bilateral mandibular condyle marrows. These results concur with previous studies showing a significant change of T2 in skeletal muscles, but not in the marrows (Adams *et al*, 1992). The shifts in T2 for the masseter, medial pterygoid and lateral pterygoid muscles were clearly caused by gum chewing, since there were no differences in T2 values over the whole image.

The mean ΔT2 values of each muscle after 5 min of chewing suggested that the overall activities of the ipsilateral masseter and medial pterygoid muscles were first and second highest, respectively, among the six muscles examined during unilateral gum chewing, followed by the contralateral lateral pterygoid and masseter muscles. The ipsilateral lateral pterygoid and contralateral medial pterygoid muscles clearly showed lower mean ΔT2 values than the other four muscles. These results concur with previous electromyographic studies showing that the activity of the ipsilateral masseter muscle was higher than that of the contralateral masseter muscle during mastication (Miyawaki *et al*, 2001; Proeschel and Raum, 2003). Other electromyographic studies have shown that the activity of the inferior head of the lateral pterygoid muscle increases during contralateral movement and protrusion (Phanachet *et al*, 2002), and with isometric contralateral force (Uchida *et al*, 2001, 2002). Therefore, our results might reflect the activity of the contralateral lateral pterygoid muscle associated with lateral jaw movement during unilateral mastication. In addition, a previous electromyographic study showed that the superior head of the lateral pterygoid muscle is so strongly active that the condyle cannot move and stays in the temporomandibular fossa during ipsilateral horizontal rotation of the mandible and in the intercuspal position (Hiraba *et al*, 2000). The present results suggest that the forward traction of the contralateral mandibular condyle, which is performed by the inferior head of the lateral pterygoid muscle, requires greater muscle activity than the stabilization of the ipsilateral mandibular condyle, which is performed by the superior head of the lateral pterygoid muscles, during unilateral mastication. Further research using the respective VOIs of the superior and inferior heads of the lateral pterygoid muscle is required for more detailed analysis of the lateral pterygoid muscle.

The mean ΔT2 value of the ipsilateral medial pterygoid muscle was higher (although not significantly) than that of the contralateral medial pterygoid muscle during unilateral gum chewing. In contrast, a previous FDG-PET study showed that the activity of the contralateral medial pterygoid muscle, which is associated with a forward force to pull on the contralateral angle of the mandible, was higher than that of the ipsilateral medial pterygoid muscle during lateral excursion (Yamaguchi *et al*, 2006). Another study showed that the medial pterygoid muscle was associated with the vertical and anterior bite forces, and that the activity of the contralateral medial pterygoid muscle early in the closing phase was associated with marked forward and lateral movement of the jaw toward the chewing side during unilateral chewing (Wood, 1986). The higher mean ΔT2 value of the ipsilateral medial pterygoid muscle compared with the contralateral side found in the current study suggests that the medial pterygoid muscle plays a more important role in exerting vertical

bite force with the ipsilateral side than anterior bite force with the contralateral side, in association with adjustment of the jaw position during unilateral mastication.

Few reports on the activities of the medial and lateral pterygoid muscles during mastication are available because of methodological limitations of electromyography. The present mfMRI results quantitatively demonstrate the important contributions of the ipsilateral medial pterygoid and contralateral lateral pterygoid muscles to unilateral mastication.

There was no significant difference among the mean ΔT2 values of all muscles after 10 min of chewing, although there was a significant difference between the mean ΔT2 values for the ipsilateral masseter and contralateral medial pterygoid muscles after 5 min of chewing. The signal intensity of the anterior tibialis muscle in T2-weighted echo-planar images has been found to approach a plateau after about 5 min of exercise in repeated submaximal ankle dorsiflexion against a rubber tube at a constant rate (Jenner *et al*, 1994). Similarly, in the present study, the mean T2 values for the ipsilateral masseter, ipsilateral medial pterygoid and contralateral lateral pterygoid muscles approached a plateau after 5 min of chewing, perhaps because unilateral mastication of three pieces of chewing gum places a large load on these muscles. In addition, the convergence of ΔT2 values might be due to so-called "alternation" of synergistic activity among the masticatory muscles. Alternation of synergistic activity between the masseter and anterior temporalis muscles during sustained static contractions has been reported and interpreted as a protective mechanism against muscle fatigue (Hellsing and Lindstrom, 1983; Farella *et al*, 2009). In either case, this phenomenon suggests that the ipsilateral masseter, ipsilateral medial pterygoid and contralateral lateral pterygoid muscles do more work than other non-plateau muscles during unilateral gum chewing. A further investigation of the correlation between the type and intensity of jaw exercise and the time to reach a plateau is required for establishment of the mean ΔT2 as a parameter for estimation of masticatory activity.

This study has several limitations, including the small sample size and the inclusion of only young male subjects. Comparison of mean ΔT2 values with functional data could not be accomplished because it was difficult to record functional data such as jaw movement parameters and bite force in the strong magnetic field. The axial slices were not appropriate to fractionate muscle components such as the superior and inferior heads of the lateral pterygoid muscles, so analysis of the regional activities of masticatory muscles was not performed. Additional studies are needed to clarify the relationship between functional data for jaw movement and the regional activities of masticatory muscles.

Intramuscular regions of the masseter and temporal muscles show a different pattern of change in activity as a function of bite-force direction during clenching in electromyographic recordings using a wire electrode (Blanksma and Van Eijden, 1990; Blanksma *et al*, 1992). Furthermore, intramuscular heterogeneity of masticatory activities during gum chewing and lateral excursion has been proposed based on 3-dimensional quantification of glucose metabolism using FDG-PET (Rikimaru *et al*, 2001; Yamaguchi *et al*, 2006). However, the details remain unclear as in intramuscular electromyographic recording it is difficult to insert the electrode into a specific region of the muscle and the FDG-PET image has little anatomic information. In contrast, mfMRI provides simultaneous information on anatomic structures and masticatory activities with high spatial resolution in a non-invasive manner. Therefore, mfMRI may be suitable for analysis of intramuscular 3-dimensional activities of masticatory muscles and has already been used to examine the distribution of muscle activation within human triceps surae muscles (Kinugasa *et al*, 2005, 2006). This method has potential applications in basic research into stomatognathic function and in clinical diagnosis of muscle disorders.

In summary, the present study provides the first simultaneous quantification of the overall activities of the bilateral masseter, medial pterygoid and lateral pterygoid muscles during unilateral mastication. Our results affirm the importance of the ipsilateral masseter muscle in unilateral mastication, and quantitatively demonstrate the additional important contributions of the ipsilateral medial pterygoid and contralateral lateral pterygoid muscles during this process.

Acknowledgements

We thank Mr. Osamu Imaizumi for operating the MRI scanner. Gratitude is expressed to the staff at the Division of Aging and Geriatric Dentistry, Tohoku University Graduate School of Dentistry, for their support, and to the staff at the Kansei Fukushi Research Center, Tohoku Fukushi University, for their collaboration. This study was supported by Grants-in-Aid (Nos. 18791419 and 20791414 to S. Yamaguchi, No. 18390510 to M. Watanabe) for Scientific Research from the Japan Society for the Promotion of Science.

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