Available online at www.sciencedirect.com
ScienceDirect
Journal of Prosthodontic Research 55 (2011) 89–97
Journal of Prosthodontic Research
www.elsevier.com/locate/jpor

Original article

Chewing-induced regional brain activity in edentulous patients who received mandibular implant-supported overdentures: A preliminary report

Katsuhiko Kimoto DDS, PhD[a,h,*], Yumie Ono PhD[b,h], Atsumichi Tachibana PhD[c], Yoshiyuki Hirano PhD[d], Takero Otsuka DDS, PhD[e,h], Akinori Ohno DDS[a,h], Katsuhiko Yamaya CDT[f], Takayuki Obata MD, PhD[g], Minoru Onozuka PhD[b,h]

[a] *Division of Fixed Prosthodontics, Department of Oral & Maxillofacial Rehabilitation, Kanagawa Dental College, 82 Inaoka Yokosuka, Kanagawa 238-8580, Japan*
[b] *Department of Physiology and Neuroscience, Kanagawa Dental College, Yokosuka, Kanagawa, Japan*
[c] *ADAM Center Long Island University, NY, USA*
[d] *Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA*
[e] *Department of Craniofacial Growth & Development Dentistry, Kanagawa Dental College, Yokosuka, Kanagawa, Japan*
[f] *Department of Dental Laboratory, Kanagawa Dental College Hospital, Yokosuka, Kanagawa, Japan*
[g] *Department of Biophysics, Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan*
[h] *Research Center of Brain and Oral Science, Kanagawa Dental College, Yokosuka, Kanagawa, Japan*

Received 20 April 2010; received in revised form 17 August 2010; accepted 16 September 2010
Available online 15 October 2010

Abstract

Purpose: We used functional magnetic resonance imaging (fMRI) to investigate the change in brain regional activity during gum chewing when edentulous subjects switched from mandibular complete dentures to implant-supported removable overdentures.
Methods: Four edentulous patients (3 males and 1 female, aged 64 to 79 years) participated in the study. All subjects received a set of new maxillary and mandibular complete dentures (CD), followed by a maxillary complete denture and a new mandibular implant-supported removable overdentures (IOD). A 3-T fMRI scanner produced images of the regional brain activity for each subject that showed changes in the blood-oxygenation-level-dependent (BOLD) contrast in the axial orientation during gum-chewing with CD and IOD.
Results: Region-of-interest analysis showed that IOD treatment significantly suppressed chewing-induced brain activity in the prefrontal cortex. The chewing-induced brain activities in the primary sensorimotor cortex and cerebellum tended to decrease with IOD treatment, however they did not reach to significance level. There was no change in brain activity in the supplementary motor area, thalamus and insula between gum chewing with CD and IOD. Group comparison using statistical parametrical mapping further showed that, within the prefrontal cortex, the neural activity of the frontal pole significantly decreased during gum-chewing with IOD when compared to that with CD ($P < 0.05$).
Conclusion: Despite the limitation of a small sample size, these results suggest that the gum-chewing task in elderly edentulous patients resulted in differential neural activity in the frontal pole within the prefrontal cortex between the 2 prosthodontic therapies—mandibular CD and IOD.

Keywords: Functional magnetic resonance imaging (fMRI); Mandibular implant-supported overdentures; Blood oxygenation level-dependent (BOLD); Chewing

1. Introduction

Dental implants have a significant effect on the current prosthodontic therapy for edentulous patients. Particularly, a mandibular removable implant-supported overdentures (IOD) supported by 2 or more implants is a treatment option for elderly edentulous patients who are dissatisfied with conventional complete dentures (CD). This option provides great patient satisfaction, chewing ability, and comfort [1,2].

An anterior short bar or single attachment improves overdenture retention [3–5]. Previously, we showed that a mandibular IOD anchored with an anterior short bar is an effective prosthodontic therapy which increases chewing ability even for subjects who are already satisfied with their conventional CD [6].

Chewing increases the cerebral blood flow in dentate subjects. Cerebral blood-flow imaging, using positron emission

* Corresponding author at: Division of Fixed Prosthodontics, Department of Oral & Maxillofacial Rehabilitation, Kanagawa Dental College, 82 Inaoka-cho, Yokosuka, Kanagawa 238-8580, Japan. Tel.: +81 468 22 9532; fax: +81 468 22 9532.
E-mail address: kimotokt@kdcnet.ac.jp (K. Kimoto).

1883-1958/$ – see front matter © 2010 Japan Prosthodontic Society. Published by Elsevier Ireland. All rights reserved.
doi:10.1016/j.jpor.2010.09.006

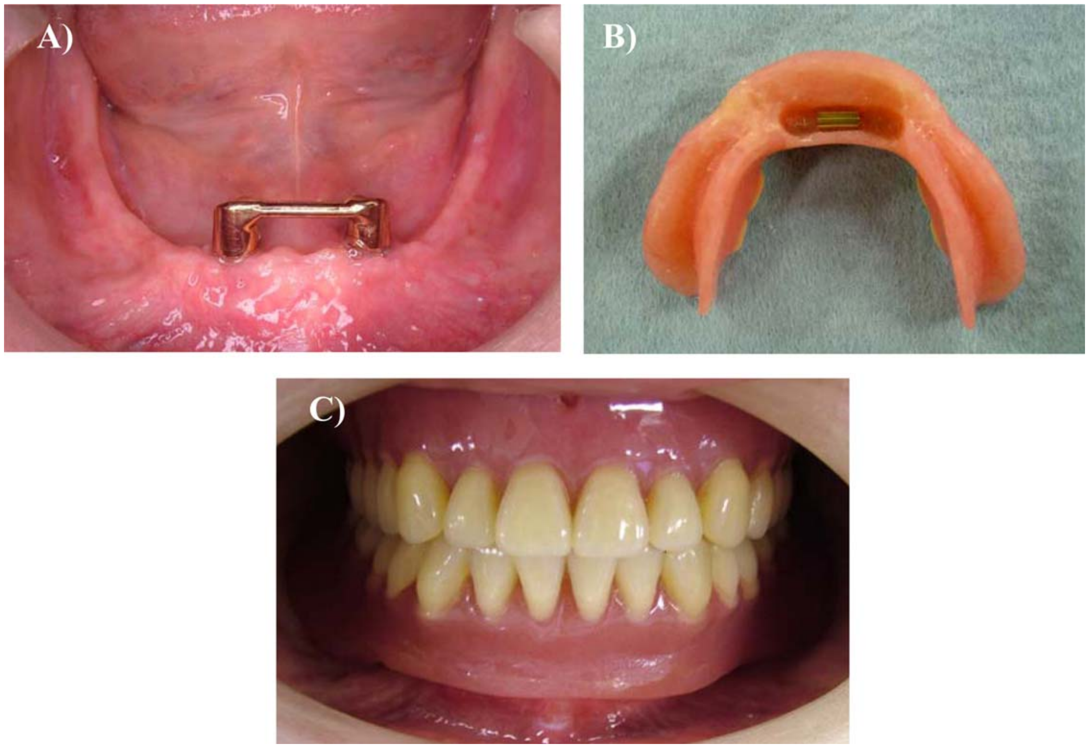

Fig. 1. Subject with mandibular implant-supported removal overdentures. (A) Dolder bar attached to 2 implants; (b) mandibular complete denture with metal clip; (C) maxillary complete denture and mandibular implant-supported overdentures in place.

tomography (PET), showed the increases of blood flow in various cortical areas [7,8]. Studies using functional magnetic resonance imaging (fMRI) further revealed that chewing increases blood-oxygenation-level-dependent (BOLD) signals in the primary sensorimotor cortex, supplementary motor area, insula, thalamus, cerebellum, and prefrontal cortex [9–11]. The chewing-increased neuronal activity in these brain regions is supposed to contribute the ameliorative effect of chewing on the process of working memory, consequently enhancing cognitive performance [12,13].

However, the relationship between prosthodontic or implant therapy and regional brain activity during chewing is unclear. Therefore, the aim of this study was to investigate the neural activity in the brain during gum-chewing by using fMRI when edentulous patients used mandibular CD or IOD.

2. Materials and methods

2.1. Subjects

Four edentulous patients (3 males and 1 female, aged 64–79 years) at Kanagawa Dental College Hospital in Yokosuka, Japan, who were willing to undergo new CD treatment, were selected to participate in the study. None of the four subjects had any psychiatric or neurological disease. All subjects could understand written and spoken Japanese, and they gave a written informed consent to participate in this study.

The ethics committees of Kanagawa Dental College and the National Institute of Radiological Sciences reviewed and approved the protocol for this study.

2.2. Treatment protocol

All subjects received a set of new maxillary and mandibular CDs at first. After adapting for 1 month, we acquired the regional brain activity during chewing a gum using the CD with a 3-T MRI scanner (GE, Milwaukee, WI, USA). After the first fMRI scan, 2 implants were surgically placed bilaterally in the canine region according to the standard Brånemark-system protocol (Nobel Biocare AB, Göteborg, Sweden). After 3 months, each subject received a maxillary CD and a new mandibular removable IOD with metal clip retainers to attach the Dolder bar that connected the 2 Brånemark implants (Fig. 1). Again, after adapting with IOD for 1 month, the second fMRI scan was acquired during the same task of chewing a gum for each subject but with IOD.

2.3. Task paradigm

The fMRI task paradigm consisted of 4 periods of rhythmic gum-chewing for 30 s, separated by resting periods of the same duration, during which the participants abstained from chewing. The gum was odorless, tasteless, and moderately hard (5.6×10^4 poise; General Laboratory of Lotte Co Ltd., Saitama, Japan). Instructions on the timing of chewing and resting periods were given on a screen located at the back of a scanner via an LCD projector. Subjects could see the instructions inside the scanner through a small non-magnetic mirror mounted to an eight-channel phased-array coil (GE, Milwaukee, WI, USA) surrounding the subject's head. During the chewing period, the word ''gum'' was presented on the screen at a rate of 1 Hz, a

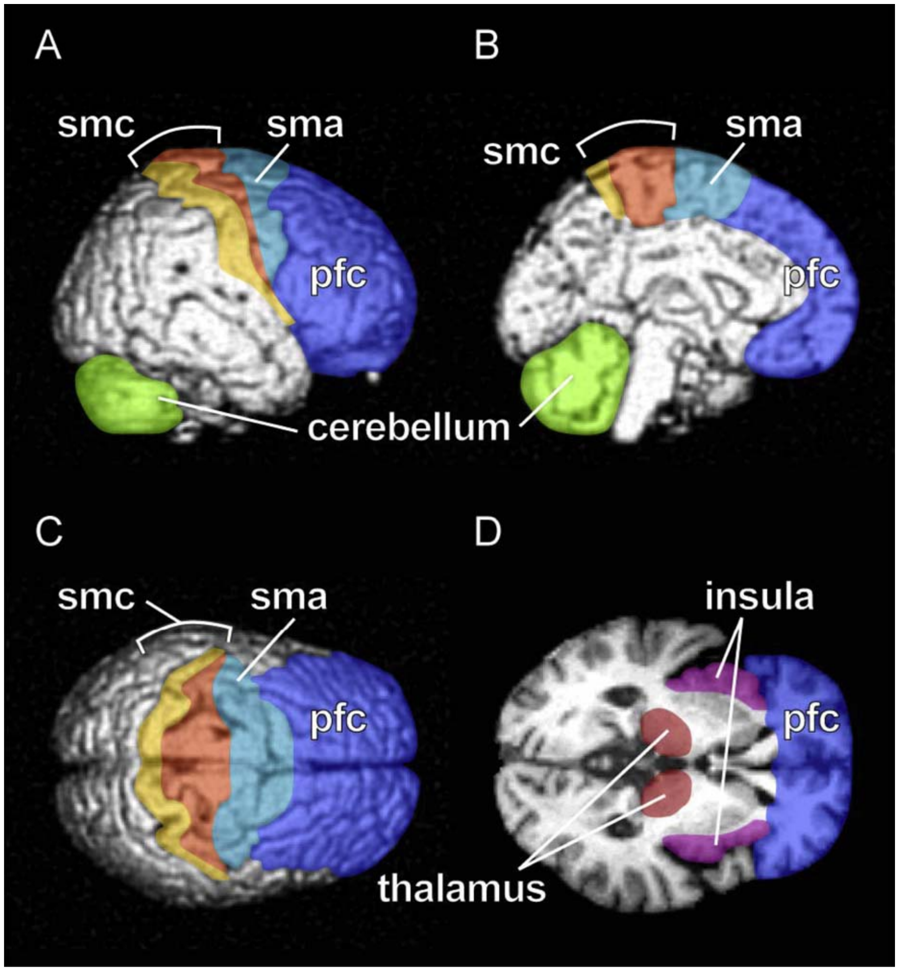

Fig. 2. Anatomical structure of ROIs. (A) Surface view of the right hemisphere. (B) Sagittal cross-section view at the longitudinal fissure of cerebrum. (C) Upper surface view of the cerebrum. (D) Horizontal view of the cerebrum at the level that contains the anterior and the posterior commissure. smc: the primary sensorimotor cortex. smc is consisted with two brain regions of the primary sensory area (yellow) and the primary motor area (orange). sma: supplementary motor area; pfc: prefrontal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

normal adult's chewing rate [14], and subjects were encouraged to chew the gum according to the instruction. During the entire resting period, a cross mark "+" was shown at the center of the screen as a fixation point to prevent head movement.

2.4. Image acquisition and data analysis

Gradient echo EPI (TE: 30 ms; TR: 2 s; field of view: 240 mm; slice thickness: 3.8 mm; gap: 0.2 mm; matrix: 64×64; 32 slices) and anatomical images were acquired with a 3-T MRI scanner (GE, Milwaukee, WI, USA). Data from the first 15 volumes were discarded because of the possibility they were contaminated by transient magnetization. Correction for head motion was applied using Statistical Parametric Mapping software (SPM5; University College London, London, UK). A total of 270 successive functional images obtained from each subject were normalized to the MNI (Montreal Neurological Institute) template [15] and spatially smoothed by an 8-mm Gaussian kernel. Voxel-based statistical analysis by a general linear-model approach [16] was performed using SPM5. In short, the BOLD signals were fitted to a linear regression model with reduction of global changes using proportional scaling. The estimated slope of the regression model, beta value, was defined as the index of brain activity related to chewing. Provided with beta contrast map, we calculated statistical-contrast images of all subjects for group analysis by means of T statistics (paired *t*-test, uncorrected for multiple comparisons) with a random-effects model. With each voxel, we calculated T value by dividing beta value by the standard error of the slope. We considered P values < 0.05 to be statistically significant. The resulting areas of activation were characterized in terms of statistical significance and spatial extent (>50 voxels). MNI coordinates of local-maximum voxels found in the resulting areas were transformed to Talairach coordinates [17], on the basis of which we determined the corresponding Brodmann area using the Talairach client software [18,19].

Our previous fMRI study [9,10] had identified 6 regions of interest (ROIs) that were robustly activated by gum-chewing in dentate subjects regardless of their age: the primary sensorimotor cortex, supplementary motor area, insula, thalamus, cerebellum, and prefrontal cortex (Fig. 2) Therefore, we further studied the changes in regional brain activity in these 6 regions when the subjects chewed with CD and IOD. Mask images were generated using a software package called MARINA [20]

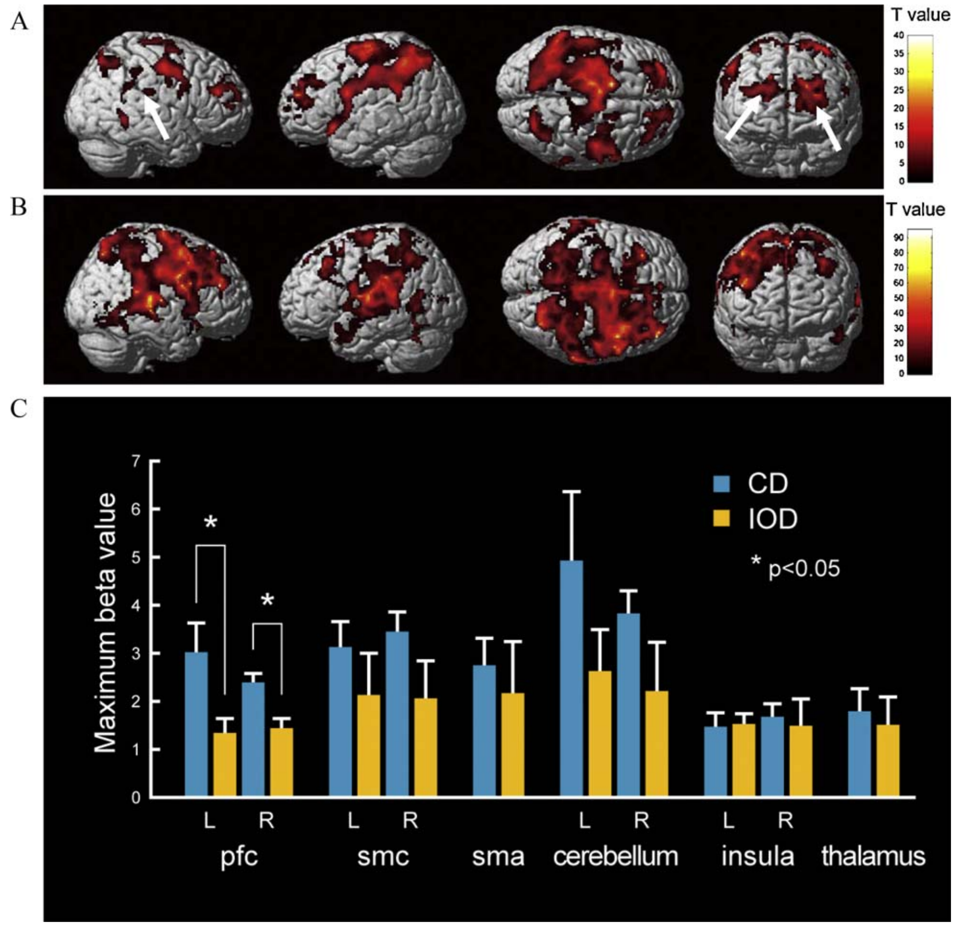

Fig. 3. Regional brain activity during chewing. (A) Significant signal increase due to gum-chewing with maxillary and mandibular complete dentures (CD) ($n = 4$); (B) Significant signal increase due to gum-chewing with maxillary complete denture and mandibular implant-supported overdentures (IOD) ($n = 4$); (C) Changes in regional brain activity in the 6 regions of interest (ROIs). Each column represents mean $\pm$ SEM. $^*P < 0.05$. The vertical axis shows the maximum beta value. CD: complete dentures; IOD: implant-supported removable overdentures; pfc: prefrontal cortex; smc: primary sensorimotor cortex; sma: supplementary motor area.

to extract the ROIs from normalized beta-value contrasts of each subject. In each ROI we used the paired *t*-test to compare the maximum beta value attained when the subject chewed with the CD to the maximum beta value attained when he or she chewed with the IOD. All values shown are mean $\pm$ SEM.

We used beta value for the ROI analysis and *T* value for visual representation of the regional brain activity with statistically significant difference, respectively. Generally, the former indicates a raw value showing how many times the BOLD signals increased between rest and chewing periods. The latter is also an index related to the amplitude of beta value, however the statistical robustness of the beta value is taken into account. Higher *T* value means more robust regional brain activity with repetitive chewing task.

2.5. Subject satisfaction

At 3 months after IOD implantation, the assessor measured the subject satisfaction using a set of 100-mm visual analog scales (VAS). The left end of each VAS was labeled ‘‘far less satisfied than before,’’ and the right end was labeled ‘‘far more satisfied than before.’’ We obtained individual assessments of how satisfied each subject was with each of the following: chewing function, cleaning, odor, security, and speech. Then we evaluated the degree of change perceived with CD and IOD therapy [21].

3. Results

3.1. Group analysis of chewing-induced regional brain activity in CD and IOD

Fig. 3A and B shows voxel-based comparison of regional brain activity when subjects chewed a gum using CD and IOD, respectively (group analysis, $n = 4$). The locations of the most significant foci of activation in the above mentioned 6 brain regions (Fig. 2) are summarized in Table 1. We observed that gum-chewing with CD significantly and bilaterally increased the BOLD signals in 5 brain regions: the primary sensorimotor cortex, supplementary motor area, thalamus, cerebellum, and prefrontal cortex. We could not find statistically significant chewing-related activation in the insula which was obvious in our previous study with dentate subjects [9,10]. Gum-chewing with IOD significantly and bilaterally increased the BOLD signals in 5 brain regions: the primary sensorimotor cortex, supplementary motor area, insula, thalamus, and prefrontal cortex. It unilaterally

Table 1
Location of significant increases in the fMRI signals during chewing.

Subject	ROI	R/L	MNI			Local maximum T values	BA
			x	y	z		
CD	smc	R	62	−6	32	3.18	3,1,2
		L	−52	−6	28	4.32	3,1,2
	Ereueiium	R	18	−56	−18	3.67	Cerebellum lobule 6
		L	−18	−66	−14	4.81	Cerebellum lobule 6
	Thalamus	R	18	−18	6	2.39	
		L	−16	−30	0	4.21	
	sma	R	10	−8	68	5.16	6
		L	−8	−8	66	14.23	6
	Insula	R				NA	
		L				NA	
	pfc	R	16	40	38	14.93	9,10
		L	−14	42	26	39.72	9,10
IOD		R	52	2	26	32.41	4
	smc	L	−52	0	22	11.82	4
		R				NA	
	Ereoenum	L	−38	−62	−32	9.80	Lobule crus 1
	Thalamus	R	14	−12	14	21.34	
		L	−14	−26	10	14.17	
	sma	R	6	12	64	16.25	6
		L	−8	−14	56	10.52	6
	Insula	R	40	2	8	9.49	
		L	−46	6	2	3.53	
	pfc	R	44	42	22	94.92	10
		L	−34	28	44	28.74	8
CD minus IOD	pfc	R	36	46	22	9.77	8,9,10
		L	−32	22	50	8.36	8
		R				NA	
	sma	L	−6	−12	68	3.60	6
	Occipital	R	2	−80	18	7.20	18,30
		L				NA	
	Temporal lobe	R	42	−46	−20	8.23	37
		L	−50	10	−32	5.21	21
		R				NA	
	Ereoenum	L	−14	−34	−22	3.98	Cerebellum lobule 4–5
	Parietal	R	20	−68	46	9.12	7
	Lobe	L				NA	

CD: mandibular complete dentures; IOD: mandibular implant-supported removable overdentures; CD minus IOD: more prominent activation during chewing with CD than during chewing with IOD; smc: primary sensorimotor cortex; sma: supplementary motor area; pfc: prefrontal cortex. $P < 0.05$ (uncorrelated for multiple comparison), extent threshold $k = 50$ voxels.

increased the BOLD signal in the cerebellum. A different pattern of brain activity associated with chewing with both CD and IOD was observed in the right primary sensorimotor cortex and prefrontal cortex (Fig. 3A and B, white arrowheads).

3.2. ROI analysis

Fig. 3C shows the change in maximum beta values during gum chewing between CD and IOD. Statistically significant changes were observed in the prefrontal cortex; the chewing-induced brain activity was significantly decreased after IOD treatment ($P = 0.03$ and $P = 0.04$ in the left and right prefrontal cortex, respectively; paired t-test). Similar tendency was observed in the primary sensorimotor cortex ($P = 0.31$ and $P = 0.15$ in the left and right primary sensorimotor cortex, respectively) and the cerebellum ($P = 0.27$ and $P = 0.25$ in the left and right cerebellum, respectively) even though they did not reach to significance level. The other brain regions, namely the supplementary motor area, thalamus and insula, showed comparable regional brain activity between CD and IOD.

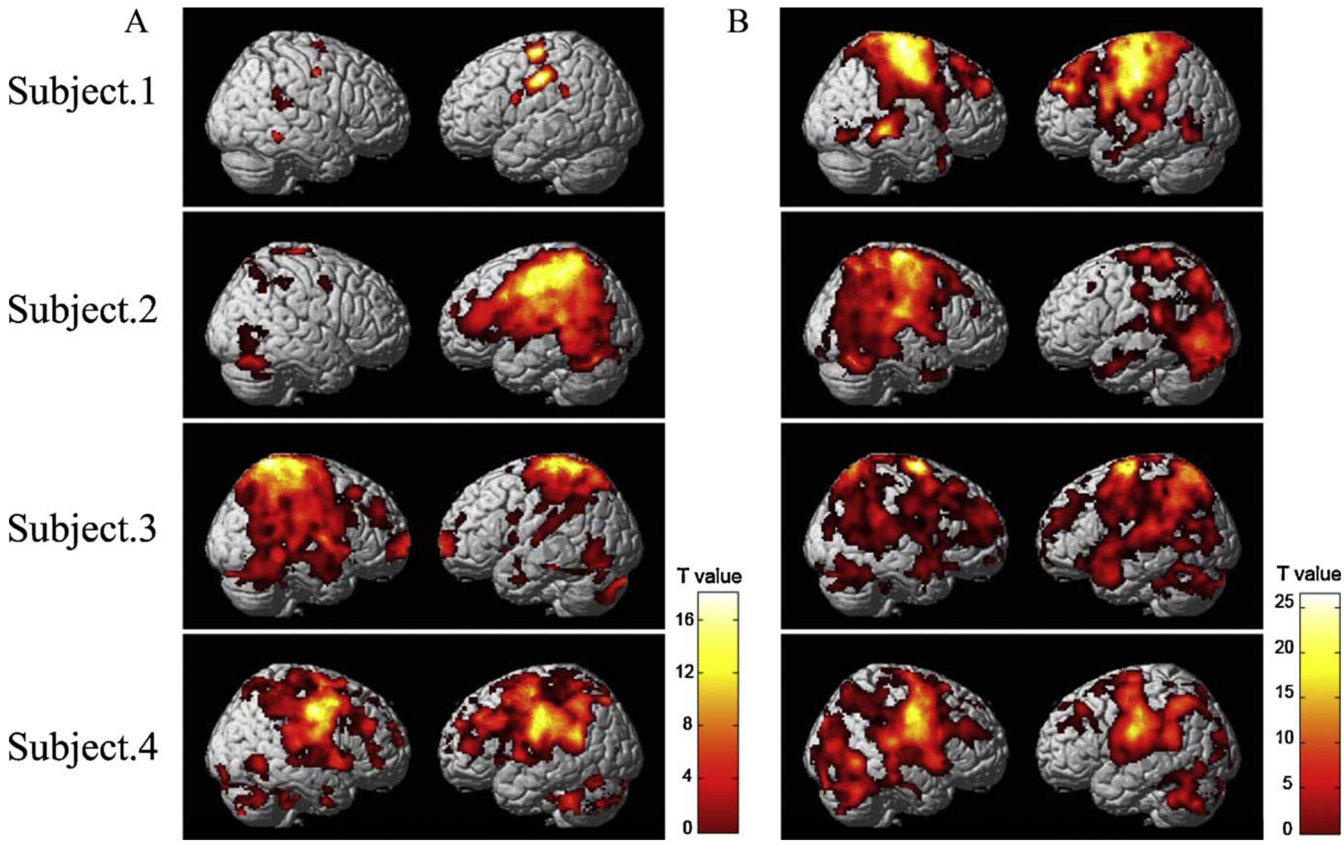

Fig. 4. Individual analysis of regional brain activity during chewing. (A) Significant signal increase due to gum-chewing with maxillary and mandibular complete dentures (CD). (B) Significant signal increase due to gum-chewing with maxillary complete denture and mandibular implant-supported overdentures (IOD).

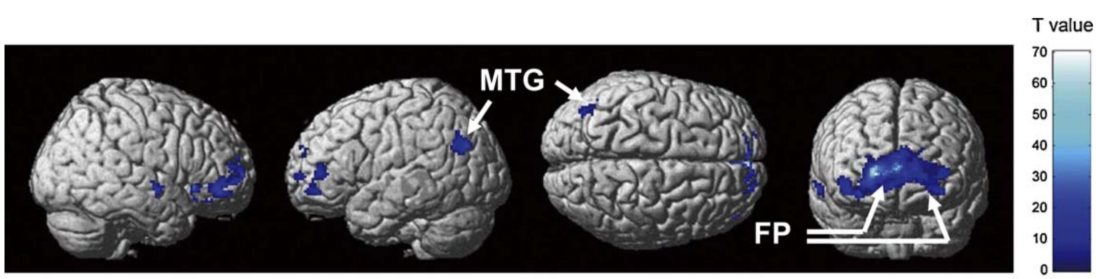

Fig. 5. More prominent activation was observed during chewing with maxillary and mandibular complete denture (CD) than with a maxillary complete denture and mandibular implant-supported overdentures (IOD). The results shown are revealed by group analysis of all subjects with a random-effects model. Highlighted area shows significantly decreased brain activity during chewing with IOD than with CD (paired *t*-test, uncorrected for multiple comparisons, $P < 0.05$). The areas with statistically significant suppression of regional brain activity in the right cerebellum, left putamen, and right insular (listed in Table 1) were not shown in the figure since these regions were located in deep inside of the brain. FP: frontal pole; MTG: middle temporal gyrus.

3.3. Individual analysis

To further investigate individual differences in neuronal activity during gum chewing, we also compared chewing-increased brain activities in CD and IOD with every subject. Fig. 4 clearly indicates a different pattern of brain activity for each subject. In subjects 1 and 2, the unilateral brain activity in the primary sensorimotor cortex was barely detectable during gum-chewing with CD, while all subjects exhibited bilateral brain activity in much of the area, including the primary sensorimotor cortex, during chewing with IOD.

3.4. Comparison of gum-chewing with CD and IOD

Despite the large individual differences of regional brain activities shown in Fig. 4, group comparison between CD and IOD clearly indicated that IOD treatment bilaterally suppressed chewing-induced neuronal activity in the frontal pole (FP; Brodmann's area 10 (BA10)) within the prefrontal cortex (Fig. 5). Unilateral suppression of regional brain activity was found in the right cerebellum, left putamen, right middle temporal gyrus (MTG), and right insula (Fig. 5 and Table 1).

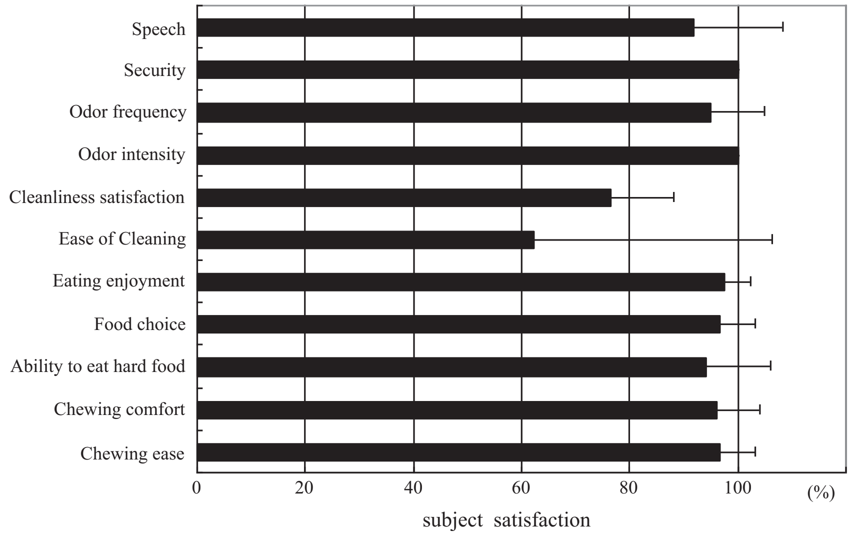

Fig. 6. Subject satisfaction rating.

3.5. Subject satisfaction

The mean VAS score and standard deviation of the satisfaction ratings for each subject are presented in Fig. 6. A high score and a rating of almost full satisfaction (except for ease of cleaning and Cleanliness satisfaction) were achieved after activating the implant. This finding indicates that the subjective impression of gum-chewing with IOD is significantly better than that with CD.

4. Discussion

In previous studies, some researchers used multi-channel near-infrared optical topography (NIRS) to perform functional brain imaging of partially edentulous patients treated with dental implant prostheses who performed a maximum voluntary clenching task. It is notable that oral rehabilitation by prosthodontic or implant therapy increases cerebral cortex activation in specific regions [22,23]. However, little is known about whether oral rehabilitation is related to regional brain activity. To the best of our knowledge, our use of fMRI to investigate the relationship between chewing and regional brain activation in elderly edentulous subjects who chew with a mandibular CD or an IOD is the first experiment of its kind.

Individual analysis showed that gum-chewing with CD resulted in almost no neural activity in the primary sensorimotor cortex of some subjects (Fig. 4), while robust and strong neural activity in this area has been reported in previous studies with dentate subjects. Another fMRI study showed that the primary sensorimotor cortex was not activated in edentulous subjects who performed a clenching task while wearing complete dentures [24], suggesting that this phenomenon depends on denture quality and mobility, general oral condition, and the adaptability of the subject. Together with the absence of activation in the insula during gum-chewing with CD (Table 1), our current results suggest that the chewing-related brain activity with subjects wearing CD is somehow altered from that with dentate subjects.

Larger T values in the statistical-contrast images in chewing with IOD than with CD (Figs. 3A and B and 4, and Table 1) indicate more stable neuronal activation in chewing with IOD than with CD. Furthermore, the spatial pattern of neuronal activity in subjects with IOD is more similar to that of dentate subjects when compared with CD. Among six regions where robust activation has been previously shown during gum chewing in dentate subjects [9,10], only five regions were activated when edentulous subject chewed a gum with CD. However, the IOD treatment recovered the neuronal activation in the insula which was absent in gum chewing with CD, resulting in the activation of all the six regions (Table 1). These results raise two hypotheses: (1) CD treatment might alter the chewing-induced regional brain activity possibly due to the denture mobility and the change of general oral condition, and (2) IOD treatment might return the chewing-induced regional brain activity to the pattern similar to the dentate subject.

The ROI analysis showed that chewing with IOD resulted in a decrease in the maximum beta value than chewing with CD in the prefrontal cortex, primary sensorimotor cortex, and cerebellum. How is the neural activity reduced by chewing with IOD? Based on previous findings, there are several possible explanations for the observed phenomenon. As to the latter two regions concerning motor execution, the reduction of brain activity might reflect more smooth manipulation of the masticatory organ during chewing with IOD than that with CD. Using fMRI, Morgen et al. [25] have reported that repetition of a simple motor task, such as finger flexion or extension, causes a specific reduction in the activation in executive motor regions. Chewing is basically a maintained rhythmic pattern under the control of the central pattern generator located in the pons and medulla [26]. Healthy subjects with normal occlusion have a regular, rhythmic, and stable chewing pattern, while subjects with malocclusion or a temporomandibular disorder have an irregular and kinematically unstable chewing pattern [27,28]. The higher beta values in the restricted area of the brain (Fig. 3C) and the smaller T values in the corresponding ROI (Fig. 3A and B, and Table 1) in chewing with CD might reflect the irregular and unstable chewing pattern when patients struggled to chew a gum with CD. Chewing with IOD, therefore, might be closer to the chewing pattern of subjects with normal occlusion and increase the chewing ability. In fact, subjects gave the items of ‘‘ability to eat hard food’’ and ‘‘chewing ease and comfort’’ high satisfaction scores (Fig. 6). Care should be taken that the decrease of maximum beta value in each ROI does not indicate general suppression of brain activity. Indeed, when the total sum of beta values within the ROI was compared, there was no statistically significant difference between conditions of CD and IOD in any region (data not shown). The decrease of maximum beta value in chewing with IOD might be due to the stabilization of neural activation pattern with the regular, rhythmic, and stable chewing pattern using IOD.

Another interesting point is the suppressed neural activity in the prefrontal cortex, with patients using IOD (Fig. 5). Previous studies have already shown that there are some differences in neural activity in the area of the prefrontal cortex during chewing [10,12,29]. Our study shows that the neural activity in the frontal pole (FP) (BA10) within the prefrontal cortex, is less when chewing gum with IOD than when chewing with CD. The prefrontal cortex has strong connections to the limbic system via its medial and orbital efferent connections that terminate in the amygdala, thalamus, and parahippocampal regions. In particular, an extensive reciprocal connection between the prefrontal cortex and the amygdala supports the idea that these structures take part in common functions, such as emotional and social behavior, stress, learning, and memory [30–33]. Moreover, several brain imaging studies indicate that the reduced metabolism in the FP associates with improvement of mood. For example, a PET study showed a significant decrease in the metabolic rate in the FP of a patient who responded positively to antidepressant treatment. In addition, decreased activity in the FP occurs frequently during therapy for severe and treatment-resistant depression [34,35]. Together with our current result, the suppressed brain activity in the FP after IOD treatment might reflect the improved mood, such as easiness and comfort with chewing. Indeed, in their subjective assessment all participants answered that chewing with IOD is ‘‘far better’’ than with CD.

Because of the small sample size of our study, we consider our result to be preliminary. However, if a larger sample confirms the result, then it will be possible that stimulating chewing in the elderly, with implant therapy or other means, will effectively treat depression or loss of interest or pleasure. However, such a hope must remain tentative as the mechanism underlying chewing-induced regional activation of the brain is unclear at present. Further studies are necessary to determine the mechanism with which gum-chewing stimulates the prefrontal cortex.

5. Conclusion

With the caveat that our sample size is small, the gum-chewing task in elderly edentulous patients caused a different amount of neural activity in the FP within the prefrontal cortex for prosthodontic therapy with a mandibular CD than for that with a mandibular IOD.

Acknowledgment

This work was partly supported by the Open Research Center of Brain and Oral Science, Kanagawa Dental College.

References

[1] Fine JS, Heydecke G. Implant overdenture versus convetional denture. In: Feine JS, Carlsson GE, editors. Implant overdenture. The standard of care for edentulous patients: Implant overdentures-the standard of care for edentulous patients. Chicago: Quintessence; 2004 . p. 37–45.
[2] Fueki K, Kimoto K, Ogawa T, Garrett NR. Effect of implant-supported or retained dentures on masticatory performance: a systematic review. J Prosthet Dent 2007;98:470–7.
[3] Sadowsky SJ. Mandibular implant-retained overdentures: a literature review. J Prosthet Dent 2001;86:468–73.
[4] Cooper LF, Moriarty JD, Guckes AD, Klee LB, Smith RG, Almgren C, et al. Five-year prospective evaluation of mandibular overdentures retained by two microthreaded, TiO blast nonsplinted implants and retentive ball anchors. Int J Oral Maxillofac Implants 2008;23:696–704.
[5] Batenburg RH, Meijer HJ, Raghoebar GM, Vissink A. Treatment concept for mandibular overdentures supported by endosseous implants: a literature review. Int J Oral Maxillofac Implants 1998;13:345–539.
[6] Kimoto K, Garrett NR. Effect of mandibular ridge height on masticatory performance with mandibular conventional and implant-assisted overdentures. Int J Oral Maxillofac Implants 2003;18:523–30.
[7] Watanabe I, Ishiyama N, Senda M. Cerebral blood flow during mastication measures with positron emission tomography. Geriatric Dent 1992;6:148–50.
[8] Momose I, Nishikawa J, Watanabe T, Sasaki Y, Senda M, Kubota K, et al. Effect of mastication on regional cerebral blood flow in humans examined by positron-emission tomography with ^{15}O-labelled water and magnetic resonance imaging. Arch Oral Biol 1997;42:57–61.
[9] Onozuka M, Fujita M, Watanabe K, Hirano Y, Niwa M, Nishiyama K, et al. Mapping brain region activity during chewing: a functional magnetic resonance imaging study. J Dent Res 2002;81:743–6.
[10] Onozuka M, Fujita M, Watanabe K, Hirano Y, Niwa M, Nishiyama K, et al. Age-related changes in brain regional activity during chewing: a functional magnetic resonance imaging study. J Dent Res 2003;82:657–60.
[11] Takahashi T, Miyamoto T, Terao A, Yokoyama A. Cerebral activation related to the control of mastication during changes in food hardness. Neuroscience 2007;145:791–4.
[12] Hirano Y, Obata T, Kashikura K, Nonaka H, Tachibana A, Ikehira H, et al. Effects of chewing in working memory processing. Neurosci Lett 2008; 436:189–92.
[13] Ono Y, Dowaki K, Ishiyama A, Onozuka M. Gum chewing maintains working memory acquisition. Int J Bioelectromagnetism 2008;11:130–4.
[14] Throckmorton GS, Buschang BH, Hayasaki H, Phelan T. The effects of chewing rates on mandibular kinematics. J Oral Rehabil 2001;28:328–34.
[15] Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994;18:192–205.
[16] Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995;2:189–210.
[17] Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York: Thieme; 1988.
[18] Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 2000;10:120–31.
[19] Lancaster JL, Rainey LH, Summerlin JL, Freitas CS, Fox PT, Evans AC, et al. Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. Hum Brain Mapp 1997;5:238–42. 1997.
[20] Walter B, Blecker C, Kirsch P, Sammer G, Schienle A, Stark R. MARINA. An easy to use tool for the creation of MAsks for Region of INterest

Analyses. Neuroimage 2003;19(Suppl. 1):e1899. Available athttp://www.bion.de (downloads).

[21] Kapur KK, Garrett NR, Hamada MO, Roumanas ED, Freymiller E, Han T, et al. Randomized clinical trial comparing the efficacy of mandibular implant-supported overdentures and conventional dentures in diabetic patients. Part III: comparisons of patient satisfaction. J Prosthet Dent 1999;82:416–27.

[22] Miyamoto I, Yoshida K, Tsuboi Y, Iizuka T. Rehabilitation with dental prosthesis can increase cerebral regional blood volume. Clin Oral Implants Res 2005;16:723–7.

[23] Narita N, Kamiya K, Yamamura K, Kawasaki S, Matsumoto T, Tanaka N. Chewing-related prefrontal cortex activation while wearing partial denture prosthesis: pilot study. J Prosthet Res 2009;53:126–35.

[24] Yan C, Ye L, Zhen J, Ke L, Gang L. Neuroplasticity of edentulous patients with implant-supported full dentures. Eur J Oral Sci 2008; 116:387–93.

[25] Morgen K, Kadom N, Sawaki L, Tessitore A, Ohayon J, Frank J, et al. Kinematic specificity of cortical reorganization associated with motor training. Neuroimage 2004;21:1182–7.

[26] Lund JP, Kolta A. Generation of the central masticatory pattern and its modification by sensory feedback. Dysphagia 2006;21:167–74.

[27] Ahlgren J. Mechanism of mastication, a quantitative cinematographic and electromyographic study on masticatory movements in children, with special reference to occlusion the teeth. Acta Odontol Scand 1966; 24(Suppl. 44):1–109.

[28] Shiga H, Stohler CS, Kobayashi Y. The rhythmicity of the chewing movement between CND patients and normal subjects. In: Morimoto T, Matsuya T, Takada K, editors. Brain and oral functions, oral motor function and dysfunction. Amsterdam: Elsevier; 1995. p. 479–82.

[29] Takada T, Miyamoto T. A fronto-parietal network for chewing of gum: a study on human subjects with functional magnetic resonance imaging. Neurosci Lett 2004;360:137–40.

[30] Boller F, Grafman J, FitzGerald MJT, Folan-Curran J. 2nd ed., Handbook of neuropsychology, vol. 7, 2nd ed. 2002. p. 157–74.

[31] Verwer RW, Van Vulpen EH, Van Uum JF. Postnatal development of amygdaloid projections to the prefrontal cortex in the rat studied with retrograde and anterograde tracers. J Comp Neurol 1996;376:75–96.

[32] Stefanacci L, Amaral DG. Topographic organization of cortical inputs to the lateral nucleus of the macaque monkey amygdala: a retrograde tracing study. J Comp Neurol 2000;42:52–79.

[33] Roozendaal B, Koolhaas JM, Bohus B. The role of the central amygdala in stress and adaption. Acta Physiol Scand Suppl 1997;640:51–4.

[34] Pardo JV, Sheikh SA, Schwindt GC, Lee JT, Kuskowski MA, Surerus C, et al. Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism. Neuroimage 2008;42:879–89.

[35] Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry 1999;156:1149–58.